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1

EXTRAPERITONEAL RETROGRADE RADICAL CYSTECTOMY (RC) IN THE ELDERLY: LONG TERM RESULTS

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Objectives: To evaluate morbidity, overall (OS) and disease specific survival (DSS) of RC in octogenarians according to surgical approach (peritoneal *vs*. extraperitoneal), ASA score, and type of urinary diversion in the long term. *Methods:* From 2000 to 2007 105 pts 80 year-old or older received RC and urinary diversion for BC at our institution. The mean age was 83.2 years: 73 men and 32 women. 88/105 (83.9%) pts had one or more comorbidities. ASA score was used for classifying preop. risk. 21/105 (20%) were ASA 2, 55/105(52.4%) ASA 3 and 29/105 (27.6%) ASA 4. 40/105 pts (38%) received RC+lymphadenectomy through a peritoneal approach, while 65/105 pts (62%) had a retrograde extra-peritoneal RC. 53/105 (50.5%) had uretero-cutaneostomy (UCS) as diversion, while 38/105 (36.2%) had Bricker.14/105 pts (13.3%) had an orthotopic neobladder. Pathological stage was: Recurrent Tis+T1 in 11/105 pts (10.4); T2b in 15/105 (14.3%); T3a in 24/105 (22.8%); T3b in 37/105 (35.2%); T4 in 18/105 (17.1%). 23/105 patients (21.9%) were N+(pT3-T4). 81/105 patients (77.2%) were in intensive care unit for 1-6 days. 51/105 patients (48.6%) were transfused. *Results:* The mean follow-up was 46.5 months (24-96 months). Perioperative mortality was 8.5% (9/105). Mean hospital stay was 14.5 days (7-35 days). The complication rate (medical and surgical) was 36%. 8.3% of patients required a second operation. Medical and surgical complications by ASA were: ASA2=11.8%, ASA 3=(50%), ASA4=38% respectively. Complication rate according to surgical approach: Medical: extraperitoneal 40.4%, peritoneal 27%.Surgical:12.8% with extra-peritoneal route *vs*. 29.7% with intra peritoneal approach. Re-operation rate: Extraperitoneal=0.9% *vs*. 7.6% peritoneal. Mean blood loss was: 380 cc in extraperitoneal *vs*. 780 cc in the intraperitoneal approach. Complications according to diversion: Medical=45% in UCS *vs*. 34.5% in Bricker *vs*. 39.5% in orthotopic. Surgical: 24% UCS *vs*. 34.5% Bricker *vs*. 37% in orthotopic. Re.op rate: UCS=0 *vs*. 17% in Bricker *vs*. 7.1 in orthotopic. 82 pts had regular long term follow-up. After 1 year OS was 60%, after 2 years 43.6% and after 3 year 39.9%. DSS was 63.3% after 1 year and 51.2% after 2 years and 50% after 3 years. No difference in survival was seen between the extra or intra-peritoneal approach. *Conclusion:* The results of our study support the use of RC in octogenarians. Complications were acceptable. Mayor complications were correlated with high ASA score (3-4), urinary diversion (Bricker) and surgical approach (peritoneal route).

2

RADICAL PROSTATECTOMY (RP) WITH EXTENDED PELVIC LYMPHADENECTOMY (EPLND) FOR PT3B-T4 PROSTATE CANCER (PCA): LONG-TERM RESULTS OF A SINGLE CENTRE

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Introduction and Objectives: RP+EPLND has been suggested as a possible treatment option in patients with cT3 Pca by different groups. Few very long term data exist on the fate of pT3b-T4 Pca patients treated by RP+ EPLND. The objectives of this study were to evaluate the oncological outcomes of pT3b-T4 Pca patients >9 years after radical surgery and to observe side-effects. *Patients and Methods:* From March 2000 to December 2005, 602 radical prostatectomies were performed by a single surgeon. 105/602 pts. (17.4%) were staged as clinical T3. After surgery 40/105 pts. were pT3b (31) or T4 (9). The mean age was 68.1 (range 51-76) and the mean pre-op PSA was 24.5 ng/ml (range 4-130 ng/ml). All the pts. were Mo (negative CT and bone scan). Surgery: a bilateral EPLND was always performed. The number of nodes removed varied from 20 to 45 (mean 32.5). The retrograde extraponeurotic approach with removal of Denonviller fascia was used. Nerve sparing was never attemped. Additional surgical margins of the prostatic fossa (bladder neck, lateral, base and urethra) were taken after RP for a more complete staging. *Results:* P Stage: p T3b=31, p T4=9. Grade: Gleason score <6=2 (5%), Gleason score 7=7 (17.5%), Gleason score 8-10=28 (70%). Grade undetermined=3pts. 30/40 pts. (92.5%) had positive margins while 26/40 pts. (65%) had positive nodes: 20/31(64.5%) in pT3b and 6/9 (66.6%)in pT4. Mean follow-up was 110.3 months (range 86-140 mos). 2 pts. were lost to follow-up and 1 pt. died after 15 days from surgery due to pulmonary embolus. 37 pts were followed regularly. Of these 25 (67.6%) received immediate adjuvant Hormone Therapy (HT) after RP. 2 pts. had Radio (RT)-Chemotherapy+ HT and 2 pts RT+ HT. Overall survival was 57.5% (23/40 pts.). 18/40 were T3b (47.5%) and 4/40 T4 (10). DSS was 75% (30/40 pts.): 23 were pT3b (57.5) and 6 pT4 (17.5%). 8/37 pts. received RP+EPLND alone: 4/8 pts. had an undetectable PSA (0.001-0.01 ng/ml), 3 had PSA of 0.8,2.7 and 3.6 ng/ml; in 1 pt. PSA was not available. 11/25 pts. (44%) treated with immediate HT had an undetectable PSA (0.001-0.01 ng/ml), 9/25 pts (36%) had PSA progression (0.8-17.8 ng/ml) and died of the disease. Complications: mortality 1/40 (2.5%), Lymphoceles=35%. Rectal injuries=5% with

intra-op repair. *Conclusion:* The combination of RP+ EPLND and HT +/–RT resulted a valid treatment option for pts. with pT3b-T4 Pca. 9-year DSS was 75%. 10% and 27.5% of pts. with surgery alone and surgery + immediate HT had an undetectable PSA after 9 years. Larger studies are needed to confirm these results.

3

MIDDLE TERM FOLLOW-UP RESULTS OF MAGNETIC RESONANCE IMAGING EVALUATION AFTER FOCAL THERAPY FOR PROSTATE CANCER

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Introduction and Objectives: We report the mid-term MR imaging follow-up in patients who underwent focal therapy (FCA) for prostate cancer (Pca). *Patients and Methods:* Eleven patients with unifocal, low-grade (Gleason≤6) PCa were selected with trans-perineal template-guided prostate biopsy. All the patients were subsequently treated with FCA. Patients were followed up by MR imaging 24 hours after surgery, and subsequently at 3, 12 and 24 months, with a 1.5T MR system using T1w, T2w and dynamic ce-FS T1w sequences. *Results:* 24 hours after FCA, T2w images showed heterogeneous iso-hyperintensity of the treated area, with high signal intensity and hypointense perilesional rim at 3, 12 and 24 months. Post treatment ce-FS T1w MR images showed ischemia of the treated zone. MR examinations showed a mean decrease in size of treated areas of 30% at 3, 70% at 12 and 80% at 24 months. All the patients had a stable PSA level at 24 months after treatment. MR imaging follow-up revealed no evidence of nodal recurrence. *Conclusion:* MR can be a valid tool in the follow-up of PCa treated with FCA and may be used in the early evaluation of the effectiveness of treatment. Further studies with a higher number of patients and longer follow-up are required.

4

COMPARISON BETWEEN MICROFOCAL PROSTATE CANCER BIOPSY AND HISTOPATHOLOGICAL EXAMINATION AFTER RADICAL PROSTATECTOMY: OUR EXPERIENCE

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Introduction: The advent of the PSA and the diffusion of screening programs for early detection of prostate cancer in recent years has led to an increase in the diagnosis of microfocal prostate cancer (MPC). MPC is a small tumor that involves less than 5% with Gleason 6 or less of the biopsy specimen with a minimum of four glands cancer. The biopsy and clinical parameters play an important role in risk and treatment decisions. The objective of this study was to evaluate retrospectively the clinical staging in patients with prostate mapping biopsy indicative of MPC, with PSA <10 and then, once these patients underwent radical prostatectomy compare the results of the biopsy and clinical parameters before surgery with definitive histological examination. *Patients and Methods:* We examined retrospectively 78 patients (mean age 68 years, range 49-72) diagnosed with MPC, who subsequently underwent radical prostatectomy at our clinic between 2006 to 2011. We analyzed PSA, PSA density, prostate volume, digital rectal examination, transrectal prostate ultrasound, and compared these parameters with histopathological diagnosis, Gleason score on biopsy and subsequent radical prostatectomy. Biopsies were performed by the same single high experienced center (more than 300 prostate biopsies/year). Patients underwent transrectal ultrasound guided prostate biopsy, with an average of 14 samples per procedure. The presence of an MPC was associated with high grade PIN in 72% of cases. The assignment of Gleason score was possible in 86.7% of the examined cases, while for 6 biopsy specimens grading was undetermined. The PSA values were 78% lower for 10 (range 3-34), while 83% of tumors were clinically potentially insignificant. *Results:* In all 78 patients who underwent surgery after radical prostatectomy with a diagnosis of an MPC, prostate cancer was confirmed by histological analysis on the sample. In four cases the diagnosis was confirmed as MPC. In 59 patients (75.5%) was then diagnosed with organ confined cancer, unilateral (32, pT2a and 27, pT2b), multifocal bilateral cancer in 19: of these two with extraprostatic extension (pT3a), one with a bladder neck infiltration (pT4) and one with positive surgical margins. The evaluation of the biopsy Gleason score has underestimated the degree in 9 cases (11.5%) and overestimated in 6 (7.6%). There were no statistically significant correlations found between pathological stage, PSA, number of biopsies, previous histological findings, prostate volume, rectal exploration and transrectal ultrasound, while there was a significant correlation between PSA density, advanced age and increased clinical risk. *Discussion and Conclusion:* While a micro focus of Gleason score 6 prostate cancer on biopsy is commonly considered as a low risk disease, literature define a mean 20% risk of pathological upgrading and/or upstaging. In our experience, this percentage was about 24%, slightly higher than the average reported in the literature. The majority of patients with biopsy finding of MPC have after surgery a diseas increased in volume, even if organ-confined, often with involvement of both lobes of the prostate (19%). The

diagnosis of MPC does not seem to be more predictive of clinically insignificant prostate cancer. Patients with Gleason score 6 microfocal prostate cancer should be counseled that they may harbor more aggressive disease, especially when pre-treatment clinical risk factors are present, such as advanced age or high clinical prostate specific antigen density.

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2 Thong AE, Shikanov S *et al*: A single microfocus (5% or less) of Gleason 6 prostate cancer at biopsy – can we predict adverse pathological outcomes?. J Urol *180(6)*: 2436-2440, 2008.
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5
TOLERABILITY OF TRANSRECTAL PROSTATE BIOPSY WITH USE OF LIDOCAINE SPRAY: SINGLE CENTER EXPERIENCE AFTER 4 YEARS

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Introduction: Transrectal ultrasound guided prostate biopsy is now a routine, outpatient, easy to learn, quick and simple method, but still surrounded by a number of side-effects most frequently including pain and discomfort. In our view, an important component of the state of discomfort during the procedure is characterized by the tone of the anal sphincter and obstruction intrarectal ultrasound probe that causes pressure and stretching of muscle fibers and sensory nerve fibers. The aim of our study was to evaluate patients tolerance to transrectal ultrasound guided prostate biopsy using anesthesia with Lidocaine Spray(LS). *Patients and Methods:* Between September '07 and August '11, 975 consecutive male patients with elevated PSA and (or) abnormal digital rectal and (or) suspect TRUS scheduled for prostate biopsy (PB) were randomized. For this examination "end-fire" multi-frequency convex probe and needle 18 Gauge were used. Biopsy examinations were performed alternately by two experienced operators. Each examination was performed after emptying the bladder, because in our opinion the bladder repletion is an important element of discomfort during biopsy. All patients were treated with LS(10gr/100ml) applied 2 minutes before the biopsy. The first intention was to obtain 14 cores in all patients. A verbal numerical pain score (VNS) from 0 (no discomfort) to 10 (severe pain) was suggested to the biopsied patients who were asked to separately evaluate the degree of pain associated with the procedure, through two scales VNS, one for the insertion of the probe and the manoeuvres associated with it, the other only for the biopsy. *Results:* Only in 6 patients we were unable to insert TRUS probe, in 4 due to presence of fibrous anal and in 2 due to severe haemorrhoidal prolapse. The mean age of patients was 68 years (48-78), the value of the PSA was 8.2 (2.5-17.8), total prostate volume 57 ml (36-135). The number of biopsies performed in each patient was 14 (6-21). The mean pain in the visual numerical scales in patients was 3.3 (2-8) in the first questionnaire, 2.1(1-7) in the second questionnaire. The 8% of patients (79/969) declared severe or unbearable pain (score ≥7), 716 patients (74%) declared no pain at all. Only 21 patients would never repeat the same biopsy or would request a different type of anesthesia and 786 (81%) of them would repeat it in the same way. Analyzing the two questionnaires, a difference in the tolerability of the procedure is observed in the first questionnaire, but not in the second questionnaire ($p<0.001$). The patients were homogeneous in terms of pain with regard to the values of PSA and prostate gland volume. Also, patients aged >65 years tolerate the procedure better in the two questionnaires (average pain VNS was respectively 2.4 and 1.7). In the elderly there is a change in the perception of pain, due to several factors such as the decrease in the number of nociceptors and nociceptive afferents responsible for the elevation of the threshold and tolerance of pain. *Discussion and Conclusion:* In our experience, transrectal PB is generally well tolerated with LS as the only anesthesia. Our study suggests that the main elements of discomfort during the procedure are the introduction of ultrasound probe and its movements than the biopsy itself. This new technique is an excellent alternative to those currently practiced by most urologists, causing a sharp reduction of anal sphincter tone with better patient compliance and tolerability to the ultrasound probe in the performance of biopsies.

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6

RISK FACTORS OF POSITIVE SURGICAL MARGINS AND BIOCHEMICAL RECURRENCE IN PATIENTS TREATED WITH RADICAL PROSTATECTOMY

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Introduction: Radical prostatectomy (RP) continues to be the "gold standard" in the treatment of localized prostate cancer for patients with a life expectancy of 10 years. However, biochemical recurrence may occur in 25 to 43% within ten years after RP and additional treatment may be required in 35% of these patients. We investigated the factors (preoperative PSA, Gleason score, pathological T stage and extension of the tumor volume) more likely to influence biochemical recurrence in men post-RP for organ confined prostate cancer. *Patients and Methods:* From January 2002 to December 2006 282 radical retropubic prostatectomies for localized prostate cancer were performed in patients of average age 65 years (52-74). The operations were performed by two experienced surgeons in a single institution. Sixty-four patients were excluded from the study due to positive lymph node metastases or lost follow-up. Following the EAU Guidelines on Prostate Cancer, the follow-up was conducted 3.6 and 12 months post-RP during the first year, and every six months in the second year and thereafter with PSA level and digital rectal examination. None of the patients had adjuvant hormonal treatment and/or radiotherapy. PSA level >0.2 ng/ml by two subsequent measurements was defined as biochemical recurrence. To evaluate the incidence of biochemical progression we examined these factors: percentage of positive surgical margins, the seat of the margin, pathological stage (pT), pathological Gleason score, maximum extension of prostate cancer (>15 mm) and preoperative PSA. *Results:* The incidence of positive surgical margin was about 28% (79/282). With a median follow-up period of 5 years 31.6% (25/79) of the patients presented with biochemical recurrence. The preoperative serum PSA 8.7 ng/ml (3.4-16.2), average Gleason score (7.1±1.3), pathological T stage >=3 (11/25) and maximum extension of tumor >=15 mm (10/25). A univariate analysis showed that positive surgical margin had a positive statistical association with pathological T stage score (p=0,03), extension of prostate cancer (p=0.02) and biochemical recurrence (p=0.035). The most common location of a positive surgical margin was in the apex of the prostate, which was about 58% (46/79). Sixty-seven percent (31/46) of patients with positive surgical margin in apex were also positive in the prostate lobe; other locations were prostate lobe 30% (24/79), seminal vesicle 11% (9/79). The multivariate analysis showed that positive surgical margin had a positive statistical association with pathological T stage score and extension of prostate cancer. Neither univariaten or multivariate analysis showed any statistical relationship between biochemical recurrence and any other risk factors covered in this study. *Discussion and Conclusion:* There is wide consensus that biochemical recurrence occurs in a large percentage of patients following successful RP. The biochemical recurrence was detected in 33% (93/282) of patients who had been treated with RP within 5 years, which indicates that the parameters related to the disease (positive surgical margin, pathological T stage score and extension of prostate cancer) have a pivotal role in the PSA recurrence. Thus, PSA recurrence appears to be related to the disease itself rather than the surgery (RP).

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7

SERUM ISOFORM [-2]PROPSA (P2PSA) AND ITS DERIVATES, %P2PSA AND PHI (PROSTATE HEALTH INDEX), ARE MORE ACCURATE THAN THE REFERENCE STANDARD TEST (PSA) IN MEN SCHEDULED FOR REPEAT BIOPSY

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Introduction: This study tests the hypothesis that [-2]proPSA (p2PSA) and its derivates, namely %p2PSA and PHI (prostate health index), are more accurate than reference standard tests (tPSA, fPSA and %fPSA) in detecting PCa in men scheduled for repeat biopsy. *Patients and Methods:* This study was an observational prospective evaluation of a cohort of men with one or two previous negative prostate biopsies, with persistent suspicion of PCa (suspected DRE, elevated tPSA and or low %fPSA) who were scheduled for repeat biopsy. Men receiving medical therapy known to affect serum PSA (dutasteride and

finasteride), suffering from prostatitis and having had invasive treatment for benign prostatic hyperplasia (BPH), such as TURP or HoLEP, were excluded. Serum p2PSA, and its derivates, namely %p2PSA {([-2]proPSA/10)/fPSA)} and Beckman Coulter PHI (prostate health index) {[[-2]proPSA/fPSA x squart PSA} were considered the index tests and compared with the reference standard tests (tPSA, fPSA and %fPSA). All the patients underwent ambulatory repeated TRUS-guided prostate biopsies (1822 cores). The primary aim was to evaluate the accuracy of p2PSA and its derivates in detecting PCa. *Results:* From June 2010 and June 2011, 222 men underwent repeated biopsy at our single high volume centre. PCa cancer was found in 71/222 (31.9%) subjects. p2PSA, %p2PSA and PHI values were significantly higher ($p<0.0001$), and %fPSA values significantly lower ($p<0.0001$) in patients with PCa. At univariate accuracy analysis, %p2PSA (AUC: 72.5%) and PHI (AUC: 67.2%) were the most accurate predictors and significantly outperformed tPSA (AUC: 51.8%). %p2PSA significantly outperformed %fPSA (AUC: 60.2%) in the prediction of PCa ($p\leq0.001$), but not PHI ($p=0.136$). For %p2PSA a cut-off of 1.68 showed the best balance between sensitivity and specificity (respectively 67.6 and 66.9%; 95%C.I., 58.8-74.3). For PHI a cut-off of 40 showed the best balance between sensitivity and specificity (respectively 62 and 59.6%; 95%C.I., 51.3-67.5). At 90% of sensitivity, the cut-off of %p2PSA and PHI were respectively 1.23 and 28.8 with a specificity of 40.4 and 25.2%. At a %p2PSA cut-off of 1.23, a total of 153 (68.9%) biopsies could have been avoided; an overall of 6 PCa patients would have been missed but only 1 (5%) patient with a Gleason score of 7 or greater would have been missed. At a PHI cut-off of 28.8 a total of 116 (52.25%) biopsies could have been avoided; an overall of 6 PCa patients would have been missed but no patients with a Gleason score of 7 or greater would have been missed. *Discussion and Conclusion:* %p2PSA and PHI are more accurate than the reference standard tests (tPSA, fPSA and %fPSA) in predicting repeat prostate biopsy outcome and may be indicative of cancer aggressiveness.

8
DEVELOPMENT AND INTERNAL VALIDATION OF A PROSTATE HEALTH INDEX (PHI) BASED NOMOGRAM FOR PREDICTING PROSTATE CANCER AT INITIAL EXTENDED BIOPSY

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Background: The prostate health index (PHI) is a derivative of [-2]proPSA that showed a higher accuracy in predicting the presence of prostate cancer (PCa) at initial biopsy in comparison with established biomarkers. We developed and internally validated a PHI-based nomogram for predicting the presence of PCa at initial biopsy. *Patients and Methods:* The study population consisted of a contemporary cohort of 434 patients with a total PSA <50 ng/mL who were referred to our institution for an initial prostate biopsy. Outpatient transrectal ultrasound-guided prostate biopsies were performed according to a standardized institutional saturation scheme (18-22 cores). Logistic regression models were fitted to test the predictors of PCa at initial biopsy. Predictive accuracy estimates of biopsy outcome predictions were quantified using the area under the receiver-operating characteristic curve (AUC). Differences in AUCs were tested using the De Long method. Regression coefficients were used to create a nomogram that was internally validated using 200 bootstrap resamples. Finally, the extent of overestimation or underestimation of the observed PCa rate at biopsy was determined with calibration plots. *Results:* Overall, 179 (41.2%) patients were diagnosed with PCa at initial extended prostate biopsy. In accuracy analyses, PHI emerged as the most informative independent predictor of PCa (AUC: 74.5%; $p<0.001$). The inclusion of PHI to a multivariable logistic regression model based on established predictors of PCa (age and digital rectal examination) significantly increased the predictive accuracy of a 3.4% extent (from 75.6 to 79.0%; $p<0.001$). Calibration of the nomogram was good within the whole range of predicted probabilities. *Discussion and Conclusion:* We developed a nomogram based on PHI that can assist clinicians in the decision to biopsy by giving patients an individual risk of PCa. While internal validation provided evidence of good calibration and accuracy of the tool, external validation of our findings is still required.

9
RETZIUS SPARING ROBOT-ASSISTED LAPAROSCOPIC PROSTATECTOMY: INITIAL EXPERIENCE OF A CENTER WITH MORE THAN 200 ROBOTIC NERVE SPARING PROSTATECTOMIES

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Purpose: The Retzius sparing approach for Robot-assisted laparoscopic prostatectomy (RALP) passes through the

Douglas space, following a completely intrafascial plane without any dissection of the anterior compartment, which contains neurovascular bundles, Aphrodite's veil, endopelvic fascia, the Santorini plexus, pubourethral ligaments, and all of the structures thought to play a role in maintenance of continence and potency. After seeing the Retzius sparing technique developed by Prof. Bocciardi, we realized the great potential of this approach that respects, like no other, the anatomical relationships. *Patients and Methods:* From September 2011 to December 2011 we performed seven robotic radical prostatectomies with the Retzius sparing approach. The average age of patients was 54 years (45-59 years), the mean PSA 7.4 ng/ml (4.2-8.3 ng/ml), Gleason score <7.% Ca/core <30%, the mean volume was 48 ml (38-54 ml). *Results:* After removal of the catheter in the fifth day we had 3 urinary retentions, then the catheter was repositioned and removed the tenth day. In the other 4 cases after removing the catheter in the fifth day, the patients were continent without the need to use pads, mean blood loss was 270 ml (150-340), the average surgical time was 150 min. (125-170 min), and no procedure was converted to another technical approach. *Conclusion:* The technique is easily reproducible for a urologist who has experience in nerve sparing RALP. With this technique it is not necessary to dissect the seminal vesicles to increase the operating space, and the respect of anatomical structures and anatomical relationship is absolute. Functional results are promising, and we think that this is the best technique for the treatment of low-risk prostate cancer (D'Amico risk classification).

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RE-BIOPSY OF PROSTATE AFTER DIAGNOSIS OF PROSTATIC INTRAEPITHELIAL NEOPLASIA AND ATYPICAL SMALL GLAND PROLIFERATION

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Introduction: Isolated high grade prostatic intraepithelial (HGPIN) and/or atypical small acinar proliferation (ASAP) on prostate biopsy increases the risk of identifying cancer on repeat biopsy. The aim of this study was to assess the incidence of diagnosis of HGPIN and ASAP at urology reference center. We report the results of repeated prostate biopsy for HGPIN and/or ASAP, and propose an optimal evaluation of the indexes and findings on repeated biopsies. *Patients and Methods:* We reviewed the reports from 1018 prostate biopsies that had been analyzed between July 1, 2007 - December 31, 2010 and findings were categorized into carcinoma (PCa), benign, PIN and ASAP. The mean age of patients was 66 years and mean number of biopsied fragments was 12. We investigated repeated prostate biopsies in patients who had been diagnosed with PIN and ASAP. The second biopsy was carried out about 4 months after diagnosis of ASAP and 6 months after diagnosis of high grade PIN. All patients diagnosed with HGPIN or ASAP on second biopsy were subjected to a third transrectal biopsy. *Results:* Of 1018 prostate biopsies, ASAP was diagnosed in 38 (3.7%) patients [Group A, HGPIN in 56 (18%) [Group B] and HGPIN + ASAP in 17 (1.7%) [Group C]. All three groups of patients (n:111) underwent a second transrectal prostate biopsy. The histopathological findings of the second biopsy in the three groups of patients were: Group A: PCa 23.6% (9/38), HGPIN 18.4% (7/38), ASAP 5.2% (2/38); Group B: PCa 17.8% (10/56), HGPIN 25% (14/56), ASAP 5.3% (3/56); Group C: PCa 64.7% (11/17), HGPIN 11.7% (2/17), ASAP 23.5% (4/17). Patients who still had a second biopsy with the diagnosis of HGPIN or ASAP were subjected after about 6 months to a third transrectal biopsy with a mean number of 16 biopsies. In Group A: 40% (4/10), in Group B: 17.6% (3/17) and in Group C: % 16.6 (1/6) of the patients had a diagnosis of prostate cancer at the third biopsy. The positivity rates of the second and third biopsy are 27% (30/111) and 25% (8/32) respectively. 21% (8 of 38) of cancers are diagnosed at the third biopsy. The incidence of HGPIN was 18%, ASAP 3,7% and HGPIN plus ASAP was identified in 1,7% of 1018 biopsies analyzed. There was no difference between groups where cancer was or was not diagnosed on repeated biopsy in relation to age and serum PSA levels. *Conclusion:* Data presented are important because they derive from a reference urology department which conducts a large number of biopsy analyses every year, and can be seen as an indicator of management adopted by the urologist when facing a diagnosis of PIN and ASAP. The numbers we found are also important since they are based on extended biopsies rather than restricted to sextants where the mean number of fragments was 12, including biopsies that can be regarded as presenting saturation with 24 fragments. Although in literature there are conflicting experiences about the manner and frequency of re-biopsy after a diagnosis of HGPIN or ASAP, in our experience the diagnosis that most frequently led to repeated biopsy was HGPIN + ASAP. Prostate cancer was most often diagnosed after the initial diagnosis of ASAP. In addition, our results suggest that patients with a diagnosis of HGPIN or ASAP in two consecutive biopsies should be subjected to a third biopsy.

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11
ROLE OF THE MIR-501 IN RENAL CARCINOMAS

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Background: MicroRNAs (miR) are small, noncoding RNAs that regulate gene expression. In particular, miRs are involved in many biological processes, including differentiation, proliferation and cell death. In addition to their physiological functions, miRs are found to be aberrantly expressed in many carcinomas including renal tumors and to play oncogenic or tumor suppressive roles in cancer cells (1-2). Because, we have observed by microarray analysis that some miRs (miR 142-5p, 601, 362, 196b, 202 and 501) were differentially expressed in autosomal dominant polycystic kidney disease (ADPKD) which is an hyperproliferative disease, we have analyzed the expression of these miRs in kidney carcinomas to better understand their role in renal tumorigenesis. In particular, we have studied the most common renal neoplasms as clear cell (ccRCC), papillary (pRCC), chromophobe (chRCC), with respect to normal kidney tissues. *Materials and Methods:* We selected and analyzed 39 post-nephrectomy fresh frozen tissues (including 23 neoplastic samples: 14 ccRCC, 6 pRCC, 3 chRCC), and 13 paraffin-embedded tumors samples (7 ccRCC, 4 pRCC, 2 chRCC) with matched normal tissues. Total RNA was extracted with TRIZOL (fresh frozen tissues) or the RecoverAll® Total Nucleic Acid Isolation kit (paraffin-embedded tissues). Microarray analysis was performed in normal kidney and ADPKD cell lines following the manufacturer's protocols of microarray facility (Lab of Dr. Negrini, University of Ferrara). Quantitative real time PCR for mature miRs was performed with TaqMan method. MicroRNA levels were expressed as $\Delta\Delta$Ct relative to reference gene U6 snRNA. MiR RNA levels in tumor sample were compared with $\Delta\Delta$ those of normal tissue as fold increase calculated by 2-Ct method (3). *Results:* By real time RT-PCR analysis of indicated miRs, only the miR-501 was found differentially expressed in kidney carcinomas compared with normal renal tissues. In particular miR-501 expression was 5.35 fold increased in ccRCC with respect to normal tissues. Conversely, in pRCC this miR was found 2.56 fold decreased compared with normal kidney. Because, the expression levels of miR-501 in ccRCC showed a extremely variable distribution, this miR may not be used as a marker for ccRCC. Moreover, no correlation between miR-501 expression and tumor grading was observed. However, the low expression of miR-501 in ccRCC as well as in pRCC samples correlated with a good prognosis, thus the downregulation of miR501 could be considered as a marker for positive prognosis in ccRCC and pRCC kidney carcinomas. *Conclusion:* Our results demonstrate that in renal carcinomas the miR-501 was significantly over-expressed in ccRCC, while was down-regulated in pRCC. High levels of miR-501 are not related with grading and metastasis in ccRCC, however, when it is down-regulated could promote a good prognosis.

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12
METANEPHRIC ADENOMA OF THE KIDNEY: STUDY OF EIGHT PATIENTS

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Background: Metanephric adenoma is a rare benign tumor of the kidney. First descriptions of metanephric adenoma (MA) was by Page and Granier in the French literature in 1979. Polycythemia is frequently associated with metanephtic adenoma, and often it might be possible to suspect the

diagnosis of this neoplasia. The differential diagnosis of MA is essentially that of two lesions: the solid variant of PRCC and epithelial-predominant Wilms tumor. *Methods:* From the beginning of 2000 till the end of 2011, we identified eight male patients with metanephric adenoma in our hospital, from which only two patients were previously selected to be operated for this tumor, whereas the other six underwent surgery for a different condition and the pathological findings showed a metanephric adenoma. *Results:* All patients are in good clinical condition except two who died because of other diseases. The mean (range 0.5-4.1 cm) dimension was about 2 cm. Methanephric adenoma is solid, and may have areas of hemorrhage, necrosis and/or cystic degeneration. Surgical excision of the tumor is considered the treatment of choice. *Conclusion:* The metanephric adenoma is a benign condition. Diagnosis by computerized tomography and percutaneous biopsy and treatment by nephron sparing surgery are reccomended.

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PREDICITIVE FACTORS OF PROGRESSION FREE SURVIVAL (PFS) AND OVERALL SURVIVAL (OS) IN ADVANCED RENAL CELL CARCINOMA (A-RCC) PATIENTS TREATED WITH TYROSINE KINASE INHIBITORS (TKIs): A RETROSPECTIVE ANALYSIS OF A MONO-INSTITUTIONAL SERIES

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Background: The introduction of targeted therapy has significanlty contributed to change in the prognosis of A-RCC's patients (pts). Nevertheless, both the optimal strategy to administer these agents and which predictive factor is able to identify the appropriate treatment are still controversial. The aim of this analysis was to screen for predictors of outcome in the context of a retrospective mono-institutional series. *Methods:* A retrospective analysis including A-RCC pts treated with Sunitinib (SU), Sorafenib (SO), or pre-planned sequential SU-SO at AOUI between January 2005 and April 2011 was performed. Descriptive statistics were adopted. The median PFS and OS were estimated using the Kaplan-Meier method. Hazard Ratios (HR) for PFS/OS and the 95% confidence intervals (CI) were derived by using the Cox univariate model. A multivariate Cox proportional hazard model was developed. *Results:* 65 pts were included; patients' baseline characteristics: male/female: 67.7%/32.3%; radical nephrectomy yes/no: 84.6%/15.3%; Fuhrman Grading 1/2/3/4: 1.5%/15.4%/38.5%/18.5%; MSKCC Score favorable/intermediate/poor: 21.5%/55.4%/12.3%; treatment SU/SO/SU-SO: 46.2%/26.2%/27.7%; >1 metastatic site yes/no: 29.2%/70.8%. Objective response (HR 6.69, 95% CI 3.03-14.78, $p<0.0001$) and MSKCC score (HR 3.21, 95% CI 1.38-7.46, $p=0.007$) were independent significant preditors for PFS at the multivariate analysis. Log-rank analysis is shown in the table:

	PFS			OS		
	Median (95% CI)	*p*	1-yr (%)	Median (95% CI)	*p*	1-yr (%)
Response						
Yes	16 (13-19)	<0.0001	77.6	n.r.	0.0009	94.7
No	4 (3-6)		15.4	10 (8-12)		40.4
MSKCC score						
Favourable	18 (3-34)	0.06	62.9	n.r.	0.04	100
Intermediate	6 (4-9)		33.3	14 (4-23)		53.4
Poor	3 (0-6)		14.3	11 (2-18)		47.6
Treatment						
SU	9 (3-14)	0.34	41.2	29 (5-52)	0.20	60.7
SO	6 (1-11)		36.5	15 (4-25)		57.1
SU-SO	7 (5-8)		36.4	n.r.		71.1

Conclusion: Despite the limitations of a retrospective study, our data confirm the value of MSKCC risk score and suggest that response may represent an independent predictor for PFS. Because of the small power, no differences according to treatment (SU, SO or SU-SO) emerged; therefore, results of comparative prospective trials, able to elucidate the optimal sequence of targeted agents, are strongly awaited.

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EFFECTS OF DUAL PI3K AND mTOR INHIBITION ON INCIDENCE AND LOCAL GROWTH OF PROSTATE CANCER BONE METASTASES

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Although phosphoinositide 3-kinase PI3K activation is associated to prostate cancer (PCa) progression, the contribution of mTOR and its interaction partners toward regulating PCa progression and metastasis remains poorly understood. The main aims of this report are: (I) to verify if the inhibition of PI3K/Akt/mTOR pathway by using the dual PI3K/mTOR kinase inhibitor, X480, was able to modulate cell proliferation and apoptosis in prostate cancer cells; (II) to compare the effects of X480 with the mTOR inhibitor, X414; (III) to verify the effects of these drugs on the production of proteases involved in cell migration and metastases and (IV) the final endpoint of this study is to examine the role of PI3K/AKT/mTOR inhibition in the incidence of bone metastases as well as its role on the growth of tumor cells in the bone microenvironment. We analyzed the cytotoxic effects and biochemical arrangement induced by these compounds by using two nontumor prostate epithelial cell lines and a series of 8 prostate cancer cell lines and 11 prostate cancer cell derivatives. *In vivo*, male nude mice were injected with PC3cells by intracardiac (metastatic model) and intratibial (local growth) method. Dual inhibition of PI3K/mTOR signaling, using X480 attenuated cell proliferation and induced apoptosis in prostate cancer cells. The effects were more marked in presence of a PTEN loss and Akt activation (by increased EGFR/Her2 activity or PIK3CA mutation). mTor inhibition by X414 was also able to reduce cell proliferation and to induce apoptosis. Cell migration and invasion experiments indicated that the inhibition of the PI3K/mTor pathway was associatedwith marked reduction of metastatic potential. The analyses of *in vivo* experiments revealed a significant reduction of metastases incidence and tumor burden after treatment with X480 ($p<0.05$). Evaluation of tumor growth in bones after intratibial injection revealed a significant reduction both after X480 and X414 treatments. Tibiae obtained 35 daysafter intratibial injection of nude mice wereanalyzed by Xray and microCT and scored as: score 0 (absence of tumor growth after xRay and microCT analyses), score 1 (osteolytic lesions visible only to microCT analyses and <5 mm^2), score 2 (lesions visible only microCT and >5 mm^2), score 3 (lesions visible to xRay without cortical impairment), score 4 (Xray visible lesions with cortical impairment with/without fractures) and score 5 (extended osteolysis with extra-tibial growth). X480 was able to significantly reduce tumor burden (4/20 tibiae with score >3) relative to those observed in untreated animals (12/20 tibiae with score >3, $p<0.05$). Although mTor selective inhibition by X414 was able to reduce tumor burden (7/20 tibiae with score >3), this was not significant. However, histo-morphometric analyses revealed that X414 treated animals showed significant reduction of tumor mass ($p<0.05$). These findings provide the rationale for including PI3K/Akt/mTOR kinase inhibitors as part of the therapeutic regimen for PCa patients and suggest that dual inhibition of PI3K and mTor may more effectively inhibit metastasis and tumor host interaction in the bone microenvironment than inhibition of mTor alone.

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EFFECTS OF 1D11 AN ANTIBODY AGAINST TRANSFORMING GROWTH FACTOR BETA (TGF-B) ON INCIDENCE AND LOCAL GROWTH OF PROSTATE CANCER BONE METASTASES

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Transforming growth factor beta (TGFβ) plays an important role in prostate cancer (PCa) development and this growth factor has been implicated in the pathogenesis of PCa-derived bone metastases. The main aims of this report are: to verify if the inhibition of TGFβ pathway, by using the pan-neutralizing anti-TGF-β antibody (1D11), was able to modulate cell proliferation and apoptosis in prostate cancer cells and to examine the role TGFβ inhibition in the incidence of bone metastases as well as its role on the growth of tumor cells in

the bone microenvironment. 1D11 is a murine monoclonal antibody against all three TGFβ isoforms and has been used as a surrogate for a fully human antibody (GC1008) currently in clinical development. We analyzed the effect of 1D11 on the growth of C4-2B and PC-3 bone derived PCa cells *in vitro* by measuring radiolabeled thymidine incorporation into DNA as well as the biochemical arrangement induced by treatmnent. *In vivo*, male nude mice were injected with PC3cells by intracardiac (metastatic model) and intratibial (local growth) method. We monitored the tumor burden and bone responses in vehicle control, 1D11 and 13C4 (isotype control antibody) treated mice. PC3 and C4-2B cells are TGF-β1 responsive and have an intact constitutive TGF-β signal transduction pathway as confirmed by pSmad2 induction and growth inhibition when stimulated with TGF-β1. As expected, 1D11 but not 13C4, inhibited the TGF-β1-induced pathway activation and growth inhibition of PC-3 and C4-2B cells. The analyses of *in vivo* experiments revealed a significant reduction of metastases incidence and tumor burden after treatment with 1D11 ($p<0.05$) with significant less bone loss due to reduced osteoclast activity in PC-3 tumor-bearing bones than in the untreated mice. Tibiae obtained 35 days after intratibial injection of nude mice were analyzed by Xray and microCT and scored as: score 0 (absence of tumor growth after xRay and microCT analyses), score 1 (osteolytic lesions visible only to microCT analyses and <5 mm^2), score 2 (lesions visible only microCT and >5 mm^2), score 3 (lesions visible to xRay without cortical impairment), score 4 (Xray visible lesions with cortical impairment with/without fractures) and score 5 (extended osteolysis with extra-tibial growth). 1D11 was able to significantly reduce tumor burden (6/20 tibiae with score >3) relative to those observed in untreated animals (14/20 tibiae with score >3, $p<0.05$). In summary, we report for the first time that TGF-β neutralization with a monoclonal antibody (1D11) can control PCa bone metastases and may be a useful therapeutic approach in men with advance PCa.

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SELECTIVE INHIBITORS OF NUCLEAR EXPORT (SINE) ACTIVATE MULTIPLE TUMOR SUPPRESSOR PATHWAYS AND KILL PROSTATE CANCER CELLS ACROSS MULTIPLE GENOTYPES *IN VITRO* AND *IN VIVO*

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CRM1 (Xpo1) is a key nuclear export protein which controls the nuclear export of multiple tumor suppressor proteins (TSP) and cell proliferation pathways including p53, p21, FOXO, PI3K/AKT, Wnt/β-catenin and NF-κB. Mislocalization of TSP can abrogate their functions as well as render chemotherapies ineffective. Induction of nuclear expression of TSP and chemotherapy targets, by CRM1 inhibition can restore their tumor suppressor functions and increase drug sensitivity. We have developed orally active, small molecule SINE that irreversibly and potently inhibit CRM1 mediated nuclear export of multiple TSP and other cargoes (IC_{50} <100 nM). Here, we describe *in vitro* results using SINE compounds, KPT-185 *in vitro* and KPT-251 *in vitro* and *in vivo* on seven prostate cancer (PrCa) cell lines representing distinct differentiation/progression states of disease and genotypes: LAPC-4 (Androgen receptor [AR] positive, androgen dependent with low Akt/mTOR activities, p53 wt); LnCaP (AR positive, androgen dependent with high Akt/mTOR activities, p53 wt); LnCaP-C81 and LnCaP-C4-2B (AR positive, androgen independent with high Akt/mTOR activities, p53 wt); 22rv1 (AR positive, androgen independent with low Akt/mTOR activities, p53 wt); PC3 (AR negative, with high Akt/mTOR activites and no p53 function (p53 del) and DU145 (AR negative, with low Akt/mTOR activites and mutant p53). Benign prostatic hyperplasia line (BPH1) and Prostatic epithelial line (EPN) were used as non-neoplastic controls. We show that SINE block CRM1 mediated nuclear export of FOXO and p53 with a IC_{50} values <100 nM in both PrCa and non-neoplastic cell lines. KPT compounds are selectively cytotoxic to PrCa lines with EC_{50}s between 10 and 1000 nM, and show limited cytotoxicity on the nonneoplastic EPN and BPH1 lines (EC_{50} >5-20 SINE cytotoxic effects are independent of p53 status, and induce caspase-3 activation. SINE display synergistic effects in combination with cisplatin and docetaxel *in vitro* with combination indices between 0.3 and 0.8. *In vivo* results indicate that KPT-251 show a dose-dependent inhibition of tumor growth. KPT251 was also additive when administered at 30 mg/kg/5 days/week per os with docetaxel and cisplatin by using the aggressive p53 wt 22rv1 xenografts. Taken together, CRM1 inhibition represents a completely novel, neoplasia-selective and well tolerated target for use as single agent or in combination with chemotherapy for PrCa.

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PROGNOSTIC FACTORS OF KIDNEY TUMORS IN T3 STAGE: ROLE OF PERIRENAL FAT INFILTRATION, RENAL SINUS INFILTRATION AND VENOUS THROMBOSIS

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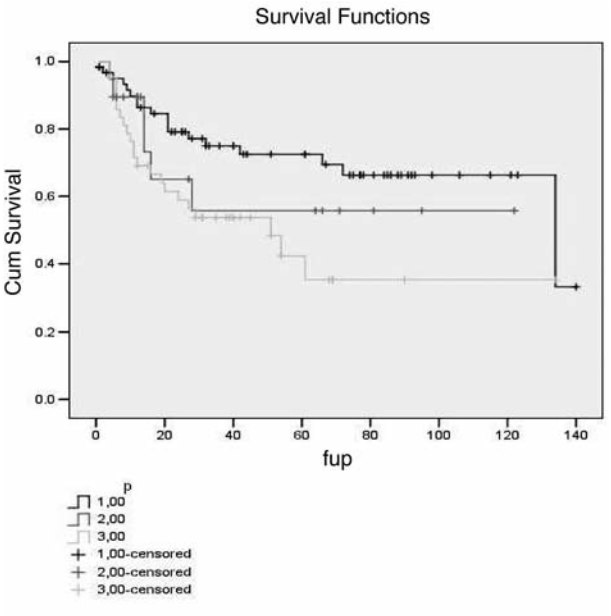

Introduction: The outcome predictors for renal cell cancer (RCC) remains controversial; although many parameters have been tested for prognostic significance, only a few have achieved widespread acceptance in clinical practice. The prognostic significance of perirenal fat or sinus infiltration, and venous tumor thrombus extension in patients with renal cell carcinoma (RCC) is a matter of many controversies in the current literature. *Patients and Methods:* We analyzed the pathological finding and clinical follow-up of 593 patients who underwent radical nephrectomy for RCC from 2000 to 2011 at our institution. The mean age was 63.9±11.8, the mean tumor size was 7.39 cm ± 2.73 cm. Among these we selected 125 patients with T3 stage at pathological evaluation and grouped them as follows: group A (63 patients) with invasion of peritumoral fat and/or hilar fat, group B (19 patients) with renal vein trombosis or vena cava trombosis, group C (43 patients) with both venous trombosis and the peritumoral and/or hilar fat invasion. We evaluated the cancer specific survival (CSS) between the three groups using Kaplan Meier survival curves for the univariate analysis and Cox regression model for multivariate analysis. Results: The mean follow-up was 41.44 months (±35.27, range 1-140 months), the median survival was 31 months. 98 patients underwent lymphadenectomy. The histological subtypes of our group were: clear cell carcinoma 102 (79.4%), papillary 17(14%), cromophobe 4(2.9%), NAS 2(3.7%); The Furhman Grading was: G2 32(25.9%), G3 69(54.1%), G4 24(20%); lymph node involvement was noted in 19 (16.4%) and distant metastases in 18 (16%). At univariate analysis, there was a significantly difference in CSS among the three groups (Figure 1, p=0.036). However group A had a significantly higher survival than group C (p=0.008) but not than group B (p=0.364) because of the small number of cases in the group B. At multivariate logistic regression analysis, the new grouping was not an independent prognostic factor, while tumor size, grading and distant metastases were independent prognostic factors. *Conclusion:* The current TNM staging system for RCC does not account for the simultaneous presence of perirenal fat and vein trombosis as a distinct category in the pT3. A new subgroup with the simultaneous presence of the two pathological characteristics could better identify those patients at higher risk of recurrence. Tumor size, Furhman grading, presence of distant metastases and vein trombosis are independent prognostic factors in pT3. Large prospective series are needed to validate these findings.

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NON INVASIVE DETECTION OF BLADDER CANCER BY ELECTROMAGNETIC INTERACTION

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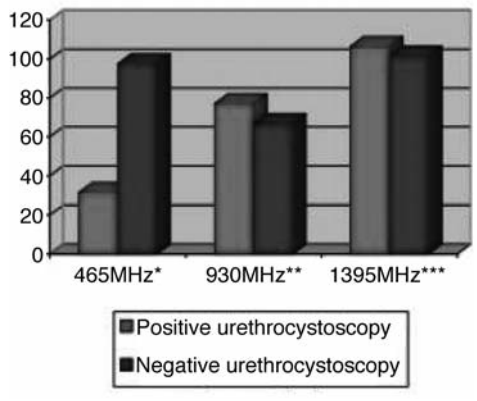
Introduction: Biological tissues interact with EM waves. Cancer behave differently to benign tissue in an EM field using the phenomena of non linear resonance. The objective of this study was to evaluate the diagnostic accuracy of bladder cancer detection using the TRIMprob, a nonlinear tunable oscillator generating extremely low energy multiple electromagnetic fields, that has been evaluated for the detection of several human cancers in clinical and experimental studies (1-3). *Patients and Methods:* 200 consecutive patients referred to Sant'Andrea's outpatients clinic for urethrocystoscopy were enrolled in the study. All patients were investigated by history, physical examination, urinalysis, urine culture and urine cytology, urethrocystoscopy and TRIMprob test. Transurethral resection of the bladder was performed in case of any suspicious lesion. Main indications for cystoscopy were gross



*p<0.0001 at Mann Whitney test
**p<0.073 at Mann Whitney test
***p<0.327 at Mann Whitney test

Figure 1. *Comparison between the mean signal intensity in the three spectral lines (465, 935 and 1395 MHz) of the TRIMprob test in patients with positive and negative urethrocystoscopy for the presence of neoplasms.*

haematuria and follow-up of patients after TURB. Patients affected by pelvic tumors, urinary tract infection, cardiac pacemakers or with other electromagnetic devices were excluded from the study. The TRIMprob was moved over the surface of the patient's pubic region while standing in front of the system receiver in two different positions, with a bladder filling of 150 ml after endoscopic examination. Two operators blinded to the patient status independently conducted the test from January 2008 to October 2010. It was considered positive when the signal at 465 MHz was set to 0 level. Nonlinear resonance was analyzed at 465, 930 and 1395 MHz. *Results:* Analysis of resonance values at 465MHz showed a statistically significant difference between patients with and without bladder cancer (p<0.0001 at Mann Whitney test). No statistically significant difference was observed in the values at 930 (p<0.073) and 1395 MHz (p<0.327). The following accuracy values were observed for the diagnosis of bladder cancer: sensitivity, 86%; specificity, 94%; positive and negative predictive value of 86% and 94% overall, diagnostic accuracy was 92%. No significant difference was found between the two different positions and operators. No correlation was seen between TRIMprob test and tumor size and/or grade. *Discussion and Conclusion:* In our experience the TRIMprob has a high diagnostic accuracy for the detection of bladder cancer in patients undergoing urethrocystoscopy for haematuria and after-TURB follow-up. Confirmation clinical and experimental studies are currently ongoing to better define the possible clinical role of the TRIMprob for the management of patients at risk of bladder cancer.

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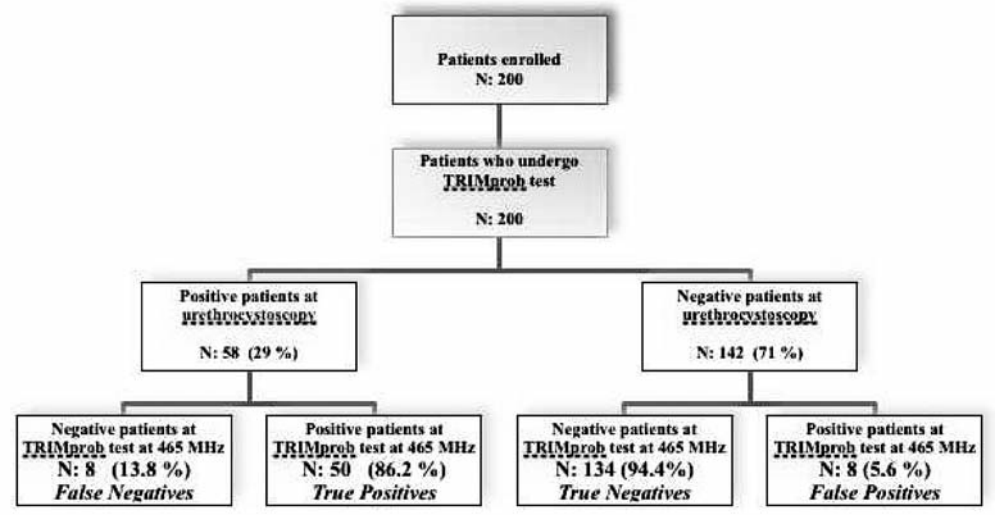

Figure 2. *Flowchart of patients undergoing cystoscopy. Patients with a significant decrease of the electro-magnetic signal at 465MHz were labelled as " positive at TRIMprob test " and those without any significant decrease were described as "negative at TRIMprob test".*

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THE USE OF UCYT+ ALLOWS TO ANTICIPATE DIAGNOSIS OF UROTHELIAL CARCINOMA (UC)

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Introduction: The aim of this retrospective study was to evaluate over a six-year period, if the use of the uCyt+ test along with the cytology examination of spontaneous urine samples would detect, as affirmed in literature (1), the presence of neoplasic cells, not revealed by cytology alone. Therefore, anticipating diagnosis months ahead with respect to the cystoscopy examination. *Patients and Methods:* The patients had previously given their informed consent that the voided urine sample would be processed separately for the standard staining in routine cytology (Papanicolaou technique) and then for the FDA approved immunofluorescent uCyt+ test developed by Fradet and Lochart in 1997. The urine samples were tested with uCyt+ and the slides were read under a fluorescent microscope at a 40x magnification according to manufacturer instructions. A total of 3728 uCyt+ tests were performed. The sample was considered positive also when there was 1 to 4 positive red and/or green fluorescent cells on the slide (Borderline Positive). A case was considered positive when there were ≥5 positive cells on the slide. *Results:* uCyt+ was Borderline Positive in 135 cases where traditional cytology was negative: 85 cases (62,3%) were false positives; 50 cases (37%) were true positives, which were confirmed during the successive cystoscopies repeated over time. This gave the possibility to anticipate diagnosis of UC to ≤12 months in 88% and to >12 months in 12%, (median 8 months. *Discussion and Conclusion:* A delayed diagnosis of UC can have important relapses on patient life quality and in some cases on their survival. There are new laboratory strategies and methods available to perform along side with urinary cytology and cystoscopy, such as uCyt+ that could help to correct the insufficiencies present in the current bladder cancer management. According to literature, the uCyt+ test, [FDA approved in the surveillance of UC patients (1)] in combination with traditional cytology increases diagnostic sensibility over 40%. The non-invasive uCyt+ test has the advantage of not provoking any collateral effects with repeated use. In fact, UC develops more frequently in ages when other illnesses are present and when frequent invasive cystoscopies are generally performed in narcosis. Furthermore, an eventual reduction of non essential instrumental exams, not only reduces bladder trauma, that repeated over time, could behave as a growth factor towards the tumor (2), but also determines a positive effect on the reduction of sanitary costs. The uCyt+ method, easily performed, detects minimum quantities of neoplastic antigens much earlier than morphological modifications visualized through traditional cytology. For example, a Borderline Positivity, also referred to one single positive cell located in the sample can help in the diagnosis of the neoplasia when it develops and/or to precauciously visualize relapses. According to our results, a positive uCyt+ test in the presence of a negative cytology exam should not be underestimated. In fact, in 50 patients, that normally would have been controlled with longer frequency intervals, a more accurate surveillance interval with contemporary urinary cytology and uCyt+ exams, diagnosed the neoplasia and/or the relapse, even when the lesion was very small (<1 cm).

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MINIMALLY INVASIVE INTRACORPOREAL URINARY DIVERSION AFTER RADICAL CYSTECTOMY IN PATIENTS WITH TRANSITIONAL CELL CARCINOMA OF THE BLADDER

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Robot-assisted radical cystectomy (RARC) and laparoscopic radical cystectomy (LRC) are becoming increasingly widespread for the treatment of bladder tumor. We present our technique of intracorporeal urinary diversion and present oncological and functional outcomes focusing specifically on the oncologic parameters and comorbidity of the procedures. *Patients and Methods:* Single hospital case series from 2009 to 2011 including 23 selected patients with high grade and/or muscle invasive urothelial cancer of the bladder without clinical evidence of lymph-node involvement and an American Society of Anesthesiologists (ASA) score <4. Group A (N=16) underwent robotic intracorporeal neobladder after robotic radical cystectomy, whereas group B (N=6) underwent laparoscopic ileal conduit after laparoscopic cystectomy. The two groups were demographically comparable. We evaluated

the mean age, clinical stage, operative time, blood loss, intraoperative complications and transfusions, type of diversion, time of catheterization, analgesic consumption, start of oral nutrition, rate of postoperative complications, length of hospital stay, pathologic diagnosis of the specimen, number of lymph nodes removed, and the oncologic outcome *Results:* The mean operative time was 320 minutes (range: 280-380 min) for group A and 280 minutes (range: 260-310 min) for group B. The mean blood loss was 640 mL (range: 370-810 mL) in group A and 410 mL (range: 300-650 mL) in group B. The mean of lymph nodes removed was 18 (range: 16-21) for group A and 13 (range: 11-16) for group B. Five patients were diagnosed with positive lymph nodes. Surgical margins were clear in all but one patient. Early complications occurred in 8 patients. Median postoperative stay was 14 d (range: 12-18). *Conclusion:* Laparoscopy/ robotic assisted radical cystectomy and minimally invasive intracorporeal urinary diversion is a safe procedure, like open surgery, but it offers the advantage of minimal invasiveness, represented by reduced analgesic consumption and early recovery of peristalsis with rapid oral nutrition.

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PROGNOSTIC ROLE OF INFILTRATION OF THE HILAR FAT IN PATIENTS WITH RCC IN STAGE T3A

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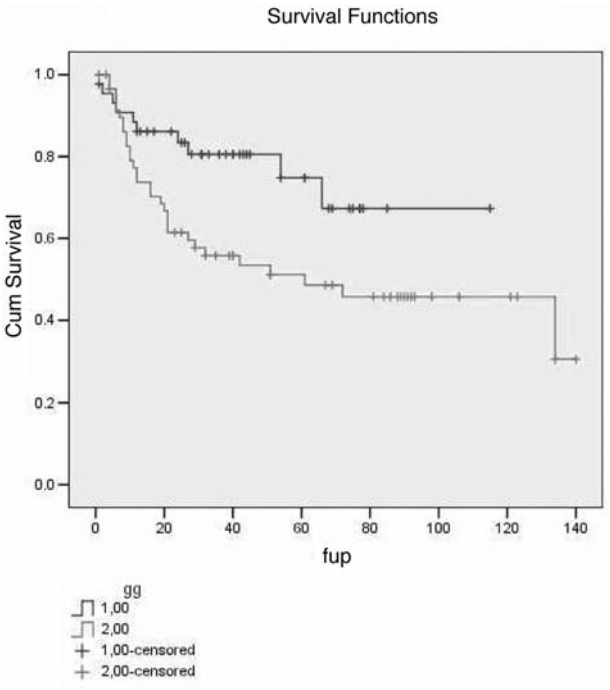
Introduction: Outcome prediction in renal cell cancer (RCC) remains controversial; only a few prognostic parameters have achieved a widespread acceptance in clinical practice. The prognostic significance of perirenal fat or sinus fat infiltration in patients with renal cell carcinoma (RCC) has attracted several controversies in the current literature. *Patients and Methods:* The pathological data and clinical follow-up of 593 patients who underwent radical or partial nephrectomy for RCC from 2000 to 2011 at our institution were analyzed. Among these, we selected 105 patients with pT3 RCC dividing them into 2 groups: group A (44 patients) with peritumoral fat invasion, group B (61 patients) with peritumoral fat and hilous fat involvement. We evaluated the cancer specific survival (CSS) between the two groups using Kaplan Meier survival curves for the univariate analysis and Cox regression model for multivariate analysis. *Results:* The median survival was 32 months; the mean age was 64.75 (SD: 11.50), the mean tumor size was 7.25 cm (SD 2.77). The mean follow-up was 42.63 months (SD 35.14). The histological subtypes of our group were: clear cell carcinoma 84 (80.02); papillary 17 (16%); cromophobe 2 (1.9%); NAS 2 (1.9%). Lymphadenectomy was performed in 80 patients. The Furhman Grading was G2 25(24.5%); G3 57 (53.8%); G4 23(21.7%). Lymph node involvement was present in 15 patients and distant metastases were present in 17 patients. We observed a better prognosis in group A than in group B, with a significant difference between the two groups (p=0.024) (Figure 1).



At multivariate logistic regression analysis, the new grouping was not an independent prognostic factor, while the pathological size and the Furhman Grade were independent adverse prognostic parameters. *Conclusion:* The present results in accordance with the results in the literature show a prognostic difference between the various subgroups in the same category of TNM, suggesting the need of a new classification. Large prospective series are needed to validate these findings.

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INTRAVESICAL ADJUVANT ELECTROMOTIVE MITOMYCIN-C IN PATIENTS WITH PRIMARY INTERMEDIATE-RISK NON-MUSCLE INVASIVE BLADDER CANCER: A RANDOMIZED CONTROLLED TRIAL

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Background: In laboratory and clinical studies, intravesical electromotive drug administration (EMDA) increased mitomycin-C (MMC) bladder uptake, improving clinical efficacy in high-risk non-muscle invasive bladder cancer (NMIBC). Our aim was to compare transurethral resection of bladder tumor (TURBT) and adjuvant intravesical electromotive EMDA/MMC with TURBT and adjuvant intravesical passive diffusion (PD) MMC and TURBT alone in patients with intermediate-risk NMIBC. *Methods:* From January 1994 to December 2003, 225 patients with primary intermediate-risk NMIBC were randomly assigned to: TURBT alone (n=75), TURBT and adjuvant intravesical 40 mg PD/MMC dissolved in 50 ml sterile water infused over 60 minutes once a week for 6 weeks (n=77), or TURBT and adjuvant intravesical 40 mg EMDA/MMC dissolved in 100 ml sterile water with 23 mA pulsed electric current for 30 minutes once a week for 6 weeks (n=73). Patients in the intravesical adjuvant EMDA/MMC and PD/MMC groups who were disease-free 3 months after induction treatment, were scheduled to receive monthly intravesical instillation for 10 months, with the same dose and methods of infusion as initial assigned treatment. All patients were assessed for safety. Our primary endpoints were recurrence rate and disease-free interval. Analyses were done with the intention to treat. *Results:* Median follow-up was 86 months (IQR 53-123). Patients assigned to receive TURBT and adjuvant intravesical EMDA/MMC had a lower rate of recurrence (26/73 [36%]) than those assigned to receive TURBT and adjuvant intravesical PD/MMC (46/77 [60%]) and TURBT alone (47/75 [63%]; log-rank $p<0.0004$). Patients assigned to receive TURBT and adjuvant intravesical EMDA/MMC also had a higher median disease-free interval (19 months, 95%CI 11-27) than those assigned to receive TURBT and adjuvant intravesical PD/MMC (10.5 months, 10-16) and TURBT alone (10 months, 7-13; log-rank $p<0.0001$). In patients who underwent adjuvant intravesical MMC local side-effects and symptoms were recorded in 19/77 (25%) in the PD/MMC group, and in 19/73 (26%) in the EMDA/MMC group. Treatment was stopped because of chemical cystitis side-effects in 3/77 (4%), and 1/73 (1%) patients of these groups, respectively. *Conclusion:* Adjuvant Intravesical EMDA/MMC is feasible and safe; moreover, it reduces recurrence rates and enhances the disease-free interval in patients with intermediate-risk NMIBC compared with TURBT and adjuvant intravesical PD/MMC and TURBT alone.

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INTRAVESICAL SEQUENTIAL BCG AND ELECTROMOTIVE MITOMYCIN-C *VERSUS* BCG ALONE FOR STAGE PT1 UROTHELIAL BLADDER CANCER

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Background: In 2006, we reported that intravesical, sequential Bacillus Calmette-Guérin (BCG) and electromotive mitomycin in patients with stage pT1 urothelial bladder cancer leads to higher disease-free interval, lower recurrence and progression, and to improved overall survival and disease-specific survival compared with BCG alone. After an additional 6 years of follow-up, we now report estimated 16-year results. *Methods:* From January 1994 through June 2002, we randomly assigned 212 patients with stage pT1 urothelial bladder cancer to 81 mg BCG infused over 120 min once a week for 6 weeks (n=105) or to 81 mg BCG infused over 120 min once a week for 2 weeks, followed by 40 mg electromotive mitomycin (intravesical electric current 20 mA for 30 min) once a week as one cycle for three cycles (n=107). Complete responders underwent maintenance treatment: those assigned BCG alone had one infusion of 81 mg BCG once a month for 10 months, and those assigned BCG and mitomycin had 40 mg electromotive mitomycin once a month for 2 months, followed by 81 mg BCG once a month as one cycle for three cycles. The primary endpoint was disease-free interval; secondary endpoints were time to progression, overall survival, and disease-specific survival. Analyses were done by intention to treat. *Results:* Median follow-up was 121 months (IQR 70.5-163.5). Patients assigned sequential BCG and electromotive mitomycin had higher disease-free interval than did those assigned BCG alone (79 months [95% CI 27-139] *vs*. 26 months [11-113]; difference between groups 53 months [39-67], log-rank $p=0.0002$). Patients assigned sequential BCG and electromotive mitomycin also had lower recurrence (45% [35-55] *vs*. 62% [50-72], difference between groups 17% [6-28], log-rank $p=0.0002$); progression (12% [3-21] *vs*. 28% [17.5-38.5], difference between groups 16% [5-27], log-rank $p=0.003$); overall mortality (44% [33-55] *vs*. 59% [43-75], difference between groups 15% [2-28], log-rank $p=0.01$); and disease-specific mortality (9% [2.5-15.5] *vs*. 23% [11–34], difference between groups 14% [4-24], log-rank $p=0.0055$). Side effects were mainly localised to the lower urinary tract. *Conclusion:* In patients with stage pT1 urothelial bladder cancer intravesical BCG combined with electromotive

mitomycin provided better results than BCG alone in terms of higher remission rates and longer remission times.

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CLINICAL STAGE I SEMINOMA: LONG TERM EXPERIENCE OF A PATIENT ORIENTED STRATEGY

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Introduction: Clinical stage I seminoma is a relatively rare disease with a very favourable prognosis. Different options are available (surveillance, radiotherapy or chemotherapy): all of them have excellent results but are characterized by possible side-effects. No clear prognostic factors are demonstrated and guidelines suggest that the choice of the best strategy is primarily related to the patient-doctor discussion. We retrospectively analyzed our experience: till 2001 the preferable strategy was radiotherapy (but from 1997 surveillance was also offered); from 2002 we offered to clinical stage I seminoma patients, after an exhaustive discussion, to choose between one of the 3 options (surveillance, radiotherapy or chemotherapy). *Patients and Methods:* 133 patients were retrospectively reviewed: 79 treated with orchiectomy from 1982 to 2001 and 54 after 2002. All of them had pure seminoma clinical stage I disease. Before 2001, patients were treated as follows: 61 with adjuvant radiotherapy, 16 with surveillance, 1 with chemotherapy and 1 with retroperitoneal lymphadenectomy. After 2002 the treatment option has been primarily indicated by the patient, irrespectively of prognostic factors: 30 adopted a surveillance program, 22 were treated with radiotherapy and 2 with chemotherapy. *Results:* 13 patients relapsed: 5 were primarily treated with radiotherapy, 1 with chemotherapy and 7 during the surveillance strategy. Only 2 patients died (both before 1994) and only one due to the disease. From 2002 most of patients preferred a surveillance program (55%; while radiotherapy 40%); very few opted for adjuvant chemotherapy. From 2008, 88% of patients seen (29 out of 33) opted for the surveillance program. The main patient's reason for choosing a surveillance program is to avoid unnecessary treatment and side-effects; the reasons for those who opted for radiotherapy are to simplify the follow-up (reduce the number of visits and CT scan) and the fear of recurrence. *Discussion:* Surveillance seems to be an optimal strategy both for patients and in our experience. Often more patients prefer the surveillance option; some patients still decide for an active adjuvant treatment, mainly radiotherapy, usually in order to reduce the fear of recurrence and the number of visits and CT scans.

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26
HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN K AND ANDROGEN RECEPTOR EXPRESSION IN RADICAL PROSTATECTOMY SPECIMENS ARE ASSOCIATED WITH PROGNOSIS

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Introduction: Prostate carcinoma (PCa) represents a major health concern in the Western Countries and new diagnostic and prognostic biomarkers, able to supplement or replace serum PSA testing, are strongly required from clinicians to improve risk stratification of patients with this tumor. Recently, studies carried out in our and in other laboratories, have shown that heterogeneous nuclear ribonucleoprotein K (hnRNP K) may play a key role in the carcinogenesis process in PCa since it is implicated in the network of mechanisms that control androgen receptor (AR) expression (1, 2). Moreover, in human prostate LNCaP cells, AR and hnRNP K colocalize in the nucleoplasm in a complex that is highly proximal to DNA (3). A lot of human tumors present an overexpression of hnRNP K and in several cases an aberrant cytoplasmic localization as well; besides a correlation between the protein expression and patient's prognosis was also observed. In the present study we have analyzed, in radical prostatectomy specimens, hnRNP K and AR expression to evaluate their diagnostic and prognostic potential and whether, *in vivo*, a relationship between the expression of the two proteins exists. *Patients and Methods:* From 1995 to 2007, 105 patients who had undergone a radical prostatectomy for biopsy proven PCa, were selected. Immunohistochemistry was carried out using anti-hnRNP K and anti-AR antibodies. For each patient both PCa and

adjacent non-cancer tissue were examined. Biochemical progression-free (BPF) and overall survival (OS) were the main end-points of the present analysis. Patients were followed at regular intervals and PSA determined. A PSA level of at least 0.4 ng/ml, which was confirmed by another assay four weeks later, was sufficient to indicate a biochemical progression. After a median follow-up time of 10.7 years (95% confidence interval (CI) 9.7-11.6), 54 patients were found to have experienced biochemical progression and 21 died. BPF and OS were calculated by means of the Kaplan–Meier method and curves compared by the log-rank test. In order to evaluate the possible interactions among all the variables under study, multi-parametric models were constructed according to Cox's technique. All the analyses were performed using SPSS version 18.0 for Windows. *Results:* In PCa, hnRNP K displayed a more frequent and stronger immunoreactivity, both cytoplasmic and nuclear, when compared with adjacent non-cancer tissue (p=0.0001). The patients with higher cytoplasmic expression (score ≥6) showed a highest risk of biochemical failure (HR=1.63, 0.84-3.16 CI 95%) and death (HR=2.23, 0.86-5.81 CI 95%) which, however, were statistically significant only in the subgroup (n=30) of patients that have been submitted to neoadjuvant endocrine therapy (HR=3.33, 1.24-8.97 CI 95%, p=0.017). Despite AR expression was much variable, an elevate percentage of AR positive cells (>75%), in the tumor tissue, was associated with a better prognosis (HR=0.29, 0.13-0.69 CI 95%, p=0.005) and multivariate analysis indicated an independent prognostic value for the AR even with respect to Gleason score, seminal vesicles and surgical margins involved, capsular penetration, PSA, pN, and neoadjuvant therapy (HR=0.28, 0.110,69 CI 95%, p=0.006). A direct correlation between nuclear hnRNP K expression and AR level was observed (p=0.005), suggesting a possible interaction between the two proteins in the nucleoplasm. Finally, lower AR (≤75%) and higher citoplasmic hnRNP K (score ≥6) were associated with poor OS (HR=1.71, 0.97-51.97 CI 95%, p=0.055). *Conclusion:* Our finding confirms that, also in PCa, an aberrant cytoplasmic expression of hnRNP K is associated with a poor prognosis. The pivotal role played by this protein might depend on a direct interaction with AR and/or on a control exerted on its expression. Moreover, cytoplasmic higher level of hnRNP K and lower percentage of AR positive cells were associated with shorter OS and therefore might be potential prognostic markers for PCa. Additional validation studies should be justified.

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PROGNOSTIC PREDICTORS FOR TIME TO CLINICAL PROGRESSION AND CASTRATION RESISTANCE IN PROSTATE CANCER CASES WITH BIOCHEMICAL PROGRESSION AFTER SURGERY TREATED WITH INTERMITTENT ANDROGEN DEPRIVATION (IAD)

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Abstract Objective: To define characteristics of the first cycle of intermittent androgen deprivation (IAD) that would predict outcomes in a long term follow-up. *Patients and Methods:* In 1996 we started a prospective study of IAD for the treatment of biochemical progression (BP) after radical prostatectomy (RP) for prostate cancer (PC). The end-points of the trial were time to clinical progression (CP) and time to castration resistance PC (CRPC). Eighty-four cases were included in the study. In all cases, after an initial induction period, an acceptable nadir to switch from on-to-off-phase of IAD was considered to be a serum PSA <1.0 ng/ml. Measurements: As possible predictors for time to CP and CRPC, we analyzed pretreatment parameters such as age, Gleason Score, serum PSA, testosterone, chromogranin A (CgA) levels, and characteristics from the first cycle of IAD. *Results:* Mean follow-up during IAD was 88.6±16.7 months; 29.7% of patients developed CRPC and 14.2% of cases showed a CP with a mean time of 88.4±14.3 months and 106.5±20.6 months, respectively. At univariate and multivariate analysis, the PSA nadir during the first on-phase period and the first off-phase interval resulted in significant and independent predictors (p<0.001) of the time to CRPC and CP. In particular for cases with a PSA nadir >0.4 ng/ml and for those with an off-phase interval </=24 weeks, the risk of CRPC and CP during IAD was 2.7-2.5 and 3.0-3.1 times that for patients with a PSA nadir </=0.1 ng/ml and with an off-phase interval >48 weeks, respectively. *Conclusion:* Cases with BP after RP selected to IAD that show at the first cycle a PSA nadir </=0.1 ng/ml and a off-phase interval >/=48 weeks may identify candidates who will experience better response to IAD treatments and delayed CP or CRPC development.

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PROSTATE CANCER UNITS FOR THE OPTIMAL MANAGEMENT OF PROSTATE CANCER

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Prostate cancer (PC) is established as one of the most important medical problems affecting the male population. An early diagnosis is necessary to implement well-balanced therapeutic options, and the correct evaluation can reduce the risk of overtreatment with its consequential adverse effects. Breast and prostate cancers, respectively, are the most common cancers in women and in men, and various similarities have been underlined. The paradigm of the patient consulting a multidisciplinary medical team has been an established standard approach in treating breast cancer. Such multidisciplinary approach can offer the same optional care for men with PC as it does for women with breast cancer. A multidisciplinary team (MDT) comprises healthcare professionals from different disciplines whose goal of providing optimal patient care is achieved through coordination and communication with one another. A Prostate Cancer Unit is a place where men can be treated by specialists in PC, working together with a multi-professional team. The MTD approach guarantees a higher probability for the PC patient to receive adequate information on the disease and on all possible therapeutic strategies, balancing advantages and related side-effects. The future of PC patients relies on a successful multidisciplinary collaboration between experienced physicians, which can lead to important advantages in all the phases and aspects of PC management. A Prostate Cancer Unit has been established from 2010 in our department and our results confirm these positive suggestions.

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DISTRIBUTION OF INFLAMMATION, PRE- MALIGNANT LESIONS AND INCIDENTAL CARCINOMA IN HISTOLOGICALLY CONFIRMED BENIGN PROSTATIC HYPERPLASIA: A RETROSPECTIVE ANALYSIS

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Objectives: We analyze our experience on BPH through 20 years of histopathological examinations performed by the same pathologist. *Methods:* We retrospectively reviewed all histopathological examinations performed during 20 years in patients undergoing surgery in our urological clinic who were diagnosed with BPH. We limited our evaluation to the following variables in each BPH case analyzed: inflammatory aspects associated with BPH, presence of focal acinar atrophy, atypical adenomatous hyperplasia (AAH), prostatic intraepithelial neoplasia (PIN), incidental prostate carcinoma (IC). These histological variables were analyzed according to some clinical parameters such as age, prostate volume and serum PSA. *Results:* The study population was comprised of 3942 cases with histological diagnosis of BPH. The mean patient age was 68.85±7.67 years. In particular, inflammatory aspects were associated with BPH in a high percentage of cases (43.1%=1700 cases), predominantly as chronic inflammation. Observation of focal acinar atrophy significantly increased according to patient decade of age (p=0.027). There was a significant trend to increase with age decades (p=0.036) for high grade PIN. A significant difference was found in IC (T1a, T1b) distribution in the different decades of age and especially in regards to both T1a and T1b tumors, there was a trend to increase with patient age (p=0.020 and p=0.025, respectively). On the contrary, the distribution of inflammatory aspects (p<0.001) and AAH (p=0.003) significantly varied according to prostate volume, and particularly in regards to chronic inflammation, there was a trend to increase depending on the prostate volume (p=0.002). Only the presence of T1b tumor but not of the other histological parameters associated to BPH, was able to significantly influence serum PSA. *Conclusion:* In our analysis different histological variables associated to BPH are differently influenced by the age of patients and prostate volume, and they differently influence serum PSA levels.

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COMBINATION THERAPY OF ETHINYLESTRADIOL AND ESTRAMUSTINE PHOSPHATO REINTRODUCES OBJECTIVE CLINICAL RESPONSES IN PATIENTS WITH CASTRATE-RESISTANT PROSTATE CANCER

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Introduction: Therapy for advanced prostate cancer centers on suppressing systemic androgens and blocking activation of the androgen receptor (AR). Despite anorchid serum androgen levels, nearly all patients develop castration-resistant disease.

We hypothesized, on the basis of an ancient experience (1), that ongoing steroidogenesis within prostate tumors and the maintenance of intratumoral androgens may contribute to castration-resistant growth. Recently Montgomery and colleagues (2), in a basic research convincingly showed that median testosterone levels within metastases from castrated men are approximately threefold higher than levels within the primary prostate cancers from untreated eugonadal men. The authors further showed up-regulated expression of steroidogenic enzymes including FASN, CYP17A1, HSD3B1, HSD17B3, CYP19A1, and UGT2B17 ($p<0.001$ for all). Indeed, several clinical studies have proposed minimizing levels of these extragonadal sources of T and its precursors by using combinations of inhibitors targeting different points of steroidogenesis such as ketoconazole and 5-α reductase inhibitors (3, 4). We evaluated whether a combination therapy of ethinylestradiol and estramustine phosphato can reintroduce objective clinical responses in patients with metastatic androgen ablation refractory prostate cancer (HRPC). *Materials and Methods:* 12 patients (5 pz Gleason score 8 (4+4), 5 pz Gleason score 9 (5+4), 2 pz Gleason score 10 (5+5)) with stage D3 disease and bone metastases who had progression despite initial responses to combined androgen blockade and in whom antiandrogen withdrawal subsequently failed discontinued combined androgen blockade and received 2 mg ethinylestradiol orally daily and oral estramustine 420 mg/daily. Serum prostate specific antigen (PSA), Eastern Cooperative Oncology Group performance status and bone pain scores were assessed at regular intervals. Median follow-up was 17 months (range 8 to 26). *Results:* All cases (90%, 95% CI 55.5 to 99.8) had an objective clinical response, defined as a greater than 50% PSA decrease (median 87.1%, range 50.2% to 94.4%). PSA normalization (less than 4 ng/ml) was achieved in 3 cases. All patients reported significant and durable improvement in bone pain (median duration 17.5 months) and performance status (median duration 18 months). The most important side-effects were: vein thrombosis (3 pz) and gastric pain (2 pz). *Conclusion:* Castrate resistant prostate cancer (CRPC) is sensitive to androgens and moreover prostate cancer could become hypersensitive to low levels of androgens and is finally established that this cancer produces androgens by itself. For the future the therapy could involve increasing estrogen dose (Estradurin® 80 mg ?) and/or using new androgen antagonist (abiraterone acetate, MDV300 ?). IAS (intracrine androgen synthesis) produces a "relative hormone refractoriness" and is the new research frontier.

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ENDOVESICAL ADJUVANT THERAPY FAILURE IN HIGH-RISK NON MUSCLE INVASIVE BLADDER CANCER (NMIBC): CHEMOSENSITIVITY TESTING AND TAYLOR THERAPY

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Introduction and Objectives: Adjuvant endovesical treatment of choice for high risk NMIBC is still debated and still open questions are: Which drug? Which dosage? Which therapy planning? Although intravesical chemo-immuno treatments is the gold standard after TURB the percentage of recurrence and progression is still high. Making a systematic overview of chemotherapy effects in urothelial bladder comprising 31974 patients we have up to 60% of recurrences at 5-8 years. Analysing BCG failure we have up to 54% of reccurences at 5 years. There is really need to introduce the concept of personalized medicine in bladder cancer management and in particular with molecular and genetic testing we should be able to predict which patients are at high risk for cancer progression and which patients will respond to treatment. *Materials and Methods:* It has been reported that some chemotherapy drugs used in intravesical regimens may induce a phenomenon known as chemotherapy-induced resistance (CIR), through the up-regulation of ATP-binding cassette proteins. Furthermore, inefficient apoptotic machinery might also lead to chemotherapy resistance, through the selection of more aggressive clones that, proliferating in the presence of the drug, may be responsible of progression of disease under treatment. We started a clinical trial with the aim to characterize, in each patient, an individual chemosensitivity profile, based on the expression of a panel of markers that are involved in the resistance to standard chemotherapy drugs. Specifically, we chose multidrug resistance protein 1 and 2 (MRP1, MRP2), belonging to the superfamily of ATP-binding cassette

transporters, which are both involved in the resistance to epirubicin, doxorubicin and mitomycin-C; human equilibrative nucleotide transporter 1 (hENT1) and deoxycytidine kinase (dCK), involved in the resistance to gemcitabine and α5β1 integrin, which represents the fibronectin receptor, and is involved in the internalization of BCG. The present analysis was also extended to apoptosis regulating genes, such as the bcl-2/bax ratio and surviving expression. 128 patients with high risk NMIBC were enrolled, all candidates for TUR-B followed by intravesical treatment. One mg of tumoral tissue from each patient was kept for molecular assay subjected to RNA extraction and RT-PCR amplifications with primers specific for these components. On the basis of densitometric analysis of the amplification bands obtained by normalisation with the GAPDH internal controls, we obtained for each patient a chemosensitivity molecular profile. We considered high, intermediate and low sensitivity to mitomycin c, epirubicin, and doxorubicin a ratio MRP/GAPDH <1, =1, >1 respectively. For gemcitabine resistance, we considered sensitivity, intermediate sensitivity and resistance a ratio hENT-dCK/GAPDH >1, =1 and <1 respectively. Sensitivity to BCG was evaluated as follows: high, intermediate, low sensitivity in the presence of α5β1/GAPDH >1; =1; <1 respectively. We then compared both the molecular profiles of chemosensitivity to the clinical response to the intravesical regimen adopted in the first 6 months of follow-up. *Results:* This chemosensitivity test was able to predict response to treatment in 93% of patients. The assay is easy to perform with low costs and rapid time of execution. *Conclusion:* Our results are encouraging in the view of an individualised therapeutic approach, to provide a higher treatment success rate while sparing patients unnecessary toxicity from drugs that are not suited for their tumors.

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PROGNOSTIC VALUE OF CIRCULATING TUMOR CELLS IN NON MUSCLE INVASIVE BLADDER CANCER: A CELL SEARCH ANALYSIS

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Introduction: Although most cases of bladder cancer patients present with a disease that is confined to mucosa (Ta) or submucosa (T1), recurrence rate in this cohort of patients is greater than 50%. Furthermore, some non-muscle-invasive bladder cancer (NMIBC), more frequently T1G3, present with biological features of invasiveness, leading to cancer death after bladder-sparing treatment within 5 years in about 16-23% of cases. Circulating tumor cells (CTCs) play a crucial role for distant failure in different types of solid tumors. Their enumeration through Cell Search system (Veridex) is widely used for prognostic information in patients with metastatic breast, colon and prostate cancer. Recent studies have shown that CTCs are released in circulation in a very early phase of cancer disease where their presence is associated with a worse prognosis of patients and CTC count could reflect the ongoing progression of cancer disease. *Patients and Methods:* Primary endpoint of the present study was to investigate the prognostic significance of CTCs in NMIBC patients; to this purpose the presence of CTCs has been used to predict time to first recurrence (TFR) and time to progression (TTP) in a follow-up of 24 months. Secondary endpoints were the association between CTC presence and known prognostic variables such as T, G and presence of CIS. In a prospective study, 44 patients were enrolled all with histopathological diagnosis of NMIBC. According to T, 18/44 (41%) were Ta and 26/44 (59%) were T1. 9/44 (20%) were G1, 9/44 (20%) were G2 and 26/44 (59%) were G3. Concomitant presence of CIS was found in 8/44 (18%) patients. A population of 20 healthy donors was included as negative control when needed. Blood drawings were carried out in all patients at the first diagnosis, 1h before TURB. Patients were then included in a follow-up programme which consisted of cystoscopy and urinary cytology every 3 months and a URO-CT every 12 months. CellSearch system (Veridex) was used for CTCs enumeration. Briefly, the method is an immunomagnetic cell enrichment which uses antibodies targeting epithelial cell adhesion molecule (EpCAM) and nucleus labeling with fluorescent dye. *Results:* CTC were detectable in 8/44 patients (18%), and in 0/20 healthy volunteers. CTC were found in 8/26 (31%) patients with T1 tumors, and in 0/18 patients with Ta (p=0.0275). CTC presence was also found associated to concomitant presence of CIS; in the group of patients with CIS, CTC were found in 5/8 (62.5%) compared to 3/36 (8.3%) found in the group without CIS (p=0.00228). For what concerns TTP, of the 8 CTC+ patients, 7 experienced the event within the end of follow-up, with a median TTP of 12 months. No events were observed in the 36 CTC- patients (p<0.001). For what concerns TFR, there were once again 7 events in the CTC+ group within end of follow-up, with a median TFR of 13 months and 13 events in the CTC- group. *Conclusion:* Evaluation of circulating tumor cells from blood could provide a non-invasive source of representative tumor material; although the prognostic significance of CTC count has been more extensively validated in a metastatic setting, a growing body of evidence is now demonstrating their role in early staged tumors as well. We suggest that NMIBC patients with

similar stage and detectable CTCs may be considered at higher risk for recurrence and progression, and therefore be candidates for more accurate surveillance and more aggressive treatment options.

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MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING OF THE PROSTATE AND PCA3 URINARY TEST: IS TIME TO RE-EVALUATE PROSTATE BIOPSY?

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Introduction: The deficiencies of serum PSA as a prostate-cancer-specific diagnostic test are well recognized thus creating a new diagnostic dilemma: only a fraction of men with increased serum PSA have detectable prostate cancer. Men with at least one negative biopsy often have persistently increased serum PSA, primarily attributable to enlarged gland and benign prostatic hyperplasia (BPH). However, a significant proportion of men with slightly increased serum PSA (2.5-4.0 ng/mL) either have, or will develop, clinically significant prostate cancer [1]. Although biopsy remains the gold standard for prostate cancer detection, more accurate tests with better specificity are needed to decide whether or not to biopsy the prostate. In recent clinical trials the potential diagnostic value of the PCA3 urine test was soon established as well as the role of combined proton 1H-magnetic resonance spectroscopic imaging (1H-MRSI) and dynamic contrast-enhanced imaging magnetic resonance (DCEMR) in the management of prostate cancer. The aim of our study is to evaluate the ability of 1H-MRSI/DCEMR combined with PCA3 urinary test to improve PCa biopsy detection in cases of PSA increase and precious negative prostate biopsy. *Patients and Methods:* This is a prospective single-center study on patients with prior negative random TRUS-guided prostate biopsy and persistent elevated PSA levels. Including criteria: a first random TRUS-guided prostate biopsy negative for prostate adenocarcinoma or high-grade prostate intraepithelial neoplasia, persistent elevated PSA levels (total PSA ≥4 ng/mL and <10 ng/mL; mean 6.37 ng/mL), and negative digital rectal examination. Exclusion criteria for the study were previous hormonal, surgical, or radiation therapies for prostate diseases, urine not collected after (digital rectal exam) DRE and prior to prostate biopsy, inadequate prostate biopsy with less than 10 cores and cases in which a MR with a complete MRSI and DCEMR study was not possible. All the patient were submitted to1H-MRSI/DCEMR; before that patient's urine were collected by an expert Urologist, following an attentive prostate massage (3 compressions for each prostatic lobe), in order to perform PCA3 assay. All the biopsies were performed according to a standard biopsy protocol: 10-core laterally directed random TRUS-guided prostate biopsy (two cores from the basal portion lateral and paramedial, two from the midgland lateral and paramedial, and one from the apex, on each side of the gland) for each patient, plus additional biopsies from other areas suspicious for PCa at MR. *Results:* The total number of urinary sediments that could be analyzed successfully were 95,3% (41 on 43 specimens). The performance of the PCA3 test was evaluated in terms of sensitivity and specificity by comparing the PCA3 score to biopsy results. The overall sensitivity and specificity of a PCA3 score ≥35 alone for positive biopsy in this cohort were 76.9% and 66.6 %, respectively, with a Positive Predictive Value (PPV) of 80 % and a Negative Predictive Value (NPV) of 62.5%; as for MR sensitivity and specificity were, respectively, 92.8% and 86.6% with a Positive Predictive Value (PPV) of 92.8 % and a Negative Predictive Value (NPV) of 86.6%. The sensitivity and specificity of PCA3, MRI and their combination were explored using receiver operating characteristic (ROC) analysis. The area under the ROC curve was 0.755 for PCA3, 0.864 for MR and 0.92 for 1H-MRSIDCEMR/PCA3. *Discussion and Conclusion:* Our results show that the combination of both diagnostic methods may lead to a very high diagnostic accuracy compared to other test individually. This finding should be confirmed in a large prospective study.

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"THREE-U-STITCHES" TECHNIQUE FOR URETHROVESICAL ANASTOMOSIS DURING RADICAL PROSTATECTOMY: THE KNOTLESS METHOD

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Introduction: The aim of this study was to describe a new technique for urethrovesical anastomosis, which is applicable both in laparoscopy as in open surgery, to accelerate and simplify one of the critical surgical steps during radical prostatectomy. *Materials and Methods:* The technique consists

in placing three "U" stitches of Monocryl 2-0 between the bladder neck and urethral stump. The margins are approached by double passage of the suture, without performing any node. The sutures are fixed on the bladder side with application of Lapra-Ty clips distant from the joining point of the mucosal margins. *Results:* We applied the technique on a total of 116 patients that underwent radical prostatectomy, of which 26 open radical retropubic prostatectomy (RRP) and 90 laparoscopic extraperitoneal radical prostatectomy (LERP). With this method we achieved an important reduction of the time needed to complete the anastomosis, particularly in laparoscopy. The optimal combination of the margins, the absence of nodes and the minimum trauma to the urethral wall enable to create an anastomosis both "sealed" and "tension free" allowing a quick "welding" of the margins and early catheter removal with a good stretch of the final anastomosis. The results are excellent in terms of urinary continence and in terms of absence of postoperative stenotic complications. *Conclusion:* The functional results added to ease and speed of execution, especially in laparoscopy, make this technique, in our opinion, a viable alternative to popular anastomotic techniques.

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T1G3 HIGH-RISK NMIBC (NON-MUSCLE INVASIVE BLADDER CANCER): CONSERVATIVE TREATMENT *VERSUS* IMMEDIATE CYSTECTOMY

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Background: The management of stage T1 poorly differentiated G3 bladder cancer invading the lamina propria continues to be debated. These tumours are associated with a high risk of recurrence and progression; concomitant carcinoma *in situ* and/or multifocality are negative prognostic factors. Choosing between a preserving approach such as trans-urethral resection of the bladder (TURB) followed by maintenance bacillus Calmette-Guerin (BCG) and an invasive approach like cystectomy is critical. *Patients and Methods:* Overall, 80 patients underwent TURB and RE-TURB followed by intra-vesical induction treatment with BCG plus maintenance (Group A) while 72 patients underwent immediate radical cystectomy with extended lymphadenectomy (Group B). Patients were divided into 3 subgroups: uni-focal tumours, multi-focal tumours and carcinoma *in situ* associated lesions. In Group A, time to first recurrence and time to progression were analysed. A comparison was made between Group A and Group B regarding progression-free survival, cancer-specific survival and overall survival with a median follow-up time of 8.3 years. *Results:* In Group A patients, 42 recurrences (52.5%) were reported in a median time of 10.4 months (range 3-26) and 25 progressions (31.2%) in a median time of 25 months (range 3-68). Regarding time to first recurrence and time to progression, both the KaplanMeier survival curves obtained are significant and *p*-values are, respectively, 0.0263 and 0.0011. Comparing Groups A and B patients, 25 progressions (31.2%) in a median time of 25 months (range 3-68) and 18 progressions (25%) in a median time of 25.9 months (range 4-72), respectively, were recorded. Regarding overall survival, at 10 years, 24 deaths (42.5%) occurred in a median time of 55.4 months (range 12-94) in Group A and 42 deaths (58.3%) in a median time of 54.9 months (10-100) in Group B. Cancer-specific survival was evaluated in Group A with a total of 18 deaths (22.5%) in a median time of 47.5 months (range 16-78), and in Group B with a total of 16 deaths (22.2%) in a median time of 45.7 months (range 16-88). The progression-free survival Kaplan-Meier curve is not significant, the p value being 0.3801; the overall survival curve is significant with a p value of 0.0487 while the cancer specific survival curve is not significant with a p value of 0.9762. *Discussion:* In Group A, considering "time to first recurrence", the difference is greater between unifocal lesions and multifocal or Cis-associated lesions. Conversely, for "time to progression", there is a greater difference between unifocal and multifocal tumours and Cis-associated tumours. Looking at "progression-free survival" in Group A and Group B patients, there is no statistically significant difference, like in cancer-specific survival. A statistically significant difference was observed in overall survival being in favour of conservative treatment thus reflecting that conservative treatment is not burdened by all the surgical and post-operative complications of cystectomy. *Conclusion:* Although NMIBC invading the lamina propria, stage G3, with or without Cis-associated lesions are burdened both by a high volume of recurrences and progressions, cystectomy could be considered a too aggressive approach. New biological markers are now needed which are able to predict the behaviour of the cancer and to guide the decision-making process between conservative or aggressive treatment.

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ROLE OF PERCUTANEOUS BIOPSY IN THE DIAGNOSIS OF THE SMALL RENAL MASSES: OUR EXPERIENCE

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Introduction: The common and widespread use of "imaging" techniques has increased the incidental diagnosis of small renal masses (SRM), defined as solid masses with contrast enhancement and of size smaller than 4 cm, potentially malignant (1). The problem is that such lesions may be benign or with a low aggressive potential, therefore a histological analysis would be useful aiming at reducing the risk of an invasive surgical treatment, especially on elderly patients or with serious comorbilities. For this reason, over the last years the role of renal biopsy has increased in importance as an effective method to diagnose SRMs and for the definition of the correct therapy. *Materials and Methods:* Between January 2009 and January 2012, 16 patients (average age: 59) with incidental US diagnosis, then confirmed by CT scan to be of average size of 3.4 cm (range 2.8-4.0 cm), underwent US-guided percutaneous biopsy; among those one with transplanted kidney. The test has been run on day-surgery mode, local anesthesia, with the patient lying prone or on the side in function of the lesion's position, using a 16 G needle biopsy gun, with coaxial US guide (Toshiba Aplio). The average number of cores was 3, with average length of 0.8 cm. The average duration of the test was 20 minutes. Each procedure was executed by a single, expert operator who, after the biopsy, also verified *via* microscope the presence of renal tissue. After an observation period of 24 hours the patients were discharged. *Results:* In 11 patients the biopsy resulted RCC positive; in 2 patients it resulted non diagnostic, then one of the two repeated the test and resulted positive. One of the patients with positive biopsy is now awaiting surgery treatment. The patient with RCC on the transplanted kidney has been subjected to mass cryo-ablation. No major complications have been observed but high fever in one patient, resolved with adequate therapy within 24 hours after the test. One RCC positive patient deceased for intercurrent pathologies. 5 patients have been subjected to VLAP nefrectomy for unfeasibility of the nephron sparing surgery treatment, and 5 to VLAP partial nefrectomy. The histological analysis proved the presence of RCC in all the patients who underwent radical surgery (3 pT1aG1 + 1 G4 sarcomatoid tumor), whereas only 4 patients who underwent conservative surgery were diagnosed with RCC (pT1aG1). The patient subjected to non-diagnostic biopsy was diagnosed with angiomyolipoma. The execution of the biopsy test did not cause complications during the surgical treatment. The median follow-up time was 15 months, during which no seeding-correlated relapsed cancers have been observed. *Discussion:* The increase in SRM incidence made the percutaneous biopsy become more widespread with a consequent impact on the therapy definition: avoidance of surgery in case of benign lesions or use of a conservative surgical treatment or even adoption of a surveillance therapy. In literature a sensitivity of 70-100% and a specificity of 100% are documented, with a low complications rate (seeding <0.01%, bleeding <1%) and a 76-100% concordance of the core to the definitive histological analysis. In 15-44% of cases it was possible to avoid the surgical treatment for a benign pathology (2). Even in case of non-diagnostic biopsy, the repetition is recommended for the high effectiveness and low complications rate (3). The only limitation of the studies here documented is that they are not based on common and standardized criteria because they are leveraging on retrospective experience of different clinical centers. *Conclusion:* SRM biopsy is a safe, effective, easily reproducible procedure with high clinical interest. The data gathered in our experience, even though exiguous, confirm what documented in literature but further studies are needed to confirm the actual utility in the clinical practice.

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CASE OF SPERMATIC CORD AND TESTICLE ANGIOMYOLIPOMA

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Introduction: The angiomyolipoma (AML or Amartoma) is a mesenchymal tumour, in most cases a benign one, consisting of differentiated cells in their correct location but forming a disorganised mass. It is composed of varying proportions of vascular cells, immature smooth muscle cells and fat cells. Its incidence in general population is about 0.3 and 7%. AML are typically found in the kidney and are strongly associated with a genetic disease, Tuberous Sclerosisi (1). There are some rare cases of angiomyolipoma observed in different anatomic sites, that makes more difficult the differential diagnosis with malignant neoplasia. In literature there are only two cases of testicle angiomyolipoma described (2, 3). The present is the third case described. The patient was 53 years old, suffering of motor deficit due to congenital brain disease. He had hypertension in therapy. He reported, in March, the appearence

of a sudden testicular pain. The blood tests were normal, except for white cells (12,65 h/mm^3). At the examination the left testis and epididymis were harder and painfull at palpation. Scrotum Ultrasound showed bilateral scattered microcalcifications. Variation change of structure of the head of left epididymis, which appeared hypoechoic and encreased in volume in comparison with the opposite side, was observed vascularization bilaterally was preserved. An antibiotic (Rocefin 1 fl im/die) and anti-inflammatory therapy was prescribed. After two weeks, since the symptoms did not completely disappear, the patient underwent to a new ultrasound evaluation at another clinic. Scrotum Ultrasound: right testicle normal for place, shape, size, aberrant ultrasound structure for the presence of micro-calcifications of 1-2 mm size. Left testicle roundish, 38×03×30 mm. The tissue appeared abnormal for the presence of several calcifications (1-3 mm). Left epididymis normal for size but hypoechoic as for inflammation status. Light left pampinoform venous plexus dilatation was present. At this point the patient underwent a surgical exploration of left testicle by inguinal approach which ended in orchiectomy. Gross examination showed a soft brownish mass, measuring 4×3×3 cm, replacing the most of the testicular parenchyma, with widespread haemorrhagic appearance of the cut surface and well circumscribed margins. Microscopic examination showed medium-to-large calibre thick-walled blood vessels with ectatic lumina, surrounded by sclerotic fibrous strands and interlacing smooth muscle bundles in a fatty context. The peripheral narrow zone of residual parenchyma displayed diffuse necrotic and haemorrhagic infarction of the seminiferous tubules, interstitial xantogranulomatous flogistic infiltrate with scattered siderophages and blood cells extravasation. Tunica albuginea was irregularly thickened, epididymis globally preserved. Immunohistochemical staining was performed to assay CD34 positivity of the blood vessels, SMA positivity of the smooth muscle fibers and negativity of S100 and HMB-45 stains. *Discussion:* Given the rarity of the case, this neoplasia is not part of the approved list of histology of testicular tumors. This implies that the diagnosis and eventually treatment have never been standardized (4). Most of the angiomyolipomas are benign but there are cases of renal and extrarenal malignant angiomyolipomas. Pathologic and immunohistochemical features of our case as well as the case reported by Saito *et al*. (3), are indicative for benign testicular angiomyolipoma from non-germinal cells. Clinical and ultrasound features make the differential diagnosis of malignant tesicular tumors very diffcult. Our case of angiomyolipoma is the first case in which the tumor is not identifiable by ultrasound as a solid intratesticular mass, but associated to testicular microlithiasis, uncommon condition characterized by calcium deposits within the seminiferous tubules. This condition was first described by Doherty *et al*. (5), on ultrasound, seen as multiple, uniform, nonshadowing echogenic foci of 1-3 mm, usually bilaterally symmetric (6). Reported prevalence range is from 0.6 to 9%. The condition is often associated with germ cell tumor (GCT) or intratubular germ cell neoplasia. To our opinion, radical orchiectomy is still the best therapeutic approach.

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BIPOLAR TURBT NARROW BAND IMAGING (NBI) ASSISTED. DOES IT IMPROVE DETECTION AND RE-TREATMENT RATES? PRELIMINARY EXPERIENCE IN A SINGLE CENTRE

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Introduction: Narrow Banding Imaging (NBI) was developed with the goal of enhancing the definition of small lesions of the bladder that could be missed during White Light Endoscopy. The aim of this study was to evaluate the efficacy to identify non-muscle invasive bladder cancer by comparing the predictive power of the white light cystoscopy *versus* NBI cystoscopy and white light endoscopic resection *versus* the NBI one. *Patients and Methods:* From June 2010 to June 2011, 482 patients, 301 male and 181 female, affected by non-muscle invasive bladder, underwent NBI Bipolar TURBT. Histological findings are shown in the table below.

Neoplasms	Pumnpl	Ta	T1
Primitive neoplasms	49	159	74
Recurrence neoplasms	30	115	55

The average age was 67.7 yrs. (range 46-88). All patients underwent preoperative white light cystoscopy: topography and characterization of neoplasms and/or suspicious lesions followed by a similar evaluation using NBI. Then all the patients underwent resection of the previously identified lesions performed at first using white light followed by NBI resection of the bed and surgical margins. All the removed tissue send separately for histological evaluation after mapping the areas of resection on a topographic sheet. All lesions of the lateral side walls were resected after preoperative additional anesthesia (obturator ipsilateral nerve block). Follow-up was carried out according to the EAU Guidelines for non-muscle invasive bladder tumors. *Results:* The use of NBI cystoscopy revealed a total of 325 patients (67.4%) affected by white light non-visible lesions, but only in 200 patients (41.4%), the histological findings showed neoplasms of the bladder. Overall, with the use of NBI cystoscopy and NBI TURBt, we identified 125 (25.9%) benign lesions (*i.e.*, chronic inflammation, reactive urothelial hyperplasia). In the T1HG primitive bladder neoplasms group we observed a 40.2% (29/72 pts) cases free of disease, a relapse rate of 59.7% (43/72 pts), and a progression rate of 14% (10/72 pts). The table below shows the detailed results.

T Neoplasms (pts)	Cystoscopy WL	Cystoscopy NBI	TURBT WL	TURBT NBI
PUNMPL (pts)	31	72	17	58
Ta (pts)	208	165	201	70
T1 (pts)	77	88	64	72
Primitive PUNMPL (pts)	21	40	9	38
Primitive Ta (pts)	115	78	108	49
Primitive T1 (pts)	49	37	43	29
Recurrent PUNMPL (pts)	10	22	8	20
Recurrent Ta (pts)	93	87	93	21
Recurrent T1 (pts)	28	51	21	43

Mean post-surgical hospitalization and catheterization periods were, respectively, 36 and 12 hours; besides mean post surgical Hb value was 14.8 gr/dl. No pts. were submitted to haemotrasfusion. Early adverse events (EAs) included dysuria in 27.6% (133 pts.), urgency in 21.6% (104 pts.), haematuria in 21.4% (104 pts) and AUR with re-catheterization for clots in 10.4% (50 pts). *Conclusion:* Despite the high rate of NBI false positives lesions (over 25%), the combination of white light and NBI appears to allow a better diagnostic and therapeutic approach of bladder tumours, especially in T1 lesions. The high rate of false positives could depend on artifacts produced during white light endoscopy. However, NBI TURBt in overall T1HG superficial disease patients identifies subjects with high rate of early progression (41.9%), who need an immediate radical surgical treatment.

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THE PREDICTIVE ROLE OF NBI RE-TURB IN THE EVALUATION OF T1HG BLADDER NEOPLASM RECURRENCE AND PROGRESSION RATE. PRELIMINARY EXPERIENCE

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Introduction: High grade bladder neoplasia (T1HG TCC) represent a true therapeutic challenge because of a 20-30% risk of progression. Sometimes a restaging TURBt better predicts early stage progression. Small or flat cancerous lesions of the bladder surface may be missed during white light imaging (WLI) cystoscopy. Different optical imaging techniques have been developed in an effort to minimize this failure. We investigated whether narrow band imaging (NBI) could improve the detection during follow-up of high-grade disease recurrence and progression rate (T1HG bladder neoplasm). *Patients and Methods:* From 6/2010 to 6/2011 a cohort of 276 patients presenting primary bladder neoplasms underwent TURBt with Bipolar Surgimaster Scalpel in saline (TURis); out of this number 72 (26,1%) were T1HG. After a month HG cancer patients underwent re-TURBT of the previously resected area using NBI light to better characterize the "bottom of resection" and surgical margins: the aim was to evaluate, more precisely, recurrence and progression free survival time. The subsequent follow-up consisted of NBI cystoscopy with multiple biopsies, (randomly and in the previous zone of resection) every 3 months, urinary oncocytology on 3 specimens and kidney/bladder ultrasound every 6 months. The average follow-up was 12 (6-18) months. *Results:* The T1HG cancer group showed a 40.2% (29/72 pts) free of disease, a relapse rate of 59.7% (43/72 pts) and a progression rate of 13.8% (10/72 pts). After NBI re-TURB we found an overall persistence of TCC in 31 (43.1%) cases: 23 (31.9%) high grade (HG) non muscle invasive disease and 8 (11.1%) high grade (HG) muscle invasive bladder cancer (T2HG). In the recurrence group (31 pts) 21 pts (29.1%) underwent WLI TURBt, while the remaining 10 (13.8%) NBI resection (located in the bed of resection in 2 cases (2.7%) and in surgical margins in 5 (6.9%)). Patients with a high grade (HG) muscle invasion disease (T2HG) were 6 (8.3%): 2 recurrences in the bed and 4 in the surgical margins related to NBI re-TURBt but only 2 (2.7%) in WL re-TURBT. We observed disease progression in 2 patients after 6 and 12 months respectively. In the group of 41 (56.9%) patients T0, the NBI and WL reTURB showed a recurrence in 12 pts (16.6%) and a progression in just 2 (2.7%) who presented a recurrence after 3 months, associated with CIS. The

multivariate analysis showed that the most important variable of early progression was the histopathological findings at re-TURBt (p=0.01) followed by the results of the NBI re-TURBt (p=0.001), presence of CIS (p=0.02) and absence of recurrence within 3 months (p=0.02). *Conclusion:* NBI re-TURBt in T1HG patients identifies subjects with high risk of early progression disease who need an immediate radical surgical treatment (early cystectomy).

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PAPILLARY UROTHELIAL NEOPLASM OF LOW MALIGNANT POTENTIAL (PUNLMP): OUR LONG TERM EXPERIENCE

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Introduction: The present study evaluates behavior of de-novo primary bladder PUNLMP lesions (Primary-PUNLMP) as well as Surveillance-PUNLMP (diagnosed during follow-up of a higher grade urothelial neoplasm. *Patients and Methods:* From January 2006 to June 2011, 608 patients (Males=430, Female=178; mean age 71.8+9.2 years) underwent transurethral resection (TURBT) of all visible tumours. We retrospectively analysed our TURBT database and identified all patients with a histological examination revealed a PUNLMP lesion type. *Results:* We identified a total a 61 PUNLMP of the bladder; 22 (36.07%) pts categorized as Primary-PUNLMP and remaining 39 (63.93%) pts as Surveillance-PUNLMP. During follow-up, 36 mo. (range: 6-66 mo), in the Primary-PUNLMP group, 12/22 (54.5%) patients did not develop any recurrences *vs*. 13/39 (33.3%) in the Surveillance-PUNLMP group. In the first group, 4/22 (18,8%) pts developed PUNLMP recurrence (1-2 episodes in 1-4 yrs) and 7/22 (31.8%) progression to a higher grade lesions within 1-4 yrs. Grade progression was non invasive low grade urothelial carcinoma (LG-TCC) in 6 pts (27.2%) and non invasive high grade urothelial carcinoma (HG-TCC) in 1 pts (4.5%). None of our Primary-PUNLMP pts developed muscle-invasive carcinoma or died because of disease progression. Tumour size did not correlate with likelihood for recurrence. In the second group, 26/39 pts (66.6%) showed PUNLMP during surveillance for higher grade urinary bladder's lesions. These included 16 (41.02%) prior LG-TCC, 9 (23.07%) prior HG-TCC and 1 (2.56%) found in cystectomy for invasive neoplasm in bladder diverticula. Grade progression to LG-TCC was in 11 pts (28.2%) while progression to HG-TCC in 6 (15.3%). Two patients (5.12%) died in HG-TCC group and one (2.56%) in the LG-TCC after developing of a HG upper urinary tract cancer. *Conclusion:* Bladder PUNLMP can occur either as a de novo lesion or during surveillance for prior higher grade urinary bladder urothelial neoplasm. None of our PrimaryPUNLMP pts developed invasive carcinoma or died because of the disease despite a 66% recurrence and 43.5% grade progression rates. Surveillance PUNLMP was associated with a worse outcome (27.8% grade/stage progression, 3.27% deaths because of disease progression) most likely due to their initial higher grade/stage urothelial neoplasm.

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URINARY DIVERSION CHOICE AFTER PELVIC EXENTERATION FOR RECURRENT CERVICAL CANCER: SINGLE INSTITUTION 13 YEARS EXPERIENCE

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Introduction: Pelvic exenteration (PE) was initially utilized for the palliative surgical management of recurrent gynecologic cancers, then it evolved into a curative intervention for advanced and recurrent gynecologic cancers confined to the central pelvis. Its exenterative time is characterized by pelvic viscera removal and blood vessels ligation, often difficult because of previous surgery and radiotherapy, and a reconstructive phase that needs multidisciplinary approach. The aim of this study was to compare urologic complication in patients with Indiana pouch(IP) *versus* ileal conduit (IC) as urinary diversion after pelvic anterior or total exenteration for recurrent cervical cancer. *Patients and Methods:* From 1997 to 2011 at IEO 151 PE were performed, 83 PE for cervical cancer. In our series 54% of women presented with a persistent disease, 38% had a recurrence, 8% recurrence persistence after neoadjuvant chemotherapy; 60% had a central pattern of recurrence, while 40% a lateral one. 40 underwent anterior PE and 43 total PE. 39 women received an IC as urinary diversion, and 44 received an IP. 43 needed a colostomy. *Results:* In our series overall 5 years survival for cervical cancer was 48% *versus* 80% in patients receiving an urinary diversion for transitional cells tumor. Overall the time to the first complication was 1.33 years. According to urinary diversion overall survival was longer for having undergone IP *versus* IC, but survival free of complications was higher for IC with a mean time to the first complication of 2.1 years *versus* 0.8 years of IC (p=0.06). As far as urinary diversion related complication is concerned a total of 45 (54.2%) women experienced a complication, 28 (65.1%) of IP and 17

(43.6%) of IC. In particular 38 (24 *vs*. 14) patients had hydronephrosis, 8 (4 *vs*. 4) had U-I leakage, 1 had a pouch leak, 4 (2 *vs*. 2) had a urostoma stenosis, 1 IC patient had a renal abcess and 2 IP formed stones. Overall 7 patients experienced 2 urinary diversion related complications and 3 more than 2. According to Clavien classification 23.6% of these were Clavien I, 43.6% were Clavien IIIa (needing often the intervention of radiologist), 20% were Clavien IIIb and 12.7 % were Clavien IVa. Considering the occurrence of hydronephrosis and comparing IEO gynecologic series (39 IC *vs*. 44 IP) with IEO urologic series (190 IC *vs*. 115 neobladder) we noted that hydronephrosis occurred in 45.7% of gynecologic group (35.9 % *vs*. 54.5 %) *vs*. 8.2% of urologic group (9.5% *vs*. 7.3%), even if it occurred earlier in urologic group (11.8 months *versus* 19.08 months). Other urinary-related complications owned to IP: 3 urinary leak and 18 (42%) metabolic acidosis requiring medication (mean Na bicarbonate supplementary intake: 2g/d). DISCUSSION 35% of all CC treated will experience recurrent or persistent disease. The rate of recurrence depends on the disease FIGO staging, lymph node involvement, surgical margins, tumor size and deep infiltration. Younger age, better survival expectancy (small [<5 cm] central recurrence), and good hand dexterity should push the choice towards a continent diversion. Surgery radicality quieries (the need to remove from 2/3 to all the vagina or infraelevator PE) determine the impossibility to create an orthotopic ileobladder. The risk of complications and QoL studies are important factors to take into account when urinary diversion is chosen. CONCLUSION There are no guide lines about urinary diversion choice in cervical cancer; literature is insufficient to conclude that a urinary diversion is superior to another considering HRQOL outcomes. In our series overall survival is longer for IP *versus* IC, but survival free of complications is better for IC.

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TREATMENT OF HEMODIALYZED PATIENTS WITH METASTATIC RENAL CELL CARCINOMA WITH MTOR INHIBITORS

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Background: The purpose of this study was to investigate the safety and efficacy of mTOR inhibitors (temsirolimus and everolimus) in patients with metastatic renal cell carcinoma (mRCC) and end-stage renal disease requiring haemodialysis (HD). Renal function plays a crucial role in drug treatments: if renal excretion is significantly reduced, the drug will be eliminated more slowly and the risk of toxicity will increase proportionally to the increased blood concentration of the drug. For these reasons, the treatment of patients with cancer receiving dialysis, is a problem for medical oncologists. A few published data indicating that the use of TKIs (sunitinib and sorafenib) is feasible in this subgroup of patients, with no unexpected toxicity and a good efficacy, are currently available (1). The pharmacokinetics of temsirolimus has been studied only in case series including patients receiving hemodialysis: the study found that after a single dose of 25 mg of temsirolimus as a 30-minute intravenous infusion, neither temsirolimus nor sirolimus concentrations were significantly affected in those mRCC patients receiving HD as compared to those not receiving HD (2). *Patients and Methods:* Between December 2008 and February 2012, 8 patients undergoing HD were treated with temsirolimus and everolimus for mRCC in five Italian Institutions. We retrospectively reviewed the medical records of these patients to evaluate the administered doses of mTOR inihibitors, treatment related toxicities and the clinical response. *Results:* Five patients were males, the median age was 64 years (range 47-79), 7/8 patients had a clear cell histology. All patients were receiving HD, 4/8 pts for bilateral nephrectomy and others for previous chronic renal disease and the time interval between the start of HD and the start of mTOR inhibitors treatment was 37 months. According to Motzer's criteria, six patients were classified as good and intermediate risk. Everolimus was administered at 10 mg with a continuous schedule in five patients; three patients received temsirolimus at 25 mg as a 30-minute intravenous infusion weekly. Two patients received temsirolimus as first-line treatment, one patient as third-line; three patients received everolimus as second-line treatment, one as third-line and one as fourth-line. With regard to tolerability and safety, no unexpected adverse event (AE) was registered and no grade 4 haematological or non-haematological toxicity was reported. The most common grade 1-2 nonhaematological treatment-related AEs were fatigue (5/8 patients), dyslipidemia (4/8 patients), dyspnea (2/8 patients) and hyperglycemia in one case. A grade 3 cutaneous rash was observed in one patient treated with everolimus. The most frequent grade 1-2 haematologic toxicity was anemia (5/8 patients). None of these toxicities led to discontinuation of the treatment. Temsirolimus and everolimus were administrated at any time

regardless of the timing of HD. Among these 8 patients treated with mTOR inhibitors, stable disease was observed in 5 patients. At the time of the analysis, 2 patients had died due to disease progression. The estimated median progression-free survival of this cohort of patients was 6.3 months. *Discussion and Conclusion:* In this small retrospective series of patients with mRCC undergoing hemodialysis during mTOR inhibitors treatment, the incidence of adverse events was acceptable, and a prolonged progression free survival was observed. The use of temsirolimus and everolimus does not seem to be contraindicated in patients with mRCC receiving HD.

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INCIDENCE AND RISK FACTORS OF LYMPHOCELE OF PELVIC LYMPHADENECTOMY DURING ROBOT ASSISTED RADICAL PROSTATECTOMY

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Objective: The aim of this study was to determine the incidence and to evaluate the presence of predictive factors of lymphocele development in patients undergone pelvic lymph node dissection (PLND) during robot-assisted radical prostatectomy (RARP). *Patients and Methods:* From 1st November 2006 to 31st December 2011 we performed 1032 robot assisted radical prostatectomies for prostate cancer. Lymphadenectomy was performed if the risk of lymph node involvement, according to the MSKCC (Sloan Kettering) nomogram, was >4%. 366 patients with a follow-up >3mos, having received standard LND, were considered. All patients received subcutaneous low-dose heparin prophylaxis. Bipolar forceps, monopolar scissors and Weck clips were used during LND. *Results:* The mean follow-up was 25 months. 42 patients (11.47%) presented lymphocele at a mean of 61 days (18-168 days) from surgery: 19 (5.19%) were a- or paucisymptomatic while 23 (6.28%) patients presented with symptoms related to the lymphocele and underwent percutaneous US or CT scan guidance drainage. The drainage was maintained for a mean time of 24 days (7-46 days) 15% of lymphoceles were bilateral. According to the higher diameter 4,7 % of lymphoceles were <4 cm, 76.2% were 4-10 cm, and 18.1% were >10 cm respectively. On the logistic regression model the presence of nodal metastases (8 % *versus* 15%) was significantly higher if the limphocele occurred, while the number of removed lymph nodes (mean 11.61 *versus* mean 13,55) didn't reached the statistical significance (p=0.06); if only the symptomatic lymphocele patients were considered, the number of removed lymph nodes (mean 14.52 lymph nodes) was significantly higher (p<0.01) if compared with the patients without lymphocele. Tumor stage >pT3 was also predictive for the development of lymphocele: 67.5% *vs*. 51.8% (p<0.01). *Discussion:* The occurrence of lymphocele is one of the most frequent complications after robot assisted radical prostatectomy. The rate of delectability depends on the method of screening for lymphocele occurrence: systematic or spontaneous. If symptomatic, it may require percutaneous drainage or even laparoscopic unroofment. Higher number of removed LN, the presence of LN metastasis and extracapsular disease are significantly higher in the subgroup of patients having undergone LND and having successively experienced lymphocele occurrence. Tomic *et al*. showed that the incidence of lymphoceles in patients who had received subcutaneous low-dose heparin is higher if compared with controls. The use of clips or ligatures for ligation of lymph channels is associated with less lymphocele formation if compared to the use of fibrin sealant agents. Our study confirms Patel's observations that SV involvement, EC disease and nodal involvement are predictors of lymphocele occurrence risk in patients undergoing LND. The role of the extension of LND template in increasing the lymphocele risk is debatable as contrasting data are reported in the literature. In our study, the number of removed LN was significantly higher only in symptomatic patients. *Conclusion:* Our data show that pelvic lymph node dissection is associated with a quite high rate of lymphocele formation. In our experience percutaneous US or CT-scan guidance drainage represents the choice treatment of symptomatic patients.

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RISK OF OVERTREATMENT IN CLINICALLY NOT SIGNIFICANT PROSTATE CANCER: SINGLE CENTRE EXPERIENCE

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Aim: Clinically insignificant prostate cancer defined as cT1c stage, Gleason score ≤6, PSA ≤10 ng/ml, and tumor volume ≤0.5 mm is characterized by limited biologic malignancy and, possibly, suitable for non-radical treatment. The purpose of the study was to perform a retrospective analysis of the outcome of patients with clinically insignificant prostate cancer who underwent radical prostatectomy in order to assess the predictors of cancer-related outcome. *Patients and Methods:* From January 2004 to February 2012 we performed 1066 retropubic radical prostatectomies. Among these patients, 124 (12%) had a clinically insignificant prostate cancer, according to the biopsy criteria. Biopsy and specimen Gleason score, prostate biopsy sampling (standard *vs*. saturation), pathological stage, extraprostatic involvement and surgical margin status were evaluated. During follow-up, patients had semiannually PSA sample and clinical evaluation. *Results:* 102 patients (82%) had clinically significant prostate cancer in the prostatectomy specimen, with 82% of the patients having organ-confined disease. Gleason score was 6 in 68% of the cases. Surgical margins were positive in 22 cases (18%) and extraprostatic involvement occurred in 21 cases (17%). Concordance among biopsy and specimen Gleason score was limited, with clinical undergrading occurring in 52 cases (42%), regardless of the biopsy scheme. The median follow-up duration was 52 months. At follow-up, extraprostatic extension and surgical margin status were independent predictors of biochemical recurrence-free survival (p=0.008). *Discussion:* The risk of overtreatment ranges from 0 to 48% according to Literature data. To date, we do not have major variables predictive of clinically insignificant prostate cancer. In our experience, only 18% of the patients undergoing radical prostatectomy for clinically insignificant prostate cancer had clinically insignificant cancer in the prostatectomy specimen, whereas in 17% of the cases we found a high risk disease. *Conclusion:* Low risk prostate cancer does exist. However, predictive variables able to identify appropriately such patients are lacking. The risk of overtreatment is present but currently counterbalanced by the risk of undertreatment.

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EFFECT OF SERENOA REPENS ON THE EXPRESSION OF THE INFLAMMATORY PATTERN IN PRIMARY CELL CULTURES OF HUMAN PROSTATE CARCINOMA

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Introduction and Objectives: The aim of our study was to analyze and to compare the expression of the inflammatory pathways and the proliferative-apoptotic indexes either in classic human Prostate Cancer (PC) cell lines, such as androgen-dependent LnCap and androgen-independent PC3 cell lines or also in primary cultures of human prostate adenocarcinoma cells. On these different settings, we evaluated the effect of LSESr (Permixon) on the inflammatory factors, analyzing whether its possible antiinflammatory activity determines an effect on proliferation and apoptosis. *Materials and Methods:* We homogeneously analysed the mRNA expression of several genes related to inflammation:IL-6,CCL-5(RANTES),CCL-2,COX-1,COX-2,iNOS in LnCaP and PC3 cell lines and primary cultures obtained from 40 patients undergoing radical prostatectomy for PC. From each case, we processed tissue fragments either from PC nodules (named Tumor "T") or from normal tissue (named control "Ct"). Moreover all cultures (PC3,LNCaP and primary cultures) were treated with LSESr (Permixon) at concentrations of 44 and 88 μg/ml and we observed the effect of this drug on the expression of inflammatory-related genes and on cell growth, analysing the proliferation and apoptotic indexes, at different time periods of incubation (24, 48 and 72 hours). Finally, we analysed Nf-kB gene expression by immunofluorescence in PC3 cell line in untreated and treated conditions. *Results:* The first result was that in all cultures (PC3, LNCaP and primary cultures) all these inflammatory-related genes were expressed and all were down-regulated by LSESr. The second result obtained (LNCaP,PC3 and primary cultures) indicated a significant reduction in PC and normal cell counting related to LSESr treatment. Finally, we detected an induction of apoptotic pathway suggested by the caspase-3 activation and an induced activation of Nf-kB through its translocation in the cell nucleus after treatment with LSESr. *Conclusion:* The present study confirmed the role of inflammation in prostate carcinogenesis. For the first time in literature we showed the effect of LSESr on down-regulation of inflammatory-related genes in cell lines and in primary cultures and we showed that the inhibitory effect of LSESr (Permixon) on cell growth could be at least in part associated to the down-regulation of inflammatory-related genes and to the activation of Nf-kB pathway, as well as a pro-death response in prostate tissue.

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MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING OF THE PROSTATE CAN IMPROVE THE PREDICTIVE VALUE OF URINARY PCA3 TEST IN PATIENTS WITH ELEVATED PSA LEVELS AND PRIOR NEGATIVE BIOPSY

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Objectives: To evaluate the role of multiparametric magnetic resonance imaging (MRI) as an additional diagnostic tool to improve the accuracy of urinary PCA3 test in patients with PSA increase and previous negative prostate biopsy. *Patients and Methods:* This is a prospective randomized study on patients with prior negative TRUS-guided prostate biopsy and elevated PSA levels; 180 cases were analysed, all submitted to PCA3 assay. Patients in Group A were submitted to a second random TRUS-guided prostate biopsy,whereas patients in Group B were submitted to a multiparametric MRI examination and then to a second TRUS-guided prostate biopsy. *Results:* At the second biopsy, a histologic diagnosis of PC was found in 26 out of 84 cases (30.9%) in Group A and in 29 out of 84 cases (34.5%) in Group B. In group A sensitivity and specificity of PCA3 score were 68.0% and 74.5% respectively (PPV of 53.1%, NPV of 84.6% and accuracy of 72.6%). In Group B sensitivity and specificity of PCA3 score were 79.3% and 72.7% respectively (PPV of 60.5%, NPV of 86.9% and accuracy of 75.0%). For the PCA3 score, the area under the ROC curve (AUC) was 0.825 (95% confidence interval 0.726 to 0.899) in Group A and 0.857 (95% confidence interval 0.763 to 0.924) in Group B ($p<0.0001$). *Conclusion:* In patients with previous negative biopsy and persistently elevated PSA levels, the use of multiparametric MRI in indicating sites suitable for rebiopsy can significantly improve the sensitivity of PCA3 test for the diagnosis of PC.

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PERMANENT INTERSTITIAL BRACHYTHERAPY IN THE TREATMENT OF LOCALIZED PROSTATE CANCER: OUR EXPERIENCE

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Introduction: Since the eighties the permanent interstitial brachytherapy has been more and more utilized for the treatment of early stage prostate cancer. This has been favored by the development of implantation techniques with the aid of transrectal ultrasound and specific software for Treatment Planning System (TPS). The aim of the study was to evaluate medium and long-term therapeutic efficacy of interstitial brach therapy in the treatment of localized carcinoma. *Patients and Methods:* From March 2001 to January 2012, with a median follow-up of 45.6±31.6 months (range 1.5-120.6), 176 patients with a mean age of 71.0 years (range 47-82) underwent permanent interstitial brachytherapy with I^{125} as a primary treatment for prostate cancer. After the acquisition of morphologic and volumetric data of the gland using transrectal ultrasound, TPS allowed to define the optimal geometry of seed placement under a dosimetric plan. The needles preloaded with radioactive seeds were inserted through transperineal access, with spinal or general anesthesia, using ultrasound guide and fluoroscopy. Patients were selected according to the instructions of the American Society of Brachyterapy: Stage: T1-T2 Age <80 years PSA <10 ng/ml Life expectancy =>10 years; Gleason score <7 Prostate volume <50 cc; Qmax>15; MR/CT negative In selected cases the indication were extended. *Results:* Median D90 152±27 Gy (range 58-217). Currently 122 patients have a follow-up longer than 2 years. 105 patients (86.1%) are free from disease or biochemical recurrence. The 5 years disease-free survival was 88.7%. No patient died from prostate cancer. Univariate analysis showed that PSA ($p=0.5$), Gleason score ($p=0.35$), age ($p=0.98$) and low D90 (<145 Gy) ($p=0.45$) are not significant prognostic factors with regard to biochemical failure (ASTRO). No patient with D90<100 Gy had biochemical recurrence. 8 patients (4.5%) developed grade 3 urinary toxicity and 2 patients (1.1%) developed grade 3 rectal toxicity. *Conclusion:* Permanent interstitial brachytherapy in selected patients with low risk prostate cancer appears to be an effective treatment with results similar to those obtained by radical prostatectomy and external beam radiotherapy.

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CARDIOTOXICITY IN METASTATIC RENAL CELL CARCINOMA (mRCC) PATIENTS TREATED WITH SUNITINIB (SU)

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Background: Cardiovascular events (CVE), *e.g.* CHF (congestive heart failure) and coronary artery disease (CAD),

may occur in up to 10% of patients (pts) treated with sunitinib (SU). Cardiovascular monitoring during SU treatment may underline early signs of myocardial damage. *Patients and Methods:* We have prospectively analyzed pts naïve for therapies with tyrosine kinase inhibitors (TKIs) receiving SU as a treatment for mRCC. Between April 2007 and December 2011, a total of 33 consecutive pts, median age 65 yrs (41-80), were treated with SU. The median duration treatment was 8.3 months (0.4-22.1). All patients were analyzed for CAD risk factors (hypertension, hypercholesterolemia, diabetes, smoking), rhythm disturbances and heart failure. ECG, echocardiography and cardiology consultation were performed at baseline and every three months until progression or SU permanent discontinuation. We prospectively recorded the following pts features: left ventricular ejection fraction (LVEF), cardiovascular history, blood pressure, antihypertensive therapy. For 14/33 pts we also recorded at the same intervals patterns of mitral valve inflow. We defined cardiotoxicity as a reduction of LVEF ≥10%. *Results:* At baseline LVEF media was 66% (85%-55%) which decreased to 61% on SU treatment (77%-45%). This reduction was statistically significant (p=0.003). 16 out of 33 pts (48,5%) had a reduction of LVEF ≥10% on SU treatment. 15 of these 16 pts were asymptomatic and only one showed symptoms of CHF and temporarily discontinued SU treatment. This patient had a global myocardial hypokinesia at echocardiography. At baseline 23 pts (69.7%) had hypertensive disease (HD) but neither this CAD risk factor nor hypercholesterolemia, diabetes and smoking resulted predictive of cardiotoxicity. On SU therapy 5 out of 23 pts worsened the preexisting HD which was controlled with adequate medical treatment and did not determine a discontinuation of SU therapy. Furthermore 7 pts (21.2%) developed this adverse event. 14/33 pts were also evaluated for diastolic function. At baseline we recorded 7 pts (50%) with normal mitral valve inflow pattern and 7 (50%) with impaired left ventricular (LV) relaxation. On SU therapy pts with this last pattern did not experience changes, but 6/7 pts (85.7%) with normal pattern at baseline developed an impaired LV relaxation pattern. *Conclusion:* Cardiac damage is often underestimated but it is manageable with careful cardiovascular monitoring and medical treatment at first signs of myocardial damage. Since an early identification and treatment of pts at risk to develop CHF may reduce this dreadful event and treatment discontinuation, it is important to record CAD risk factors and cardiac function at baseline and to monitor cardiac function during SU therapy. Analysis of diastolic function may play a useful role in early detection of myocardial damage.

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KETOCONAZOLE IN THE TREATMENT OF CASTRATION RESISTANT PROSTATE CANCER (CRPC): EFFICACY OF LOW-DOSES

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Background: The management of rising PSA in CRPC remains controversial. Among second-line hormonal therapy options ketoconazole, an antimycotic that affects the synthesis of androgens and other steroids, has shown direct cytotoxic effects in prostate cancer. This retrospective study describes our experience with low doses of ketoconazole and prednisone treatment for CRPC. *Patients and Methods:* From 4/2007 to 12/2011, 65 patients with progressive CRPC who were previously treated with maximal androgen blockade received 200 mg ketoconazole orally bid with orally replacement prednisone (5 mg bid) and maintained LHRH-agonists. Performance status of all patients was ECOG0. Overall, 34/65 (52.3%) patients had only bone metastases, 12/65 (18.5%) had nodal metastases, 17/65 (26.2%) both and only 2/65 (3.1%) had bone plus lung metastases. All patients had low tumor burden and PSADT >6 months. Thirty-six out of 53 patients with bone metastases received concomitant zoledronic acid. PSA response was defined as a >50% fall in PSA from baseline and PSA nadir was calculated. Progression was defined by objective disease progression or PSA increase of >50% above nadir or >25% above baseline. Patients were monitored clinically and with serial PSA measurements every 1-month. *Results:* Median age was 74.05 (range: 52.8-84.4) years; median baseline PSA was 29.95 (range: 1.18-1348.8) ng/ml; median duration of the treatment was 5.87 (range: 0.57-52.4) months. All pts were evaluable for PSA response. At a median F.U. of 15.4 mos. 19/65 patients (29.2%) showed a decrease in PSA >50%, with a median TTP of 17.23 mos for responders. Overall TTP was 5.86 mos

and it was not affected by metastatic sites (p=0.71). Toxicity was mild and no patients discontinued therapy because of side-effects. Five out of 65 patients had G2 (CTC.AE 4) nausea and moderate elevated transaminases. No acute hepatitis or adrenal insufficiency was observed. *Conclusion:* Our data confirm that low-dose ketoconazole is an effective and well-tolerated treatment in patients with CRPC and should be considered in the subset of patients with low-volume disease and a rising PSA level despite maximal androgen blockade.

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ZERO – ISCHEMIA LAPAROSCOPIC PARTIAL NEPHRECTOMY: PRELIMINARY EXPERIENCE

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Background: Ischemic injury impacts functional outcomes in patients undergone laparoscopic partial nephrectomy. Efforts to reduce ischemia time are necessary to minimize postoperative renal injury. We evaluated the feasibility and safety of laparoscopic assisted partial nephrectomy without hilar clamping. *Patients and Methods:* Clinical data were prospectively collected. Since January 2011, 22 consecutive patients underwent zero ischemia laparoscopic partial nephrectomy through a retroperitoneal approach. In all cases a sutureless haemostasis was performed. *Results:* Zero-ischaemia laparoscopic partial nephrectomy was successfully completed in all cases. The median tumour size was 3.7 cm (range: 2.5-5). Warm ischaemia time was zero in all patients. The median operative time was 175 minutes (range: 120-230) and estimated blood loss was 200 mL. Median hospital stay was 5 days (3-7). There were no intraoperative complications. 3 patients had postoperative complications (delayed renal hemorrhage) that required blood transfusions but not surgical therapy. In 1 patients final pathological examinations revealed a positive surgical margin. Pathology confirmed renal cell carcinoma in all cases. Median pre- and postoperative serum creatinine (0.95 and 1.05 mg/dl) were similar. *Discussion and Conclusion:* Our preliminary experience with zero-ischemia laparoscopic partial nephrectomy is encouraging.

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ACETYLCHOLINE IS A PROMOTING FACTOR FOR HUMAN UROTHELIUM? RESULTS OBTAINED IN THE UROTSA CELL LINE

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Introduction: The urothelium is increasingly recognized as a highly active tissue which responds to various signals and generates and releases mediators contributing importantly to the regulation of bladder function. Specifically, the urothelium of various species has been shown to contain the necessary transporters and enzymes for the synthesis of acetylcholine (ACh) including the vesicular acetylcholine transporter (VAChT) and choline acetyltransferase (ChAT). Beside ChAT, carnitine acetyltransferase (CarAT), which could also synthesize ACh, has been found in the mouse and human urothelium. An autocrine and/or paracrine loop of ACh and muscarinic receptors has been implicated in the remodelling of tissues other than the bladder and may be associated with malignant growth. Against this background, we have used

UROtsa cells, an immortalized cell line derived from normal human urothelium, which is widely used to study human urothelium physiology and pathophysiology, to investigate 1) the presence of the non-neuronal cholinergic muscarinic system, 2) the signaling of muscarinic receptors and 3) the involvement of muscarinic subtypes and specific signaling pathways in urothelial proliferation responses. *Materials and Methods:* UROtsa cells were cultured in D-MEM supplemented with 5% fetal bovine serum. Cells were treated for up to 3 days with different drugs: the agonist carbachol (CCh), the non selective antagonist atropine and the M3 selective antagonists darifenacin and J104129, and different selective antagonists of ERK and PI3-Kinase pathways. Total RNA was extracted and retrotranscribed, to evaluate the gene expression of the chosen cholinergic markers (muscarinic receptor, VAChT, ChAT, CarAT) by quantitative RT-PCR (Q-RT-PCR). Immunofluorence was conducted to evaluate the protein expression of the cholinergic enzymes. Adenylyl cyclase activity and IP3 measurement were carried out using commercially available radioimmunoassay kits (Perkin Elmer, Milano, Italy) on UROtsa cell extracts. Cell proliferation was determined by the evaluation of [^{3}H]- thymidine incorporation and by the MTT adsorbance assay. The statistical analysis was carried out using the one-way ANOVA, with a *post-hoc* test for multiple comparisons, considering $p<0.05$ as threshold for significant difference. *Results:* Q-RT-PCR studies demonstrated the presence of an ACh synthesis/storage mechanism in UROtsa cells. Indeed, we detected mRNA for ChAT, CarAT and muscarinic receptor subtypes M1-M5 (range of expression that is: M3>M2>M5>M1>M4), while no PCR product was obtained for VAChT. Immunofluorescence confirmed the presence of ChAT and CarAT at the protein level. By radioimmunoassay, we demonstrated that muscarinic receptor mRNAs were translated into their proteins, functionally linked to their known second messenger pathways. Effects of muscarinic receptor stimulation on UROtsa cell proliferation were explored and results demonstrated that CCh (1-100 μM) concentration-dependently enhanced cell proliferation. This phenomenon was antagonized by the non selective muscarinic receptor antagonist atropine and the M3-selective antagonists darifenacin and J104129. The increase in cell proliferation evoked by 50 μM CCh was blocked by either 1 μM PD98059 or 1 μM U0126, indicating that the stimulation of proliferation involved the ERK pathway. Similar experiments with consistent results for all three PI3-kinase inhibitors demonstrated involvement of that pathway as well. *Discussion and Conclusion:* UROtsa cells expressed the machinery for ACh synthesis and functionally active muscarinic receptors. The cholinergic receptor agonist CCh stimulated UROtsa cell proliferation *via* a pathway apparently involving M3-receptors, ERK and PI-3 kinase. Our results on the stimulation of urothelial cell proliferation induced by cholinergic agonists and mediated by ERK and PI3 kinase pathways pose attention on the role of ACh as a possible cell proliferation promoter in different pathological scenarios, either in benign settings as well as in promoting the progressive cell degeneration giving rise to the urothelial cancer.

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IS INVASION OF MUSCULAR LAYER REALLY EFFECTIVE IN PROGNOSTIC EVALUATION OF MICROPAPILLARY TRANSITIONAL CELL CARCINOMA AFTER CYSTECTOMY?

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Introduction: Micropapillary transitional bladder cancer is one of the most aggressive subtypes of urothelial carcinoma. Almost rare, it is considered not responsive to conservative treatment (*e.g.* BCG). Our aim was to evaluate if evidence of pT1 disease after radical cystectomy was associated to a better prognosis in relation to pT2 disease. *Patients and Methods:* From 1998, we stored perspectively data about all diagnoses of micropapillary bladder carcinoma (n=78). In 23 cases, radical cystectomy has been performed as first treatment. At definitive analysis pT1 (n=7) or pT2 (n=16) were detected, by confirmation of micropapillary disease features. In every case, an uretero-ileo-cuteaneostomy was performed (Wallace II type). Mean follow-up period was 36 months (3-103). Analysis of OS in two groups was carried out by *t*-test and Mann-Whytney test. *Results:* Mean OS in pT1 group was 32.86 m (15-71), in pT2 38.2 (3-103). In fact in both tests, *p*-value was quite high (*t*-test: 0.35, *U*-test: 0.44), showing a quite significant similarity in prognosis between two groups. *Discussion:* A quite high *p*-value in two tests could suggest that also increment of number of patients would not bring a quite significant change in results. Absence of invasion of muscular layer in fact is not related to better prognosis, and in these patients a quite strict follow-up must be proposed. At least, follow-up must be strict as in muscle-invasive disease. On the other side, in literature (level 1a, EAU Guidelines) debate about use of adjuvant chemotherapy is still going on. In fact, we suggest that, if performed, adjuvant chemotherapy could be proposed also in pT1 patients. So, it could be confirmed that radical cystectomy is mandatory not only because BCG is not effective, but also because NMI disease seems so aggressive as pT2 disease.

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IS SURGICAL APPROACH TO "ATYPICAL" METASTASIS FROM RENAL CELL CARCINOMA EFFECTIVE?

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Introduction: Clinical characteristics and oncologic results are objects of this study in patients who underwent surgical removal of metastasis from renal cell carcinoma (RCC) in atypical sites (atypical metastasis – AM – *i.e.* metastasis in sites other than chest, liver, bone, adrenal, brain, kidney, lymph nodes), compared to patients submitted to metastasectomy due to a lung metastasis (LM). *Patients and Methods:* We collected data from an institutional database of about 1800 patients surgically treated for a RCC. We retrospectively identified 37 cases undergone metastasectomy for AM, and 57 patients operated for LM. We compared clinico-pathological features of the primary RCC and metastasis and Cancer Specific Survival (CSS) from metastasectomy of patients with AM and LM. We performed univariate and multivariable analysis applying a Cox regression model to evaluate CSS. *Results:* The patients with AM and LM were followed for an average of 40.8 and 50.7 months from metastasectomy, respectively (p=0.372). No significant differences between patients with AM and LM were found in the characteristics of the primary tumour. In the cases with AM and LM the diagnosis was simultaneous with that of the primary tumour in 32.4% and 24.6%, (p=0.40) respectively, and, when metachronous, occurred at an average distance of 53.4 and 44.3 months (p=0.370). More frequently, in the cases with AM other metastases had been diagnosed in the previous medical history (35.2% *vs*. 8.8%, p=0.001) or simultaneously (48.6% *vs*. 8.8%, p=0.001). *Discussion:* CSS from metastasectomy was affected by the synchronicity in diagnosis between metastasis and primary tumour, and by the simultaneous presence of other metastases, while the type of metastasis (AM *vs*. LM) did not affect CSS. In fact, metastasectomy in atypical metastasis is effective at least as in lung metastasis. AMs are an exceptional presentation of metastatic RCC, but the role of surgery is similar to that of pulmonary metastases. In these cases, metastasectomy is accepted as a possible care, and in AM the CSS after metastasectomy is alike.

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RATIONAL BASIS AND FIRST CLINICAL EXPERIENCE WITH AUTOLOGOUS SPECIFIC T-CELL THERAPY IN ADVANCED RENAL CELL CANCER

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Background: Although renal cell carcinoma (RCC) is considered to be an immunogenic tumor, T cell-based immunotherapy (IT) in metastatic RCC have so far shown limited success. We recently demonstrated the feasibility of expanding large amounts of autologous anti-tumor cytotoxic T-cells (CTLs), derived from peripheral blood of patients affected by different types of solid tumor. *Patients and Methods:* CTLs were generated stimulating CD8-enriched lymphocytes with Dendritic Cells pulsed with fresh autologous apoptotic tumor cells, in the presence of IL-12 and IL-7. Specific anti-tumor CTLs were then rapidly expanded in an antigen-independent way. The major advantage of this approach is that it involves the use of whole tumor cells as the source of tumor antigens, circumventing the requirements for the definition of specific tumor antigens or the presence of a defined HLA specificities. In a pilot study, we have treated with specific anti-tumor CTLs several patients with different tumors, including one patient affected by RCC. *Results:* Here we briefly report on the case of a 62 years old male with clear-cell RCC (diagnosed in 1999 and initially treated with nephrectomy) who, in 2005, had large tumor masses in the residual kidney and soft tissues as well as lung metastases, in progression after the failure of 2 lines of conventional therapy (namely, IFN-alfa plus Vinblastine and IL-2). Patient received lymphoablation with fludarabine and cyclophosphamide followed by CTL infusions on day +14 and +28 and every 2 to 4 months thereafter (median CTL n. 1.6×108, range 0.83-4). Disease remained stable according to RECIST criteria for 3 years, then progressive renal dysfunction, mainly due to an increase in the kidney lesions, occurred, while all the other metastatic sites remained stable. Patient underwent a second nephrectomy and continued CTL therapy during dialytic replacement therapy. Disease remained stable for additional 3 years, then progressed at many sites, including brain. Treatment with Sorafenib was attempted, with no benefit and patient died of progressive disease in a few months. All the CTL infusions were well tolerated, and there was no evidence of clinically significant autoimmunity. The adverse effects were minor and did not require medical intervention. Immunological monitoring demonstrated that CTL infusions can induce an increase in specific anti-tumor response measured in the peripheral blood of the treated patient. Since that first case, two additional patients have been treated recently, within an ongoing compassionate use program in RCC, confirming the feasibility and safety of the procedure. Enrollment is presently continuing at our site. *Conclusion:*

Treatment with specific autologous antitumor CTLs is safe and induced immunological response and clinical benefit in one patient with RCC. The ongoing study will define, in a larger series. whether this form of immunotherapy has a role in advanced heavily pre-treated RCC patients.

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ASSOCIATION OF PREOPERATIVE PLASMA LEVELS OF INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN-3 (IGFBP-3) WITH GLEASON SUM UPGRADING

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Background: About 43% of men with low Gleason grade prostate cancer (PCa) at biopsy will be finally diagnosed with high-grade PCa at radical prostatectomy (RP). Gleason sum at RP is a good indicator of biochemical recurrence and poor clinical outcome. Therefore, there is a need to improve clinical evaluation of PCa aggressiveness in order to choose an appropriate treatment. To this aim an easy-available tool is represented by circulating biomarkers. Among these, the best candidates are some molecules involved in PCa pathogenesis such as IGFBP-2 and IGFBP-3, IL-6, and its soluble receptor (SIL-6R). *Patients and Methods:* In this study, we evaluated the ability of preoperative IGFBP-2, IGFBP-3, IL-6, and SIL-6R serum levels to predict Gleason score upgrade in PCa patients undergoing radical prostatectomy. During a 1-year period, a total of 52 subjects with PCa, age ranging from 51 to 75 (median=64 years), were enrolled at our institution. Inclusion criteria were no evidence of active infection or inflammatory disease, no neo-adjuvant androgen therapy, PSA <20 ng/ml, clinical stage <IIc. Patients were classified by clinical stage, pathologic Gleason sum, and significant GSU. Significant GSU is defined as a Gleason sum increase between biopsy and RP either from <6 to >7 or from 7 to 8.Clinical stage was assigned by the attending urologist according to the 2002 TNM system. Between 14 and 16 needle biopsy cores were obtained under transrectal-ultrasound (TRUS) guidance: 40 (74%) had 14 cores taken and 15 (27%) had 16 cores taken. Primary and secondary Gleason score were assigned by the same pathology *Results:* We found that IGFBP-3 median levels were significantly lower in patients who showed Gleason upgrading from biopsy to RP (p=0.024). We also found an association between biopsy T-stage and Gleason Upgrade (p=0.011). Using multivariate logistic regression model, we demonstrated that the association of IGFBP-3 serum levels together with biopsy T-stage and biopsy Gleason score was useful to calculate a prognostic risk score. ROC curve analysis of risk score showed a good ability to predict GSU (AUC=0.81; 95% CI 0.69-0.93). *Discussion and Conclusion:* Our results suggest that preoperative IGFBP-3 circulating levels determination may be useful to predict Gleason score upgrading alone and/or in combination with biopsy T-stage and biopsy Gleason score.

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PROSTATE CANCER BEYOND SURGERY. PSYCHOSOCIAL PROBLEMS AND UNMET NEEDS

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Background: Prostate cancer is the most common neoplasm in male population after the fifth decade of life. Despite great advances in medical and surgical treatments, a prostate cancer

diagnosis still involves a profound alteration of the psychological status of the patient, considering also the important role of prostate in personal and social life. The tendency to underestimate emotional distress in cancer patients has been repeatedly emphasized. This trend deprives patients of the opportunity to undergo psycho educational and psychotherapeutic interventions of proven effectiveness. Aim of this study is therefore the assessment of the patient's unmet needs and distress, especially with regard to the specific complications of radical prostatectomy such as urinary incontinence and erectile dysfunction. *Patients and Methods:* From 2008 to 2010, 120 patients (mean age 65.97, SD 5.9) were enrolled in the study for a psycho oncological evaluation. All patients underwent retropubic radical prostatectomy for organ-confined prostatic cancer about one year before and were free of malignancy at the moment of the enrollment. After the surgical treatment at the third consecutive rise in PSA, 24 patients underwent radiotherapy, 19 hormonal therapy and 1 chemotherapy. All participants administered a semi-structured interview, properly designed for the study, on unmet needs and a battery of self-assessment instruments such as the FACT-P and the Hospital Anxiety and Depression scale respectively to assess the health-related quality of life and to detect states of depression and anxiety. *Results:* The interview showed that although 77% of patients became affected by impotence and 58% by urinary incontinence they were overall satisfied with the information received at the moment of the diagnosis and treatment. 87% reported having had an active role in the treatment choice, 94% believed to have been given adequate information to choose between different treatment options, 85% thought to have been adequately prepared for the adverse affects of the treatment, 90% estimated that doctors have given attention to their needs for information as to the recent positive changes in the doctor-patient communication field. In a limited percentage of cases, however, 23% of patients highlighted unresolved psychosocial problems such as the reduction of self-confidence as result of the diagnosis and treatment, 16% concerns about the diagnosis, 10% a pessimistic vision of the future, 10% a lack of acceptance of the disease, 25% heavy negative emotional effects related to impotence and incontinence and 17% sexual problems that might affect the relationship with family members. The presence of unmet needs and negative psychosocial consequences of the intervention was associated with worse general and specific quality of life and higher levels of anxiety and depression. *Discussion and Conclusion:* In this study a detailed investigation of the emotional state and unmet needs through a properly designed interview that documented in a significant proportion of patients the presence of difficulties and problems whose clinical significance is suggested by its association with worse quality of life and greater severity of psychopathological symptoms. The results suggest that it is very important to foster a good fit to pay attention both to the adequacy of information and informed consent in the short to medium-term, to psychological needs and the psychosocial consequences of diagnosis and treatment in follow-up also in patients with a better prognosis. This possibility is certainly achievable through a virtuous and effective integration between urology and psycho oncology units.

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SYSTEMATIC-EVALUATION OF THREE SOFTWARE-SOLUTIONS FOR AUTOMATIC SEGMENTATION FOR REDELINEATION OF TARGET AND OAR IN PROSTATE-CANCER

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Aim: To validate, in the context of adaptive radiotherapy, three commercial software solutions for atlas-based segmentation through a comparison with manual delineation of target and OAR in five patients affected by prostate tumor. *Patients and Methods:* Five previously treated high-risk prostate cancer patients (PSA>20 ng/mL, Gleason score 8-10 or c/pT3a/b) were enrolled in the study. The clinical target volume (CTV) encompassed the prostate and seminal vesicles (definitive irradiation, three patients) or prostatic bed (post-operative irradiation, two patients) and pelvic lymph-nodes. The defined organs at risk (OARs) were: rectum, bladder, femoral heads and bowel. In addition to the treatment planning CT (pCT) images, one CT image set was acquired for each patient during the RT course. An experienced physician manually outlined on the pCT and replanning CT (rCT) all the volumes of interest (VOI). These VOIs represented our atlas for the automatic contouring (AC) of the replanning CT. We used three software solutions (VelocityAI 2.6.2 (V), MIM 5.1.1 (M) by MIMVista corp and ABAS 2.0 (A) by CMS-Elekta to generate the AC. All the VOIs obtained with AC were successively corrected manually. Several times these were calculated and recorded: 1) for *ex novo* ROIs definition on rCT; 2) for generation of AC by the three software solutions; 3) for manual correction of AC. To compare the quality of the volumes obtained automatically by the software solutions and manually corrected with those drawn from scratch on rCT, we used the following indices: overlap coefficient (DCS), sensitivity, inclusiveness index, difference in volume, and differences of displacements on three axes (x, y, z) from the isocenter. *Results:* The time savings for all three softwares, compared to the manual contouring from

scratch, are statistically significant. On average, the shortest time it takes for the generation of automatic contours and for manual correction is always obtained with MIM. In regards to the overlap (quality) of volumes, the organs that are closer to the volumes generated manually by the physician are the femoral heads, in all software solutions. Those most susceptible to change are represented by the bowel and rectum. Furthermore, a greater uncertainty in the automatic definition of the contours has been observed in both the cranial and caudal areas. *Conclusion:* From a clinical point of view, the automated contouring workflow was shown to be significantly shorter than the manual contouring process from scratch, even though manual correction of the VOIs is always needed. For a prostate patient this is about 40 minutes less. For all patients, the time saved by using the software products was comparable and, compared to manual contouring, was statistically significant.

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THE GENITOURINARY DISEASES HEALTH-CARE AMONG PATIENTS AND GENERAL PRACTITIONER

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Introduction: A general awareness of the most common genitourinary diseases is often lacking.The aim of the present study was to investigate the attention of the general practitioner and of the patient to the genitourinary diseases. An incomplete medical history and/or an inadequate physical examination might be responsible of late diagnosis and improper management. *Patients and Methods:* A self administered questionnaire was obtained by our outpatients before the urological visit. As a preliminary step we administered a very simple questionnaire consisting of four multiple choice questions: 1) Did your general practitioner examine your external genitalia in the last five years? Did you ask for this examination? 2) Did your general practitioner prescribe any clinical investigations? 3) Have you ever seen blood in your urine? Did you advise your doctor? 4) How long time did elapse between the first symptom and our councelling? The study should be closed if less than 5 patients among the first 20 showed an improper attention to genitourinary pathology, otherwise, 200 consecutive patients at least should be entered. A further structured interview was planned in the case of doubtful results. *Results:* From December 2011 to February 2012, 327 questionnaires were obtained from 358 patients with a compliance of 91.3%. The median age of the patients was 61 years (range: 15-91). Two hundred fiftyfive (78%) were men. Out of 327 patients only 72 (22%) underwent a physical examination comprehensive of the external genitalia in the previous five years. The remaining 250 (76.4%) patients were not examined and, more relevant, they did not ask for. Forty-nine (63.6%) out of the 77 patients were examined on their specific request. Only 172 (52.6%) patients underwent laboratory and/or imaging assessment before urological councelling. Gross haematuria was the main urological symptom in 91 (27.8%) of cases. The general practitioner was not adviced of patients' symptom in 13% of cases and, when informed, a urological assessment was required in only 47%. *Discussion and Conclusion:* Our preliminary survey point out a limited attention to the genitourinary diseases both from the general practitioner and the patient. Noteworthy, in case of gross haematuria 20% of the patients did not inform the family doctor and a urological assessment was indicated in only 50% of cases.

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PLASMATIC SIL 6R/IL-6 RATIO AS A POTENTIAL PREDICTOR OF HIGH GLEASON SUM AT RADICAL PROSTATECTOMY

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Background: Approximately 40% of males with low Gleason grade clinically localized prostate cancer (PCa) at biopsy were finally diagnosed with high Gleason grade PCa at radical prostatectomy (RP). Therefore, a more reliable assessment of the Gleason grade prior to RP is required. Readily available modalities such as circulating biomarkers may be useful for this purpose. The aim of this study was to evaluate the ability of preoperative interleukin 6 (IL-6) and its soluble receptor (sIL-6R), as well as urokinase-type plasminogen activator (u-PA), its receptor (u-PAR) and the inhibitor (PAI-1) to predict Gleason score upgrading. *Patients and Methods:* A total of 51 PCa patients with biopsy Gleason score ≤7 were studied. Preoperative serum samples were collected prior to digital rectal examination (DRE) and TRUS. Blood was collected into non-heparinized tubes and serum was separated within 1 h of blood collection. The serum was stored at –80˚C and then

thawed just prior to testing. Serum levels of PSA, free-PSA and IL-6 were measured using the Immulite 2000 automated assay (DPC, Los Angeles, CA, USA). The concentrations of sIL-6R (R&D Systems, Minneapolis, MN, USA), uPA, uPAR and PAI-1 (Assaypro, Winfield, MO, USA) in serum were determined according to the manufacturer's instructions using the ELISA test. Every sample was run in duplicate and the mean was used. The differences between the two measurements were minimal. *Results:* GS upgrading was defined as a Gleason sum increase between biopsy and RP from ≤7 to >7, since this is important for the therapeutic strategy. On this basis, an upgrade was noted in 5 (10%) samples. Median sIL-6R values were found to be significantly higher in patients with GS upgrading (difference in medians, 28.40 ng/ml; 95% CI, 5.60-49.44; p=0.024). The association between sIL-6R and GS upgrading became more significant by using the sIL-6R/IL-6 ratio (difference in medians, 7.77; 95% CI, 1.72-11.28; p=0.011). Sensitivity and specificity of sIL-6R and the sIL-6R/IL-6 ratio were explored by ROC curve analysis (Figure 1).

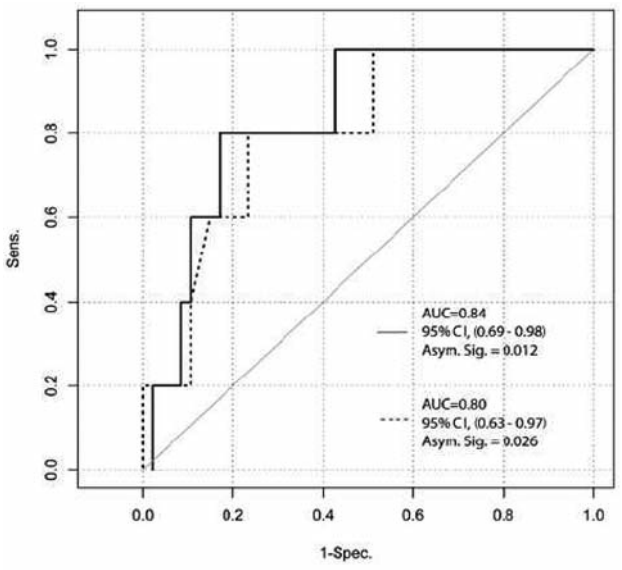

Figure 1. *ROC analysis comparing sIL-6R (--) and sIL-6R/IL-6 ratio (–).*

The results indicated an extremely good ability to predict the probability of biopsy Gleason sum upgrading of the two parameters (sIL-6R: AUC=0.80; 95% CI, 0.63-0.97; p=0.026. sIL-6R/IL-6 ratio: AUC=0.84; 95% CI, 0.69-0.98; p=0.014). The optimal cut-off point for sIL-6R was 76.5 ng/ml, providing a sensitivity of 80% and a specificity of 76%, whereas for the sIL-6R/IL-6 ratio the optimal cut-off point was 13.5 with comparable sensitivity (80%), but higher specificity (83%). Discussion and *Conclusion:* sIL-6R may be a significant circulating biomarker employed to predict GS upgrading in patients with a biopsy GS ≤7. Moreover, this ability appears to be enhanced by calculating the sIL-6R/IL-6 ratio. These findings may provide an additional 'staging tool' for PCa patients, which may be of great significance in guiding clinicians' treatment choices, according to current guidelines.

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CHANGES IN HEALTH-RELATED QUALITY OF LIFE OVER THE FIRST YEAR IN ACTIVE SURVEILLANCE

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Background: The importance of the assessment of Health-Related Quality of Life (HRQoL) has been fully acknowledged when considering the implications of prostate cancer treatments. In particular, the HRQOL of patients undergoing Active Surveillance (AS) is currently under evaluation and data are still sparse. The aim of this study was to evaluate changes in HRQoL during the first year in AS, also in comparison with data reported in the literature. *Patients and Methods:* Between November 2007 and January 2012, 132 patients were included in PRIAS-QoL study and completed self-report questionnaires at enrolment in AS protocol (Time 0). Evaluations after 10 (Time 1) and 12 months (Time 2 - after the first re-biopsy) were completed by 99 and 69 patients, respectively. Validated questionnaires assessing quality of life and psycho-social issues were administered, including Functional Assessment of Cancer Therapy – Prostate Version (FACT-P), used to measure HRQoL in terms of: physical wellbeing (PWB), social wellbeing (SWB), emotional wellbeing (EWB), functional wellbeing

(FWB), and wellbeing related to prostate cancer therapy symptoms (PCS). Descriptive analyses were performed. Correlation analyses were conducted to analyse the possible association between FACT-P subscales and PSA (ng/ml). Repeated measure analyses of variance were performed to test changes over time. Chi-square test was used to compare our data to FACT-P mean scores reported in another study (Lee, *et al*.) including patients undergoing radical prostatectomy (RP), external beam radiotherapy (EBRT), and interstitial brachytherapy (IB). Comparisons were tested as follows: a) AS to RP, EBRT, IB at T0; b) AS at T1 to RP, EBTR, IB at 12-month follow-up. *Results:* The mean age of study population at Time 0 was 66.8 years (median 67, range 47-81). Descriptive data for FACT-P normalized scores are reported in Table I.

Table I. *Descriptive analyses for FACT-P normalized scores (range 0-4).*

	Mean (SD)		
HRQoL	T0	T1	T2
PWB	3.9 (0.3)	3.8 (0.3)	3.9 (0.2)
SWB	2.9 (0.7)	2.7 (0.9)	2.9 (0.7)
EWB	3.1 (0.6)	3.2 (0.6)	3.3 (0.5)
FWB	2.7 (0.7)	2.7 (0.6)	2.7 (0.5)
PCS	3.3 (0.4)	3.3 (0.6)	3.3 (0.7)

No significant correlation was found between PSA and FACT-P. Scores that significantly changed over time were SWB and EWB, which increased from T0 and T1 (respectively p=0.001, p=0.0442) and from T0 to T2 (respectively p=0.014, p=0.0022). Repeated measure analyses of variance did not show significant changes between Time 1 and Time 2 for any of the subscales of the FACT-P. The increase in EWB showed in our data was reported also by Lee at one-year follow-up from RP (p=0.0005). When we compared means of scores of patients in AS with patients who underwent RP, IB, EBRT, we found no significant differences both at entrance in AS/before the treatment, and at follow-up evaluations. *Conclusion:* In accordance with relevant literature, our data, does not confirm the concern about potential negative impact of AS on quality of life: patients in AS did not show lower wellbeing compared to patients undergoing radical therapies. Levels of HRQoL reported by patients undergoing AS are high, in particular as far as physical and emotional wellbeing are concerned.

Prostate Cancer Program, Multidisciplinary Clinic Team at Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan; Foundations I. Monzino and ProADAMO.

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EFFECT OF DECUBITUS ON PAIN DURING TRANSRECTAL ULTRASOUND GUIDED PROSTATE BIOPSY

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Introduction: Transrectal ultrasound (TRUS)-guided prostate biopsy can be perfomed in different positions like lithotomy position, left or right lateral decubitus. Our primary objective was to assess whether patients' pain perception differs as the decubitus changes (lithotomy *vs*. left lateral decubitus). The secondary objective is to assess whether the pain is caused by the probe insertion, the core sampling or both. *Patients and Methods:* We enrolled 96 men undergoing TRUSguided prostate biopsy in our center, who accepted to sign an informed consent. Patients were randomized to perform the biopsy in lithotomy position (Group 1) or in left lateral decubitus (Group 2). All patients received a TRUS-guided periprostatic nerve block (PPNB) before core sampling. At the end of procedure we assessed pain felt at the time of probe insertion and at the time of sampling by using a ten-point visual analog scale (0-9 VAS). *Results:* Patients of both groups were comparable regarding age, total prostate-specific-antigen levels and volume prostate and number of cores. VAS scores at the time of probe insertion were lower in Group 1 than in Group 2 (mean, 1.62 *vs*. 4.85; p<0.001), while VAS scores at the time of core sampling were equal in Group 1 and Group 2 (mean, 0.24 *vs*. 0.15; p=0.342). In both groups VAS scores at the time of insertion of the probe were significantly higher than VAS scores at the time of core sampling (mean, 1.62 *vs*. 0.24; p<0.001 in Group 1 and 4.85 *vs*. 0.15; p<0.001 in Group 2). *Discussion:* In contrast to other studies which described left lateral decubitus as less painful, in our experience patients who underwent a prostate biopsy in the lithotomy position reported less pain than patients in left lateral decubitus. Furthermore our study emphasizes that the probe insertion is the most annoying moment of the prostate biopsy, suggesting the importance of PPNB, regardless of decubitus.

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ACTIVE SURVEILLANCE: IS HEALTH-RELATED QUALITY OF LIFE ASSOCIATED WITH ADJUSTMENT TO CANCER?

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Background: Health-related quality of life (HRQoL) is described as the extent to which one's usual or expected physical, emotional, and social well-being is affected by a medical condition or its treatment. HRQoL has been associated with patients' style of coping with cancer. The aim of this study was to evaluate whether Active Surveillance (AS) patients' HRQOL after 10 months is associated with styles of coping with cancer as measured by mental adjustment to cancer, entailing appraisal of the implications of cancer, the ensuing reaction, and involuntary emotional reactions. This model identifies five strategies, namely: fighting spirit (FS), anxious preoccupation (AP), fatalism (FAT), helpelessness/hoplessness (HH) and avoidance (AV). *Patients and Methods:* Between November 2007 and January 2012, 145 patients entered the PRIAS Quality of Life (QoL) study ongoing at the Prostate Cancer Program of Fondazione IRCCS Istituto Nazionale dei Tumori; 95 patients completed the assessment after 10 months follow-up (Time 1), including: a) Functional Assessment of Cancer Therapy – Prostate Version (FACT-P), used to assess HRQoL, in terms of: physical wellbeing (PWB), social wellbeing (SWB), emotional wellbeing (EWB), functional wellbeing (FWB), and wellbeing related to prostate cancer symptoms (PCS); b) Mini Mental Adjustment to Cancer scale (Mini-MAC), evaluating FS, AP, HH, FAT and AV. A global score (Q-score) (see Barnet *et al*. for definition) was calculated by using the standardized scores of the distributions for both Fact-P (Q-HRQoL) and Mini-MAC (Q-ADJ), both at Time 1. Patients who had a Q-HRQoL less or equal to 25th percentile of the distribution of Q-HRQoL were identified as "low-Q-HRQoL", while patients with scores higher than 25Th percentile were identified as "normal-Q-HRQoL". Chi-square tests were performed to test the association between HRQoL and adjustment to cancer. Results. The distribution of the Q-ADJ (mean=–0.02, SD=1.96) was divided into 4 groups: from the minimum value -6.41 to –1.96 (group 1=very low Q-ADJ), from –1.96 to –0.02 (group 2=low Q-ADJ), from –0.02 to 1.96 (group 3=high Q-ADJ), from 1.96 to the maximum value 3.17 (group 4=very high Q-ADJ). The percentage of patients with low-Q-HRQoL (Figure 1) were as follows: a) group 1=53.8% (7 patients out of 13); b) group 2=27.6% (8 out of 28); c) group 3=15.4% (6 out of 39);d) group 4=0% (no patients out of 13). Chi-square test showed a statistically significant association of worse adjustment to cancer with lower HRQoL (p=0.0001).

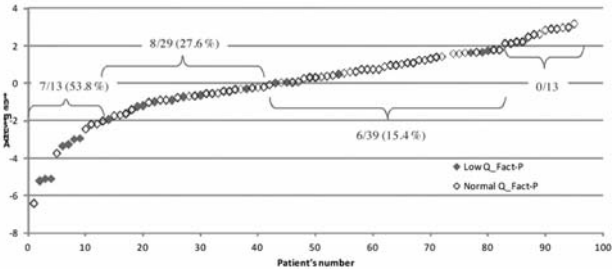

Figure 1. *Distribution of patients based on low/normal QoL and adjustment of cancer.*

Conclusion: Patients undergoing AS generally report a satisfying HRQoL. Patients who show a more active and flexible style of adjustment to cancer report higher satisfaction with their level of wellbeing than those who find it difficult to adjust to their cancer. Those men may benefit from psychological counseling aimed at acquisition of more functional coping strategies.

Prostate Cancer Program Multidisciplinary Clinic Team at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Foundations I. Monzino and ProADAMO.

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THE RISK OF LOW HEALTH-RELATED QUALITY OF LIFE IN PROSTATE CANCER PATIENTS ON ACTIVE SURVEILLANCE

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Background: The potential anxiety and psychological distress that could stem from observational management of prostate cancer (PCa) are still debated. Different studies showed that patients who choose Active surveillance (AS) report similar or higher levels of Health-Related Quality of Life (HRQoL) compared to patients who choose other therapeutic options (such as prostatectomy, radiotherapy or brachyterapy). Nonetheless, a minority of patients report some level of psychological distress. The aim of this study is to evaluate the individual factors that can be associated with the risk for AS patients to experience low levels of HRQoL. *Patients and Methods:* Between Nov 2007 and Jan 2012, 145 patients entered the PRIAS QoL study, 132 completed questionnaires at enrollment (T0) and 95 completed the assessment after 10 months follow-up (T1). The following questionnaires were administered: a) A semi-structured interview including questions related to demographic features, personal experiences and motivation to enter PRIAS (Time 0); b) Functional Assessment of Cancer Therapy – Prostate Version (FACT-P), measuring HRQoL; subscales: physical wellbeing, social wellbeing, emotional wellbeing, functional wellbeing, and wellbeing related to prostate cancer symptoms. A Q-score (see Barnet et al. for definition) was calculated (Q-HRQoL) for Time 1. The 25th percentile was used as cut-off for Q-HRQoL score, *i.e.* scores below 25th percentile=low Q-HRQoL, above 25th percentile=normal Q-HRQoL; c) Mini Mental Adjustment to Cancer scale (Mini-MAC), assessing adjustment to cancer, subscales Fighting Spirit, Helplessness/Hopelessness, Anxious Preoccupation. A Q-score was calculated (Q-ADJ) for Time 1. The 25th percentile was used as cut-off for Q-ADJ score, *i.e.* scores below 25th percentile=low Q-ADJ, above 25th percentile=normal Q-ADJ. Prostate Specific Antigen (PSA) as measured at Time 0 was collected from medical records. Kruskall-Wallis test was performed to evaluate the associations between demographic features, personal experiences, motivation to enter PRIAS and adjustment to cancer on one side and HRQoL on the other side. A logistic regression was performed to evaluate the variables that increased the risk of low HRQoL at 10 month-follow-up. *Results:* Kruskall-Wallis test showed several significant correlations between demographic features, personal experiences, motivation to enter PRIAS and adjustment to cancer and HRQoL. Amongst these, the ones that contributed to the best model were: a) the presence of a partner which was correlated with high SWB score (mean ranks 24.63 *vs*. 42.26, p=0.0410); b) presence of comorbidities which was correlated with low PWB score (mean ranks 44.24 *vs*. 34.89, p=0.0381). The variables included in the best multivariate logistic model for HRQoL at Time 1 (total p=0.0002) were: Q-ADJ (continuous variable OR=0.54, p=0.0018), PSA (continuous variable, OR=1.17, p=0.4311), presence of partner (OR=0.15, p=0.0484), presence of co-morbidities (OR=0.21, p=0.0594). The rock curve for the model is showed in Figure 1 (AUC= 0.753, 95%CI: 0.654-0.836).

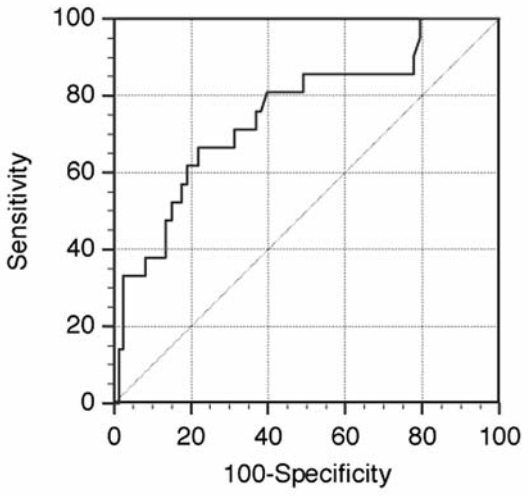

Figure 1. *Rock curve for regression model (AUC= 0.753, 95%CI: 0.654-0.836).*

Conclusion: A negative style of adjustment to the idea of living with ("untreated") cancer and increases the risk of experiencing low HRQoL. The presence of comorbities did contribute to worse HRQoL in AS, probably because it was specifically assessed by referring to PCa. PSA level at entrance in AS seem to influence the risk (17%) of experiencing low HRQoL. Patients may have protective factors such as the presence of a partner (which decreases the risk of having low HRQoL). Patients entering AS protocols could be helped in clarify how they are dealing with their cancer and whether they have the psychological and emotional support they may need in order to prevent the risk of impairment in their quality of life following cancer diagnosis and observational management of PCa.

Prostate Cancer Program Multidisciplinary Clinic Team at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; Foundations I. Monzino and ProADAMO.

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COMPARISON OF CANCER DETECTION RATES BETWEEN TRANSPERINEAL TEMPLATE *VERSUS* MD ANDERSON PROTOCOL TRANSRECTAL PROSTATE BIOPSIES

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Introduction: The optimal method to investigate persistently elevated PSA, High grade PIN or atypical small acinar proliferation (ASAP) after negative initial prostate biopsies remains unclear. Here we compared cancer detection rates of two advocated prostate re-biopsy techniques: The Transrectal MD Anderson (MDA) protocol biopsy where both peripheral and transitional zones are biopsied and transperineal template biopsy (TPT). *Materials and Methods:* Patients in our institution who underwent MDA (n=365) or TPT (n=123) biopsy following at least one negative standard biopsy were reviewed. Cancer detection and where available, histological correlation with pathology at radical prostatectomy were recorded. *Results:* MDA biopsy had a cancer detection rate of 29.3% (107/365). 61% of tumours in the MDA group were low risk, 20% intermediate risk and 19% high risk disease based on D'Amico classification. There was only a 25% grade concordance in patients who underwent radical prostatectomy. Transperineal template biopsy had a cancer detection rate of 50.4% (62/123) which was significantly higher than the 29.3% detection rate in the MDA group ($p<0.0001$, Linear regression analysis). 16% of the tumours in the TPT group were low risk disease, 45% intermediate risk disease and 39% high-risk disease. There was grade concordance in 67% of the patient who subsequently had radical prostatectomy. *Discussion and Conclusion:* TPT had higher clinically significant cancer detection rate than MDA biopsy and more accurately predicted final histology grade. We advocate TPT as first choice in the re-biopsy setting. MDA biopsy however offers a reasonable alternative when TPT may not be appropriate.

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BENEFIT OF POST-DOCETAXEL TREATMENT IN CASTRATION RESISTANT PROSTATE CANCER PATIENTS WITH POOR PERFORMANCE STATUS

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Background: The landscape of treatment of castration resistant prostate cancer (CRPC) has recently changed. New molecules have demonstrated activity after docetaxel failure, but limited data are available about treatment of patients (pts) with a poor performance status (PS). We performed a meta-analysis to determine the efficacy of second-line treatment for CRPC pts with an ECOG PS=2. *Patients and Methods:* Randomized controlled phase III trials (RCTs) in pts with CRPC who progressed after docetaxel failure, were searched in MEDLINE and PubMed databases. Abstracts from oncology meetings were also taken into account. For each trial we evaluated the hazard ratio (HR) for overall survival (OS) and the relative confidence interval (CI) limited to patients with PS=2. Statistical analyses were conducted to calculate the HR and 95% CIs by using random-effects or fixed-effects models on the basis of the heterogeneity of included studies. *Results:* 5 randomized controlled trials were found, but only 3 trials (1-3) (3149 pts) met the eligibility criteria for inclusion in the final analysis. In total, 291 patients (9.2%) had a PS 2. 181 were in the experimental arm: 15.5% received chemotherapy (CHT) with cabazitaxel and 84.5% hormonal therapy (HT) with abiraterone acetate (45.3%) or MDV3100 (39.2%). 110 pts were in the control arm and received mitoxantrone (30%) or placebo (70%). In the overall cohort the HR for OS was 0.758 (95% CI 0.574-0.999, $p=0.049$), no significant heterogeneity was observed (Q=0.510; $p=0.774$; I2=0%). The subgroup analysis revealed that the HR for pts treated with CHT was 0.81 (95% CI 0.477-1.373, $p=0.434$) and HR for pts treated with HT was 0.739 (95% CI 0.534-1.023 $p=0.068$). *Discussion and Conclusion:* In this meta-analysis, we demonstrated a significant improvement in OS also for CRPC patients with a PS=2 treated with second-line therapy after docetaxel failure compared with control patients. Considering the small number of pts with PS=2 included in the trials, it is not possible to find out the best treatment option for this subgroup of pts.

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TRANS-ARTERIAL-EMBOLIZATION (TAE) PLUS TARGET THERAPY (SUNITINIB) IN RENAL CELL CARCINOMA (RCC)

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Introduction: Surgery (radical or partial nephrectomy) remains the mainstay of treatment for RCC. Unfortunately, about one third of patients undergoing surgical resection for localized disease develops recurrence and is eligible for systemic therapy. A proportion of patients is diagnosed at an advanced stage. When surgery is not indicated, due to tumor extension or poor performance status, there is still the indication for a locoregional therapy associated to systemic treatment in order to improve symptoms. Preliminary data with the association of locoregional therapy have been published in renal cell carcinoma animal models: an increased efficacy has been showed with the combination of sorafenib and radiofrequency ablation. TAE has been proposed as a nonsurgical ablative technique for the treatment of resectable and non resectable tumors, being able to facilitate dissection reducing tissue planeoedema, bleeding and extent of tumor thrombus. Sunitinib, as antiangiogenetic therapy, is considered standard first line treatment for renal cell carcinoma (RCC). Very few data are available on the combination of systemic therapy with sunitinib and locoregional treatment of the primary tumour by TAE. *Case Report:* In september 2006, a 67 years old outpatient man, affected by type 2 diabetes mellitus and pharmacologically handled hypertension came to our attention for right flank pain, hematuria, anemia (Hgb 5.0 g/dl) and severe asthenia. The CT scan with iodine contrast showed a massive neoplasm of the right kidney (maximum diameter 15 cm), with invasion of the renal fascia, perirenal spaces, posterior abdominal wall and psoas muscle. A thrombosis of renal and cava veins at the edge of its infraepatic tract and infiltration of ipsilateral adrenal gland was evident too. The biopsy confirmed renal clear cell carcinoma. Because of the extension of disease, surgery was excluded. In order to control bleeding and to treat patient with a less invasive approach TAE was proposed. TAE with embolization of branches of the celiac trunk, renal artery, superior mesenteric artery and collateral circulation was performed. The procedure resulted in a rapid control of bleeding with improvement of clinical and laboratory parameters. From December 2006 to April 2008 four TAE sessions were carried out. No systemic therapy was prescribed before the performance status. In July 2008 due to improving of the clinical conditions sunitinib 50 mg/day (4/2 w schedule) was prescribed. Treatment was well tolerated and a tumor stabilization was evident after 6 months of therapy. A drug interruption of 4 months was spontaneously decided by the patient and a later TC scan revealed a local disease progression with recurrence of pain. A further session of TAE was planned. In July 2010 imaging confirmed stable disease of the primary tumor, but lung disease progression was observed. Sunitinib was restarted. Treatment was well tolerated without disease progression until september 2011. *Discussion:* Angiogenic factors are shown to be overexpressed in the hypoxic zone between the necrotic central area induced by TAE implying a possible role for concomitant treatment. The rationale for the combined use seems to be correlated to the pharmacological inhibition of neoangiogenesis, detected after each session of embolization (reduction of peripheric new vessels). Despite the limited experimental and clinical evidence for synergism and the skepticism for combining TAE with an antiangiogenic agent like sunitinib, mainly due to presumed increased incidence of adverse events, the combination of systemic therapy and TAE merit further investigation In our patient, surviving more than 5 years after the diagnosis, the combined use of TAE and sunitinib was well tolerated. Embolization allowed a good control of acute bleeding as well a local disease control for 20 months without related complications. Sequential therapy with TAE and Sunitinib was feasible with no cumulative side-effects.

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Author	Year	Therapy	Control	Phase of study	Type of study	No of pts	Incidence of CR (%)			
							AAs	95% CI	Control	95% CI
Yuang *et al*.	2003	Bevacizumab 10mg	Pbo	2	RCT	116	0		0	
		Bevacizumab 3mg	Pbo				0		0	
Escudier *et al*.	2007	Bevacizumab+IFN	Pbo+IFN	3	RCT	649	1.3	0-2.7	2.1	0.3-3.9
Motzer *et al*.	2007	Sunitinib	IFN	3	RCT	750	3.3	1.2-5.3	1.2	0-2.6
Rini *et al*.	2007	Bevacizumab+IFN	IFN	3	RCT	731	3.4	1.3-5.5	1.3	0-2.7
Escudier *et al*.	2009	Sorafenib	IFN	2	RCT	189	0		1.1	0-3.7
Sternberg *et al*.	2010	Pazopanib	Pbo	3	RCT	435	0.3	0-1.2	0	
Total							1.9	1.1-2.6	1.2	0.6-1.9

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ANTIANGIOGENIC AGENTS ARE INEFFECTIVE TO INCREASE COMPLETE RESPONSE RATE IN MRCC. A META-ANALYSIS

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Background: Since their approval, antiangiogenic agents (AAs) have increased overall survival (OS) in metastatic renal cell carcinoma (mRCC); moreover these agents have reported greater activity compared to interferon alpha (IFNα) with an increase of the progression free survival (PFS) and the overall response rate (ORR). Despite these advances, mRCC continue to be a fatal disease and the complete response (CR) to therapy is a rare event. We meta-analyzed the incidence of CR in pts treated with AAs and in controls in main randomized control trials (RCT) for first line therapy in mRCC. *Materials and Methods:* Pub-Med and Medline search was performed to find first line RCT with AAs *vs*. non-AAs for mRCC in patients with good or intermediate prognosis defined by MSKCC risk score. The proportion of patients with CR and the derived 95% confidence interval (CI) were calculated for each study. We also calculated the relative risk (RR) and the CIs of events in patients assigned AAs compared to control in the same study. To calculate the 95% CIs, the variance of a log-transformed study-specific RR was derived using the delta method. Statistical heterogeneity between trials included in the meta-analysis was assessed using Cochrane's Q statistic, and inconsistency was quantified with I2 statistic (100% x [Q-df)/Q]) *Results:* Six RCTs (2986 pts) were found, four were phase III and two were phase II RCTs (see table below). 2636 pts were evaluable for final analysis and randomized to receive AAs (1429 pts) or control (1022 pts had IFN and 185 had placebo). Patients were treated with bevacizumab (50%), sunitinib (23%), pazopanib (20%) and sorafenib (7%). The incidence of CR in pts treated with AAs was 1.9% (95%CI, 1.1-2.6) compared to 1.2% (95%CI, 0.6-1.9) in the overall control arms, among these the incidence of CR in the IFN was 1.5% (95%CI, 0.7-2.3). The relative risk (RR) to have a CR with AAs was 1.6 (95%CI, 0.8-3.0; Q=4.7, p=0.57; I2=0%) but the data was not significant (p=0.15). If only phase III RCTs were considered, the RR to have a CR was 1.7 (95%CI, 0.9-3.4; Q=3.6, p=0.30; I2=17.2%) with a trend for significance (p=0.08). No differences were found when AAs were compared to IFNα alone (RR=1.6, p=0.14). Among AAs, sunitinib reported the highest RR for CR (2.7; 95%CI, 0.9-8.3) with a trend for significance (p=0.088). *Conclusion:* CR is a rare event in mRCC, and even if AAs reported greater activity in term of PFS and ORR, they did not increase the curative rate of metastatic disease. Probably other biologic factors than angiogenesis may influence the CR in mRCC.

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POLYMORPHISM IN THE PROSTATE STEM CELL ANTIGEN GENE PSCA MODIFIES SURVIVAL OF BLADDER CANCER PATIENTS

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Background: Urinary bladder cancer (UBC) ranks fifth in Italian male cancer incidence with a worldwide age-standardised rates per 100,000 of 20.1 (1). A recent genome-wide association study on 969 bladder cancer cases and 957 controls showed that a missense variant (rs2294008) in the PSCA gene is consistently associated with UBC risk in US and European populations (2). Survival of UBC patients in Western countries varies widely. Although the major prognostic determinants for UBC are stage and grade of the tumour at diagnosis, there are wide unexplained differences in survival time among patients with similar disease, general condition and treatment. Until now, genetic single nucleotide polymorphisms (SNPs) have been extensively studied in relation to the modulation of cancer risk. Few studies have been conducted on the relationship between SNPs and UBC survival. The aim of the present study was to investigate the association between stem cell antigen gene PSCA variants and survival from UBC. *Materials and Methods:* The study population included all the newly diagnosed, histologically confirmed cases of UBC registered at urology departments of an academic hospital in Italy during the years 1994-2010. All subjects were men, aged 40-75 years and living in the same metropolitan area of the hospital. We genotyped cell antigen gene PSCA (rs2294008) in 320 male UBC patients. For each SNP we estimated Hazard Ratios (adjHR) adjusted for potential confounders (age, stage, grading and type of therapy) and 95% Confidence Intervals (95%CI) for survival time. *Results:* 126 patients died during the observation time, from these 30 died for the consequences of their UBC. The median survival time was 5.83 years. Among the patients who died from UBC, variant alleles of PSCA conferred a statistically significant worse survival (HR 1.68 95%CI 1.01-2.79, p=0.04). After adjustment for potential confounders the risk for variant allele carriers persisted with a borderline statistical significance (adjHR 1.76 95%CI 0.98-3.13, p=0.05). Discussion and conclusion PSCA was initially identified as a prostate-specific cell-surface marker. It is overexpressed in prostate cancer, and the level of expression increases with tumour grade and stage. It may be involved in cell proliferation and migration; monoclonal antibodies targeted to PSCA inhibit tumour growth and metastasis formation in animal models. PSCA is expressed at low levels in the transitional epithelium of normal bladder but it is overexpressed in the majority of UBCs. A functional *in vitro* study demonstrated that the variant allele significantly reduced promoter activity. The biological mechanism of PSCA involvement in the modulation of survival for UBC is not clear, however a recent study showed that the same SNP is associated with gastric cancer survival (3). In conclusion, we observed an association between PSCA polymorphism and survival in UBC. However more functional studies and replication of these in independent study populations are needed to confirm our results.

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DELIRIUM IN HOSPITALIZED ELDERLY PATIENTS UNDERGOING UROLOGIC SURGERY. INCIDENCE AND PREDICTIVE ROLE OF MULTIDIMENSIONAL GERIATRIC EVALUATION (MGE) TO DEFINE A HIGH-RISK POPULATION AND PREVENT COMPLICATIONS: RESULTS OF A PROSPECTIVE STUDY

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Introduction and Objectives: Delirium (acute derangement syndrome) is a common condition occurring in hospitalized older pts with negative consequences, including higher post-op complication rates and death, disability, permanent cognitive decline and institutionalization. It determines a longer hospitalization and an increase of costs. It's incidence ranges from 15 to 35% in postoperative phase, and from 70 to 87% in intensive care (IC). Several studies have attempted to set criteria delineating a high-risk profile to develop delirium. The objective of this prospective study was to evaluate the impact of a MGE in 3 settings of pts hospitalized for medical or surgical conditions and to

evaluate the incidence and the possible causes of delirium. *Methods:* 274 elderly pts. admitted to 2 hospitals were evaluated in 3 different settings. 62 /274 pts (22.6%) from different depts. received a MGE on request during their hospital stay (Group 1). 159/274 (58%) dismissed pts. and regularly followed as out-pts. had a MGE at home (Group 2). 53/274 pts (19.4%) admitted for an elective urological procedure had a pre-op and post-op MGE and were strictly followed (Group 3).The mean age was 80.8, 80.3 and 78.1yrs respectively. The MGE included 19 items that were recorded in all pts. (drug history, delirium rating scale .). In this last group MGE was daily applied by nurses to define incidence and clinical characteristics of delirium. F-UP was planned at 1, 3 months and 1 year after discharge to evaluate global health and specifically functional and cognitive pts. status. *Results:* In Group 1 (62 pts) 75.8% of pts had MGE positive for delirium. Older age, high number of drugs used (digitalis and antibiotics) and depression were significantly correlated with delirium. In Group 2 (159 pts) 31.4% of subjects had delirium. Sex (females), >age, worse cognitive status and types of drugs used (digitalis, neuroleptics, antidepressant) were correlated with delirium. In Group C (53 pts affected by BPH and prostate, bladder and kidney cancer) 14.6% had a MGE test positive for delirium. Presence of co-morbidities, ASA score III-IV, type of anesthesia (general *vs*. spinal) were correlated with delirium. *Conclusion:* The incidence of delirium varies between the old population. MGE is an appropriate tool to detect it. Older age, low cognitive status, depression and N of drugs used are correlated with it. In urological pts candidate for surgery, high N of co-morbidities, ASA score III-IV and type of anesthesia (general) predict the onset of delirium. Pharmacological research is ongoing to detect the variation of cholinergic agents that may also be responsible for delirium.

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WORK-UP IN PATIENTS WITHOUT A SPECIFIC RISK OF PROSTATE CANCER (PSA ≤10 NG/ML): A MULTIPARAMETRIC MRI SCORING SYSTEM

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Introduction/Background/Aim: Prostate cancer is the most widespread cancer amongst men in the Western world but its diagnosis and management are still a clinical challenge. We assessed the diagnostic performance of a combined morphological and functional Magnetic Resonance Imaging (MRI) scoring system in urological-radiological work-up in patients with a Prostate Specific Antigen (PSA) ≤10 ng/ml. *Patients and Methods:* We enrolled 186 consecutive patients with PSA value between 2.5-4 ng/ml, with abnormal findings at Digital Rectal Examination (DRE), and patients with PSA value between 4-10 ng/ml. This study was approved by the local ethical committee. Each patient provided informed consent to undergo an urological-radiological work-up including serum free/total PSA ratio (f/t PSA) assay, morphological MRI (mMRI), MR Spectroscopy (MRS), Diffusion Weighted Imaging (DWI) and Trans Rectal Ultrasonography (TRUS) biopsy. MRI data sets were scored singularly, coupled and combined (cMRI score) to assess their diagnostic performance. *Outcome Measurements and Statistical Analysis:* Scores were correlated to negative biopsies and significant/insignificant Gleason score biopsies. Receiver Operating Characteristic (ROC) curve and McNemar tests were used to compare the diagnostic performance for all techniques and derived scores. *Results:* 136 patients were included (average PSA value 6.8 ng/ml; f/t PSA 18.5%). Cancer was diagnosed in 18% of patients. Using a cut-off value=2, cMRI score showed the highest sensitivity (0.84) and negative predictive value (0.93). cMRI score showed a significant correlation with Gleason score, and a statistically different median value between significant and insignificant Gleason score. *Conclusion:* cMRI score could identify patients with a PSA ≤10 ng/ml who will have a negative work-up, thanks to its high negative predictive value, and patients at high risk for significant Gleason score cancer because of its correlation to Gleason score.

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HIGH RISK PROSTATE CANCER: MANAGEMENT ANALYSIS ACCORDING TO ONLINE-IMAGE-GUIDED-INTENSITY-MODULATED-

RADIOTHERAPY, OFFLINE-IMAGE-GUIDED-3DCONFORMAL-RT AND ALTERED *VS.* CONVENTIONAL FRACTIONATION

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Background: In most patients, recurrence is suspected as a result of an increase in PSA concentration. However, treatment planning requires precise knowledge of the location and extent of disease, which cannot be derived from biochemical data or nomograms alone. [18F]Choline PET/CT imaging is an established diagnostic tool in a single step re-staging patients with biochemical failure after primary treatment for prostate cancer (1). Actually, there are limited published data on the best method for targeting the Biological Target Volume (BTV) (2) *Aims:* 1) to analyze our experience with [18F]Choline PET/CT imaging in radiotherapy planning of postoperative recurrent prostate cancer; 2) to investigate the interobserver variability using visual method for targeting BTVs. *Methods:* Since march 2010 to March 2011, seven consecutive patients (pts) with biochemical failure after radical retropubic prostatectomy (RRP) +/– adjuvant radiotherapy (AR) were studied to discriminate local or systemic recurrence and to select second-line treatment. We acquired PET/CT imaging to detect morphologic and metabolic failure data and, subsequently, CT simulation-localization was performed. PET to CT-planning was aligned through a mutual information-like method and the match was assessed acceptable. We adopted a different strategy regarding the choice of the volumes to irradiate and the doses to prescribe in accord to prostatectomy bed recurrence (PBR) *vs*. pelvic nodal recurrence (PNR) or both. A team composed by four members, a radiation oncologist, a nuclear medicine physician and two urologist defined BTVs using visual method on contouring software. *Results:* all the pts (mean age: 70.9 years, KPS 90) had a postRRP recurrence, one postAR (66 Gy on the PB) and one androgen blockage (AB) refractory. Average time to relapse was 66 months (range 35-107). [18F]Choline PET/CT imaging detected 4 PBR, 2 PNR and one synchronous PBR + PNR. We administered 74 Gy on PBR volume, 50.4 Gy on lymphatic pelvic volume in PNR and on pelvic volume in synchronous PBR + PNR. Five pts are in AB treatment. Inter-observer variability for visual delineation of BTVs was not statistically significant in definition of site and size of PNR. Instead, we noted some incoherence in size calculation of BTV related to PBR. *Conclusion:* In postRRP recurrence pts, [18F]Choline PET/CT imaging can address to a better target volume selection and delineation adapting correct RT strategies to different biochemical, clinical and prognostic situations (3). We had acceptable interobserver variability in targeting PNR but we need more data or automated segmentation methods to obtain a better definition of BTVs.

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LAPAROSCOPIC PARTIAL NEPHRECTOMY: WHAT DOES CHANGE AFTER MORE THAN 250 PROCEDURES PERFORMED BY A SINGLE SURGEON

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Introduction: The purpose of this study was to explore the pathological outcomes of laparoscopic partial nephrectomy (LPN) for kidney tumour performed by a single surgeon in a single Institution after a decennial experience. *Materials and Methods:* We retrospectively reviewed our prospectively maintained LPN database and we reviewed the 256 pathological specimens of kidney tumours treated by LPN at our Institution by a single surgeon (F.P.) from January 2001 to January 2012. A single uro-pathologist (E.B.) performed pathological analyses according previously described criteria (1). The masses were divided into three Groups with a chronologic criterion: cases from 1 to 85 were assigned to Group A, from 86 to 170 were assigned to Group B whilst the remainder 86 cases (from 171 to 256) were assigned to Group C. The three Groups were compared according to the following variables: intra-operative variables (warm ischemia time, WIT, operative time and estimated blood losses, EBL), lesions' pathological size and weight, PADUA score (2), staging according to TNM (3), minimum and maximum resection margin, mean of excised margin and rate of positive surgical margins (PSMs). Groups were compared using Kruskall-Wallis Analysis of Variance (ANOVA) test. Univariate linear regression model was used too in order to verify the trend of studied variables along our case study (p-values<0.05 considered statistically significant). All statistical analyses were performed using the "Statistica" software program Ver. 6.0 (Tulsa, OK, USA). *Results:* Groups were similar in terms of pathological size (p=0.4675); PADUA score was significantly higher in Group C (p<0.0001) maybe due to the more extended indication of LPN with the increasing experience of the surgeon. Nevertheless, WIT constantly decreased from Group A to

Group C ($p<0.0001$) due to the same reason; moreover, EBL decreased along the case-study particularly in Group B ($p<0.0001$) and operative time slightly decreased along the learning curve. Duration of hospitalization was reduced along the case study too ($p<0.0001$). We registered an increase in the pathological weight of the lesions in Group B with respect to Groups A and C ($p<0.0001$). Out of the 256 lesions, 173 (67.6%) were defined malignant at the histo-pathological analysis: the 64.7% (55/85), 67.0% (57/85) and 70.9% (61/86), in Groups A, B and C, respectively. The distribution of malignant lesions stratified according to pathological TNM staging was: 111/173 (64.2%) pT1a, 49/173 (28.3%) pT1b, 5/173 (2.9%) pT2, 8/173 (4.6%) pT3a-b; we did not find any statistically significant difference in the distribution of TNM staging inside the Groups. Minimum thickness of peri-tumoural healthy tissue resected decreased continuously along the case study ($p<0.0001$). Maximum resection margin was stable and so the mean resected. There was no statistically significant difference in the percentage of PSM among the Groups, with an overall rate of 2.3% (4/173); in particular no PSM were recorded in Group C. Our results were confirmed by univariate linear regression model that demonstrated that moving along our case study from the first cases to the latest, WIT, duration of hospitalization and minimum margin significantly decreased ($p<0.0001$, $p=0.0474$, $p=0.0001$, respectively) while lesions' weight and PADUA score significantly increased ($p=0.0009$, $p<0.0001$). *Conclusion:* Our data suggest that, with the increase of surgeon experience along a learning curve of more than 250 laparoscopic partial nephrectomies, even if the features of the lesions treated become more difficult, WIT is strongly reduced together with duration of hospitalization of the patient. Moreover, the cold cutting during the enucleoresection of the lesion get nearer to the pseudocapsule of the tumour to treat. This feature could reduce the number of nephrons removed and so the kidney damage. Moreover the reduction of this peri-tumoral tissue does not impair the oncological effectiveness of the procedure.

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CLAMPLESS LAPAROSCOPIC PARTIAL NEPHRECTOMY: IS A HARMLESS NEPHRON-SPARING SURGERY REALLY FEASIBLE?

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Background: An evolution of a known concept of laparoscopic partial nephrectomy (LPN) has been taken into consideration in urological surgery: LPN performed by "zero-ischemia"-technique (1), with the aim of completely eliminating surgical renal ischemia. In the present study, we retrospectively evaluated our experience with clampless-LPN (cl-LPN): the aim was to evaluate the results of this technique and to compare results of cl-LPN with conventional LPN ones. *Patients and Methods:* We reviewed our prospectively maintained database: data of 117 patients who consecutively underwent LPN at our Institution from January 2009 to December 2011 were extracted. Patients were divided into 2 Groups based on operative technique: Group A: cl-LPN; Group B: conventional LPN (with clamping of renal artery). Demographic and peri-operative data, complications, pre- and post-operative serum creatinine (SCr) and estimated glomerular filtration rate (eGFR, calculated by MDRD formula (2)) were registered and compared by Student's *t*- and Chi-square-tests (p-values<0.05 considered statistically significant). All statistical analyses were performed using the "Statistica" software program Ver. 6.0 (Tulsa, OK, USA). *Results:* Out of 117 patients who underwent LPN, 41 underwent cl-LPN and constituted Group A. The remaining 76 patients who underwent conventional LPN composed Group B. Concerning Group A, lesion size at Computed Tomography scan (CT-scan) was 2.35+1.10 cm, operative time 133.53+40.54 min and Estimated Blood Losses (EBL) 201.46+109.81 mL. Results of this technique were thus compared with the results of conventional LPN: Groups were comparable about preoperative data except for CT-scan size (2.35+1.10 *vs*. 3.19+1.57, Group A *vs*. B, respectively, $p=0.0029$). On the contrary, no differences were recorded in terms of PADUA 1 score (3). Concerning perioperative data, warm ischemia time (WIT) was 0 min in all Group A cases; mean WIT in Group B was 20.90+9.27 min ($p<0.0001$); operative time (133.53+40.54 *vs*. 120.59+32.33, A *vs*. B, respectively) and EBL (201.46+109.81 *vs*. 164.27+128.68, A *vs*. B, respectively) were slightly higher in Group A even if these differences did not reach statistical significance ($p=0.0763$ and $p=0.1464$, respectively). One case (2.4%) in Group A (central tumour) was converted to conventional LPN. No differences were noted between the two Groups neither in terms of intra- nor post-operative complications. Similarly, positive surgical margins' rate and thickness of peri-tumoural

Grade	Haematologic (%)	Gastrointestinal (%)											Genitourinary (%)						
		Diarrhea	Abdominal cramps	Flatulence	Anal pain	Tenesmus	Rectal blood loss	Mucus loss	Frequency	Urgency	Incontinence	Hemorroids	Hematuria	Frequency	Urgency	Dysuria	Nocturia	Incontinence	Obstructive symptoms
1	0	18	3	3	6	15	0	0	15	3	3	3	0	32	9	21	12	6	0
2	6	3	0	12	3	29	9	0	0	0	0	21	3	12	9	9	15	0	0

healthy tissue excised were not statistically different. Finally, concerning functional results, we did not find any differences when comparing pre-operative and post-operative SCr and eGFR in both Groups, even if a trend towards a more relevant post-operative worsening of eGFR was observed in Group B with respect to Group A (p=0.0445). *Discussion and Conclusion:* Notwithstanding the limits of the study, our results suggest that cl-LPN is an emerging alternative to conventional LPN that could be a new surgical option when approaching small renal masses. By this approach kidney does not undergo ischemia and this, reasonably, limits renal damage without significant increase of blood losses and complications or impairment of pathological results. In our opinion, it is essential that the surgeon had significant laparoscopic experience before embarking on this kind of procedure, especially for the most challenging cases.

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HIGH-DOSE SALVAGE SIMULTANEOUS BOOST WITH INTENSITY-MODULATED RADIOTHERAPHY FOR RECURRENCES AFTER RADICAL PROSTATECTOMY: ACUTE TOXICITY

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Aim: There is evidence that higher doses are usually related to higher biochemical control also in patients treated for salvage radiotherapy (1). To reduce the irradiated volume, based on the experience of contouring intraprostatic lesions on magnetic resonance imaging (MRI) with spectroscopy (2) and ^{18}F – choline PET-CT (3), in our study nodal recurrences were indentified also with this modalities. Acute toxicity in patients treated with salvage intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost (SIB) in recurrences after radical prostatectomy will be reported. *Materials and Methods:* Between February 2009 and February 2012, 34 men with rising PSA identifying nodular recurrences in the prostatic bed using magnetic resonance imaging (MRI) with spectroscopy and ^{18}F – choline PET-CT were evaluated. Median age of patients was 69 years (range 48-80) with mean PSA at the beginning of radiotherapy equal to 2.55 ng/ml (range 0.11-4.98). Treatment plans were designed by using a five or seven field sliding window intensity modulated technique (IMRT) to administer an EQD_{2Gy} (considering an α/β value of 1.5 Gy for prostate cancer) as simultaneous integrated boost (SIB) to the nodular recurrences (range 73 Gy-85 Gy) and to the prostatic bed (range 64 Gy-79 Gy), 8 pts (24%) were also simultaneously irradiated on the pelvic nodes (range 45 Gy-51 Gy). Treatments were delivered by a Varian Linac (2100 CD) equipped with the Millennium multileaf collimator (120 leaves). 18 pts (53%) underwent androgen deprivation therapy (ADT). Acute toxicity was evaluated weekly during treatment using the CTCAE scale vers.4 supplemented by an in-house-developed scoring system. *Results:* No grade 3 or 4 acute gastrointestinal toxicity was developed. The percentage of patients who experienced toxicities are reported in the table. *Discussion and Conclusion:* The results of our study indicate that SIB delivered with IMRT in the rescue of patients with recurrent nodules of prostate cancer after radical prostatectomy is well tolerated and allows to

administer high doses to the disease with a reasonable rate of acute toxicity.

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ADJUVANT PARA-AORTIC RADIOTHERAPY FOR STAGE I TESTICULAR SEMINOMA: OUR EXPERIENCE

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Introduction and Aim: Testicular germ cell tumors represent the most common solid cancer in males between 20 and 40 years of age and the majority of patients present with clinical stage I disease and approximately 40% to 60% are pure seminomas. Surgery remains the most important therapy for this kind of neoplasm and present management of testicular seminoma can achieve excellent survival rates, in the order of 97-100%. Some years ago standard adjuvant management has been extended-field radiotherapy after radical inguinal orchidectomy. During the last years alternative management strategies, including surveillance and para-aortic lymph node only radiotherapy (PART) have been explored. Our work aims to evaluate efficacy and toxicity of PART for stage I testicular seminoma after surgry. *Materials and Methods:* Twenty-eight patients with stage I pure seminoma were treated with PART at Radiotherapy Department in Foggia between January 2007 and December 2010. Median age was 33 years (range between 25 and 44 years). After histological diagnosis all patients underwent orchidectomy. No patient received chemotherapy. In order to deliver radiotherapy treatment, Computed Tomography scans were obtained to contour Clinical Target Volume, Planning Target Volume and organs at risk. PART was administered 4-6 weeks after surgery with a median total dose of 21 Gy (range between 20 and 25.2 Gy) with 1.5, 1.8 or 2 Gy per fraction. We proceeded with plan optimization and DVH evaluation. We evaluated acute and late gastrointestinal (GI) and genitourinary (GU) toxicities. Moreover, relapse rate, metastasis rate, Disease Free Survival (DFS) and Overall Survival (OS) were calculated. *Results:* Median follow-up was 36 months with last controls performed in December 2011. Acute toxicity was mainly digestive, 67.8% of patients presenting moderate nausea and vomiting. No late GU or GI toxicities were noticed. No local relapse and no distant metastases were observed. Only one patient experienced controlateral testicular cancer and he was successfully treated with surgery. DFS and OS was 100% since all patients were alive in complete remission at last control. *Discussion and Conclusion:* Modern management of stage I testicular cancer has changed over last years. Our study showed that PART represents a valid option for stage I testicular seminoma. Acute toxicity is dominated by moderate gastro-intestinal side-effects but PART provides excellent results in terms of local control and survival.

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VALIDATION OF PRIAS ACTIVE SURVEILLANCE CRITERIA IN PATIENTS SUBMITTED TO RADICAL PROSTATECTOMY

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Objective: The aim of this study was to evaluate the pathological characteristics of a cohort of patients submitted to radical prostatectomy in presence of presumed indolent prostate cancer according to the Van den Bergh's criteria described for the Prostate Cancer Research International Active Surveliance (P.R.I.A.S.). *Patients and Methods:* We considered 1800 patients treated with RP between January 2003 and January 2012. All the patients had their biopsy and RP specimen evaluated in our institute. Among these patients, we identified 114 men (1%) who fulfilled the inclusion criteria for the AS of P.R.I.A.S. defined by Van Den Bergh (PSA<10; <=2 positive core, >=10 biopsy core and Gs=6 o 3+4). A single experienced uropathologist reviewed the biopsy core and the RP specimen according to the 2009 International Society of Urological Pathology (ISUP) protocol. After pathological revision, only 60 out of 114 (53%) fulfilled the pathological

characteristics mentioned above. *Results:* Among our 60 patients, 58 had organ confined disease (8 pT2a: 13%, 6 pT2b:10 %, 41 pT2c: 68%) while 2 patients had extracapsular invasion (pT3a: 3%), though no seminal vescicle involvement (pT3b) was detected in this cohort. In 50 cases (83%) the resection margins were free from cancer (R0), while 10 cases (17%) showed positive margins (R1). The pathological Gs was 6 in 18 cases (30%), 3+4 in 27 (45%), 4+3 in 14 (23%) and 8-10 in 1 (2%). According to the risk based analysis, 45 patients (75%) were at low risk of aggressive disease, while the percentage of intermediate risk patients was about 23%, and only 1 patient (2%) harboured a high risk prostate cancer. *Conclusion:* According to our study, the inclusion criteria of Prostate Cancer Research International Active Surveliance (P.R.I.A.S.) have high accuracy in the prediction of organ confined and low-intermediate risk prostate cancer. Our results seem to be consistently better than those of the actual literature, maybe thanks to the anatomopathological review performed by a single experienced uropathologist, which allowed us to exclude 53 patients who would have compromised the accuracy of our results. Thus, according to our experience, the actual Active Surveillance parameters can be safely adopted, only if the review is performed by a single uropathologist of proven experience.

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TRENDS IN PARTIAL NEPHRECTOMY USE IN ITALY: DATA FROM PIEDMONT REGION IN THE LAST DECADE

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Introduction: Recent studies have shown that partial nephrectomy (PN) has equivalent oncologic outcomes with radical nephrectomy (RN) for localized renal tumors. The most recent international guidelines for renal cell carcinoma (RCC) recommend the use of nephron sparing surgery (NSS) for renal lesions up to 7 cm in size whenever technically feasible. Despite this, PN remains underused in North America. Aim of this study was to evaluate trends in PN use during the last decade in a north-western Italian region. *Patients and Methods:* The regional archives of hospital discharge records in Piedmont region from January 2000 to December 2010 were retrospectively analysed. All procedures recorded with the ICD-9 codes 55.3, 55.4 (PN) and 55.5 (RN) performed for a primary diagnosis of renal tumor (189.0) were included in the analysis (n=6180). The surgeries were performed in 43 different urological institutions, that were stratified according to academic status and hospital nephrectomy volume (high >300, intermediate 100-300, low <100 nephrectomies in the study period). Trends in the use of PN were assessed overall and according to institution type. *Results:* The overall number of surgical procedures for renal tumors performed in Piedmont region increased significantly from 2000 to 2010 (+27%). RN is the preferred surgical treatment, but an increasing use of PN was observed over the study period. This trend is more significant in centres with high renal surgical volume (+ 19.9%) and in non academic centres (+13.7%). *Discussion and Conclusion:* PN is increasingly performed in the last decade in Piedmont region. The most significant increase in the indications to NSS was observed in institutions with high renal surgical volume. However, PN remains relatively underused and strategies to enhance conservative treatments of renal tumors should be implemented.

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FLUORESCENT CYSTOSCOPY WITH HEXAMINOLEVULINATE: DIAGNOSTIC ACCURACY FOR NON MUSCLE INVASIVE BLADDER CANCER

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Introduction: The sensitivity of white light cystoscopy (WLC) can be improved especially for the detection of flat urothelial neoplasms. Fluorescent or blue light cystoscopy (BLC) has the potential to overcome the limitations of WLC. Aim of this study was to compare the diagnostic accuracy of WLC and BLC in the diagnosis of urothelial cancer and to identify the conditions where BLC can provide the highest diagnostic advantage over WLC. *Patients and Methods:* 71 patients with a suspicious primary or recurrent bladder tumor were enrolled in the study. Patients who had intravesical instillations in the 3 months before the procedure were not eligible. After intravescical instillation of Hexaminolevulinate 85 mg one hour before the procedure, the patients underwent WLC followed by BLC. All observed lesions were reported in a diagram, biopsied or resected. Detection rate and false detection rate of the two techniques were compared. Data were stratified according to pathology of bladder lesions and bladder site where the lesions were observed. A subset analysis was also performed to assess the diagnostic accuracy of WLC and BLC in patients who had (n=36) or had not (n=35) undergone previous intravesical treatments to prevent recurrence and progression. *Results:* Overall 270 bladder

lesions were detected (102 with BLC, 7 with WLC, 161 with both techniques). At pathology 236 lesions were malignant, while 34 were benign. The detection rate was 62.2% for WLC (147/236) and 98.3% for BLC (232/236). The highest diagnostic advantage for BLC was observed for the diagnosis of carcinoma *in situ* and for lesions located at the bladder dome. The false detection rate was 12.5% for WLC (21/168) and 11,4% for BLC (30/263). Overall, 32/71 patients (45.1%) had a diagnostic advantage with BLC (diagnosis of at least one Cis, dysplastic or papillary lesion that was missed at WLC). The subset analysis showed that the detection rate of BLC is not decreased in patients who have undergone previous endovesical treatment (98.1% *vs*. 97.8%), as well as the false detection rate is not increased (11.6% *vs*. 11.4%). *Discussion and Conclusion:* BLC is a promising technique that has a significantly higher detection rate than WLC. The highest diagnostic advantage with BLC can be obtained for the diagnosis of Cis and of lesions located at the bladder dome. The detection rate of BLC is not decreased in patients who underwent previous endovesical treatments when the last instillation is not performed in the 3 months before the procedure.

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PROSTATE SPECIFIC ANTIGEN (PSA) USE AND INCIDENCE OF PROSTATE CANCER (PC) AMONG ELDERLY MEN IN NORTH-EAST ITALY: A POPULATION-BASED EVALUATION STUDY

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Purpose: The PSA blood test has changed the epidemiology of PC, creating a dramatic rise in its incidence and helping to shift the stage of disease to much earlier and potentially more curable one. PSA testing remains, however, a source of uncertainties since periodic testing may increase the risk of treating many men for screen-detected PC who would not have experienced ill effects if PC had been left undetected. The risk of over diagnosis and over treatment associated with PSA is particularly significant among elderly men, among whom it is questioned whether life expectancy is significantly reduced after PC diagnosis. The study aim was to assess, from 1998 thru 2009, PSA use and PC incidence rates in elderly men (>= 70 years) in the Friuli Venezia Giulia region (FVG), northeastern Italy. *Methods:* PC cases were identified through the population-based Cancer Registry that collects all cancer cases occurring since 1995 in resident people. Individual history of PSA testing was extracted from the regional digital health archive that provides the identification of men tested for PSA and the date of testing. Joinpoint regression analysis was used to identify significant changes over time in log-linear slopes. The annual percentage change (APC) was computed by means of generalised linear models. *Results:* From 1998 to 2007, 10377 incident PC cases have been identified, of which 56.5% were among elderly. The crude incidence rate of PC in elderly men increased from 824.2/100.000 in 1998 to 875.4 in 2007, with an APC of +6.18 (95%CI 2.01-3.16). 38.826 men (out of the approximately 70300 elderly men residing in FVG) were tested for PSA in 2009, with a total number of 58147 tests performed. Between 1998 and 2009, the percentage of elderly men aged 70-79 who underwent PSA test increased substantially (APC=13.02%), with a change in slope in 2002. Among elderly men aged 80 years or older, the APC increase was 12.80%, and 2003 the year with the change in slope. Approximately 30% of elderly men who underwent PSA were tested more than once. On average, there were 1.06 cases of newly diagnosed PC every 100 PSA tests. The number of elderly men tested for PSA who underwent ecographic examination and/or biopsy strongly declined -from 900 to 400 ecographic exams for every 10000 tested men; from 300 to 200 biopsy for every 10000 tested men. *Conclusion:* The increasing incidence of PC in FVG reflects the rising use of PSA testing also among elderly men, even for men aged 80 years or older. The huge number of PSA tests was inversely associated with the number of ecographic examinations or biopsies over the study period, indicating that PSA testing is widely used in asymptomatic elderly men.

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CONTRAST-ENHANCED ULTRASOUND FOR EVALUATION OF RCCS: IDENTIFICATION OF HIGH-RISK TUMORS THROUGH SIGNAL TIME/INTENSITY CURVES

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Aim: The aim of the study is to evaluate the efficacy of time/intensity curves (T/IS) for quantitative analysis of contrast kinetics during contrast-enhanced ultrasound (CEUS) in characterization of renal lesions. *Patients and Methods:* We

prospectively evaluated 85 renal lesions with CEUS. A quantitative analysis of enhancement was performed using a dedicated software (QONTRAST, manufactured by Esaote for Bracco Group) which elaborates colorimetric maps and process Time/Intensity (T/IS) curves on region of interest (ROI). Of the evaluated lesions, 38 underwent surgery and 47 were addressed to the active surveillance regimen due to lesion features and patients' performance status. Our study incorporates the histopathologically-confirmed lesions and the 21 of the 47 in surveillance with an available follow-up ≥2 years. The kinetic of perfusion has been classified into 4 patterns: type I "rapid wash-in, slow wash-out", type II "rapid wash-in and wash-out", type III "slow wash-in and wash-out", type IV "slow wash-in, rapid wash-out" *Results:* Lesions with type I pattern resulted clear cell RCCs (cRCC) Fuhrman G3 in 9/12 cases and cRCCs G2 with elevated cystic component in 3/12; 14 G2 cRCC and 2 cystic G1 cRCCs demonstrated type II curves; type III curves in 4 G1 cRCCs, 1 G2 cRCC and 3 papillary G2 RCCs (pRCC); 1 G2 pRCC and 1 cystic G2 cRCC with pattern type IV. The 7 centrimetric solid lesions and 14 cystic lesions in "active surveillance" regimen, all characterized by perfusion patterns III and IV appeared dimensionally stable at a minimum follow-up of 2 years. Overall, Fuhrman G3-G2 tumors showed distinctive T/IS curves (type I-II) with higher peaks of enhancement while for type III and IV curves, an ovelapping between stable lesions seems to exist, benign tumors and low-risk evolutive lesions. With regards to the small series, the T/IS curves showed a sensibility of 92.8% and a specificity of 80%. *Conclusion:* Contrast-enhanced ultrasound can be useful to better define renal lesions both in patients undergoing surgery and in cases suitable to an "active surveillance" regimen. Time/intensity curves for quantitative analysis of contrast kinetics may help in distinguishing biologically aggressive RCCs from benign/low-risk tumors. Wider series may conduce to a more accurate predictivity of T/IS curves regarding histological pattern.

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RADIOTHERAPY AND CONCOMITANT DOCETAXEL IN HIGH RISK PROSTATIC CANCER:GUONE (NORTH EAST URO ONCOLOGY GROUP) EXPERIENCE

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Background: High-very high-risk(cT3, N1, PSA ≥20 ng/ml and/or Gleason score ≥8, prostate cancer patients (pts) have a 5-years biochemical failure rate, after surgery or radiation, over 50%. Neoadjuvant, concomitant and adjuvant hormonotherapy (HT) are currently the only systemic treatments with escalation dose of radiation therapy. Because of the heterogeneity of prostate cancer cells and the desire to improve the outcome with radiotherapy (RT), weekly chemotherapy (CT) during RT in localized, high-risk prostate cancer is being explored. Docetaxel has demonstrated significant antitumor effect and impact on survival in hormone-refractory prostate cancer and a strong sensitization of tumor cells to radiation injury. *Patients and Methods:* From 2005 to 2010, 30 very high-risk pts were treated with high dose of RT and concomitant docetaxel. All pts had clinically (13/30) or pathologically (17/30) advanced disease. Clinically Advanced Tumor (CAT):median age 73 years (range 65-81); Gleason score:7 in 1, 8 in 4, 9 in 7 pts and 10 in 1 case; PSA median at Diagnosis was 9.3 (5.27-71.3) and PSA prior to RT was 0,51 ng/ml (0.05-3.83); RT median dose was 80 Gy (range 76-80). Pathologically Advanced Tumor (PAT): median age 65 years (range 57-80); Gleason Score: 8 in 4 and 9 in 13 pts; pT2c in 2, pT3a in 3, pT3b in 10 and pT4 in 2 pts; Nodes were positive in 3 pts; 6 pts were R1. PSA median at diagnosis, was 18 (4.25-56.3), PSA prior to RT was 0.65 ng/ml (0.01-4.22); RT median dose, was 70 Gy (range 66-76). Docetaxel was administered at a standard weekly dose (30 mg for pts with surface area <2 m^2 and 40 mg for pts with ≥2 m^2). The median cycle of CT was 7 (range: 2-8). All pts began HT before and during RT and continued the treatment for 2 years after RT. *Results:* At median follow-up of 36 months (8-60), 6 pts (20%) had progression disease, (median period of recurrence: 14 months). Toxicity: gastrointestinal grade I was referred by 18/30 and urological grade I by 12/30 pts. Two patients stopped CT after two cycles for systemic toxicity. *Discussion:* During the same period in the same institution 139 pts with the same pathological characteristics were treated with standard therapy: 42 with adiuvant RT+HT and 97 with radical RT+HT.At median follow-up of 29 months, 33% of pts had a relapse. *Conclusion:* These preliminary data confirmed the feasibility and the tolerability of weekly docetaxel in combination with RT in men at high risk of disease progression. No patient suffered performance status worsening during the scheduled treatment. At a median follow-up of 36 months, only 20% of pts had relapse disease and this was a remarkable result, considering that the patients were at very high risk and with the standard treatment the global relapse was 33%. For such very high-risk patients, multimodal treatments combining HT, CT and RT will, possibly, be the treatment of choice in the future; however, at the moment, such treatments are only available in clinical trials and patients should be encouraged to participate in them.

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SPLIT-CT AND STANDARD CT-UROGRAPHY: A TAILORED-IMAGING FOR RENAL AND TRANSITIONAL CANCER

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Introduction and Objectives: The gold standard in evaluating urinary system is represented by CT-urography performed as a single bolus of organoiodate contrast and 4 acquisition phases (SBT-CT). The multibolus bi-triphasic technique (SPLIT-CT) demonstrated a diagnostic value equivalent to standard CT, reducing radiation exposure in extraurological pathologies. The aim of this study was to propose the personalization of Uro-CT performed as a SBT-CT or a SPLIT-CT and to define the indications to these techniques. *Patients and Methods:* From January 2008 to December 2011 we performed 1536 CTs: every exam has been tailored depending on the pathology and patient's performance status. Overall, 975 patients (63.5%) underwent SBT-CT and 561 (36.5%) underwent SPLIT-CT. CTs always started with an unenhanced panoramic view that addressed the radiologist in tailoring the examination. SPLIT-CT consisted of a first 70 mL contrast bolus and, if necessary, an arterial acquisition phase 25-30 seconds after the first injection; after 7 minutes a 50 mL contrast bolus was injected, followed by a third bolus (50mL) 45 seconds later. Combined phase acquisition was usually performed 25-30 second after the last bolus. The CTDose (National Board of Health, Denmark) algorithm was used to calculate the effective radiation dose of the techniques. Every exam was reviewed by a single dedicated uroradiologist. *Results:* SPLIT infusion technique applies 170 mL of organoiodate contrast *versus* mean (range) 120 (100150) mL of SBT-CT. Mean dosimetric levels of bi-triphasic SPLIT technique and SBT-CT were: 12.7(r: 6-18), 20.8(r: 10-30) and 25.4(r: 12-38) mSv respectively. We performed the SPLIT-CT in case of micro/macrohaematuria, with positive urinary cytology and/or positive FISH test without previous diriment ultrasonography (US) and cystoscopy, hydronephrosis with previous non concluding US, to evaluate and follow-up urothelial tumors, in preoperatory staging of patients with muscle-invasive bladder tumors. SBT-CT was performed in patients with large reno-urothelial tumors and adbominal lesions of uncertain interpretation at US or discovered during preliminary not enhanced CT, in follow-up of renal masses after surgery and in preoperative plannig of RCCs due to the need of complementary chest evaluation. SPLIT-CT showed a high sensibility for TCC and renal parenchymal pathologies and allowed a contextual representation of vessels, parenchyma and excretory system. Moreover, in our series, SPLIT-CT seemed to have a higher diagnostic value in case of uretheral malignancies, representing the minus in lumen and the tumoral vascularization. The limit of the procedure was represented by a higher dose of contrast infused that should be considered in patients with renal failure. *Conclusion:* SPLIT technique allows a detailed study with a dosimetric reduction up to 50%, becoming fundamental in terms of cumulative dose in patients requiring long-term follow-up, specially young and female patients. Our pilot study underlines the need of multicenter randomized trials to define an operative algorithm integrating standard CT-urography and multibolus SPLIT technique.

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IDENTIFICATION OF FUNCTIONALLY ACTIVE COPY NUMBER VARIANTS ASSOCIATED WITH PROSTATE CANCER RISK

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Introduction and Background: Prostate cancer is a leading cause of cancer death in males throughout the world and demonstrates the largest estimated effect of heritability among the most common tumor types as determined by a Scandinavian twin-based registration study (1). Emerging insights into the genetics of constitutional disease etiology demonstrate that germline polymorphisms in the form of Copy Number Variants (CNVs) are associated with diseases including cancer. In order to explore for CNVs associated with prostate cancer, we examined 1,903 men from the Tyrol Early Prostate Cancer Detection Program (2). *Materials and Methods:* The Tyrol cohort is a population-based prostate cancer screening program started in 1993 that intended to evaluate the utility of intensive PSA screening in reducing prostate cancer specific death. We profiled peripheral blood samples using a high resolution short oligonucleotide platform and characterized over 5,000 CNVs using IgC2N, a computational framework (3). Results: We queried low-frequency bi-allelic CNVs from 1,903 men of Caucasian origin and discovered two CNVs strongly associated with prostate cancer risk. The first risk locus ($p=7.7\times10^{-4}$, Odds Ratio (OR)=2.78) maps to 15q21.3 and overlaps a non-coding enhancer element that contains multiple AP-1 transcription factor binding sites. Chromosome conformation capture (Hi-C) data suggested direct cis interactions with distant genes. The second risk locus ($p=2.6\times10^{-3}$, OR=4.8)

maps to the *Alpha-1,3-mannosyl-glycoprotein 4-beta-N-acetylglucosami-nyltransferase C* (*MGAT4C*) gene on 12q21.31. *In vitro* cell line assays found this gene to significantly modulate cell proliferation and migration in both benign and cancer prostate cells. Further, *MGAT4C* was significantly overexpressed in metastatic *versus* localized prostate cancer. These two risk associations were replicated in an independent PSA-screened cohort of 800 men (15q21.3, combined p=0.006; 12q21.31, combined p=0.026). *Discussion:* These findings establish non-coding and coding germline CNVs as significant risk factors for prostate cancer susceptibility and implicate their role in disease development and progression. In summary, this is the first large scale, unbiased study using this patient population to study the contribution of germline CNVs towards prostate cancer risk. *Conclusion:* We envision that CNVs can eventually be used to assess patient risk for aggressive prostate cancer at time of diagnosis.

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RADICAL NEPHRECTOMY AND CAVOATRIAL THROMBECTOMY ON NORMOTHERMIC CARDIOPULMONARY BY-PASS AND BEATING HEART: A CASE REPORT AND DESCRIPTION OF THE TECHNIQUE

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Objectives: Usually, cavoatrial kidney cancer is managed with cardiopulmonary by-pass (CBP) with deep hypothermia circulatory arrest (DHCA). In this study, we report the feasibility, safety and effectiveness of radical nephrectomy with cavoatrial thrombectomy on normothermic CPB and beating heart. *Patients:* A 71 years old healthy woman presented with lumbar pain. Abdomen US and following CT scan detected an 8 cm right renal tumor with a neoplastic thrombus (NT) extended from the right renal vein to all inferior vena cava (IVC) and to the right atrium (RA). The thrombus partially involved the right supra hepatic veins and the left renal vein. Distant metastases were not detected. *Results:* Through a laparotomic median incision, the urological equipe mobilised the right colon and exposed the right kidney. The renal vascular pedicle was exposed and the radical nephrectomy with adrenalectomy was performed. The right and left renal veins, that were obstructed by NT, were isolated. The liver was mobilized to allow the exposition of the intra and supra hepatic VCI, completely occupied by the NT. Sternotomy and pericardiotomy were performed by the heart surgery equipe. Aortic arch, superior VC and the VCI just above iliac veins were cannulated. On normothermic CBP and beating heart, right atriotomy and a "J" incision on VCI were simultaneously performed. At the same time, the urologists and heart surgeons removed the NT from the RA, the left VR and the VCI. Part of the VCI wall was infiltrated by the thrombus and was resected. RA and VCI were closed and the patient was weaned from CBP. CPB time: 91 min; Surgical time: 6 hrs. Estimated blood loss 500 ml. Autologous blood transfusion: 700 ml. Pathological report: clear cell RCC pT3c Fuhrman G3 pN1. Intensive care stay: 5 days. Post operative in-hospital stay: 7 days. A post-surgical transthoracal echocardiography demonstrated regular parameters without any residual thrombus in RA and normal cardiac function. One month later, total body CT showed a regular VCI with no signs of persistent disease. *Conclusion:* In our experience, management of T3c kidney cancer with a beating heart normothermic CBP appears a feasible, safe and effective technique. As neither hypothermia nor heart arrest are needed, our technique improves patient recovery and diminishes risks of complications. Furthermore, with cannulation of lower IVC, other vascular access for lower venous return are not necessary.

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HORMONAL THERAPY PROMOTES HORMONE-RESISTANT PHENOTYPE BY INCREASING DNMT ACTIVITY AND EXPRESSION IN PROSTATE CANCER MODELS

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We hypothesized that hormonal therapy favors the development of the hormone-resistant phenotype through epigenetic mechanisms. Human prostate cancer tissues and *in vitro* and *in vivo* models were used to verify this hypothesis. We demonstrated that tumor cells continuously treated with bicalutamide (BCLT) or cultured in androgen-depleted medium progressively acquire higher DNA methyltransferase (DNMT) activity and expression than cells cultured in standard condition. Increased DNMT expression and activity also paralleled the up-regulation of truncated AR isoforms, which favors the development of the hormone-resistant phenotype. After androgen stimulation with 12 10− M dihydrotestosterone, DNMT activity was significantly reduced in comparison with hormonal therapy. Consistent with these observations, the silencing of DNMT3a and DNMT3b significantly decreased the DNMT activity levels. These findings were also directly correlated with PTEN downregulation and activation of ERK and PI3K/Akt pathways. The use of a pan-DNMT inhibitor (5Azacitidine) greatly reduced the development of the hormone-resistant phenotype induced by longterm BCLT treatment, and this finding correlated with low DNMT activity. The regulation of DNMT activity was, in some measure, dependent on the androgen receptor, as small interfering RNA treatment targeting the androgen receptor greatly decreased the modulation of DNMT activity under androgenic and antiandrogenic stimulation. These observations were correlated *in vivo* in patients, as demonstrated by immunohistochemistry. Patients treated by BCLT before surgery had higher DNMT3a and DNMT3b expression than patients who had not undergone this treatment. Our findings provide evidence of a relationship between the castration-resistant phenotype and DNMT expression and activity in human prostate cancer.

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THE VALUE OF BIOPSY LATERALITY IN ASSOCIATION WITH PSA AND GLEASON SCORE FOR THE IDENTIFICATION OF SUBJECTS AT HIGH RISK OF RECURRENCE IN PROSTATE CANCER

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Background: Predicting patients with prostate cancer (Pca) at high risk of recurrence (HRR) is a major challenge for clinicians. Clinical T-stage poorly predicts the pathological stage and understaging occurs in up to 60% of cases. Here we determine if needle biopsy parameters improve the value of NCCN criteria for predicting men at HRR. *Methods:* A retrospective survey of 488 men who underwent RP was undertaken. Univariate and multivariate logistic regression with receiver operating characteristic (ROC) curves were generated to test which parameters were able to best individulize men at HRR when histopathologic findings were used as the reference standard. The parameters were: PSA, biopsy laterality, total number of positive biopsy cores, clinical T stage, and Gleason score. The combination of best predictors then was compared with the standard NCCN criteria in terms of ability to predict HRR. *Results:* At univariate analysis all clinical parameters [biopsy laterality (OR=2.389; 95%CI 1.49 to 3.82; $p<0.0001$); Gleason score (OR=1.678; 95%CI 1.37 to 2.046; $p<0.0001$), total number of positive biopsy cores (OR=1.488; 95%CI 1.27 to 1.74; $p<0.0001$) and PSA (OR=1.329; 95%CI 1.26 to 1.53; $p<0.0001$)] except the clinical T-stage (OR=1.136; 95%CI 0.86 to 1.49; $p=0.343$) significantly predicted men at HRR. At multivariate analysis only biopsy laterality (OR=2.453; 95%CI 1.07 to 5.61; $p=0.033$), Gleason score (OR=1.847; 95%CI 1.38 to 2.46; $p<0.0001$) and PSA (OR=1.490; 95%CI 1.29 to 1.71; $p<0.0001$) were predictors of HRR. The association of PSA, Gleason score and biopsy laterality achieved a significant larger AUC (AUC=0.835; 95%CI 0.791 to 0.873; $p<0.0001$) than the association of standard parameters used in the NCCN criteria

(clinical T-stage, PSA and Gleason score) (AUC=0.685; 95%CI 0.630 to 0.736; $p<0.0001$) in the prediction of HRR. *Conclusion:* The biopsy laterality as replacement of clinical T stage contributes significantly to improve the value of NCCN criteria for predicting subjects at HRR.

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EVALUATION OF POSTOPERATIVE RADICAL CYSTECTOMY COMPLICATIONS: A MODIFIED CLAVIEN CLASSIFICATION SYSTEM ANALYSIS

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Introduction: The modified Clavien classification system has been proposed to classify and grade complications in general surgery and in the last years it is increasingly becoming a popular method in urology. Aim of our study was to evaluate the applicability of the modified Clavien classification system (CCS). *Patients and Methods:* A consecutive series of patients with primitive or recurrent bladder cancer treated with radical cystectomy from April 2011 to August 2011 at eleven academic centres in Europe were evaluated for complications occurring up to the end of the first postoperative month. Variables analyzed for each patient were: age, sex, asa score, anticoagulation therapy, type of diversion, operation time, preoperative hydronefrosis and BMI All complications were prospectively recorded and classified according to the modified CCS. Results were presented as complication rates per grade. Chi-square and Kruskal Wallis tests and binary logistic regression analysis were used for statistical analysis. *Results:* 194 patients were prospectively enrolled. Mean age was 57.8±12.7 years; mean BMI was 21.5±2.3 Kg/m^2. Mean bladder tumors size was 3.6±3.7 cm, mean number of bladder lesions was 2±2. All patients underwent radical cystectomy. Urinary diversion consisted in orthotopic neobladder in 44 patients (23%), ileal conduit in 89 patients (46%) and ureterocutaneostomy in 61 patients (31%). Mean operative time was 307±55 minutes. Mean hospital stay was 14.5±2.4 days. 185 complications were recorded in 123 patients. Overall perioperative morbidity rate was 63%. Most of them were not serious and were classified as Clavien type I (51 cases; 27.5%) or II (91 cases, 49%). Higher grade complications were observed: Clavien type IIIa in 15 cases (8%), IIIb in 18 cases (10%); IVa in 5 cases (3%), IVb in 2 cases (1%) and V in 3 cases (1.5%). Reoperation rate was 8% (16 patients) for severe wound infection (4 patients), urinary anastomosis leakage (4 patients) and ileal perforation or occlusion (7 patients). Patients who underwent ileal conduit urinary diversion presented a higher rate of CCS type I complications (58%) when compared to other urinary diversions ($p=0.034$). No significant association was found between Age, BMI, ASA score, anti-coagulant treatment, preoperative hydronephrosis, operative time, hospital stay and CCS type I or ≥IIIb complications. Patients with CCS complications type II and IIIa presented a significant longer operative time and hospital stay in univariate and multivariate analysis ($p=0.01$) (Table I).

Table I.

	CCS type II			CCS type IIIa		
	Yes	No	*p*	Yes	No	*P*
Operative time (m)	338±108	294±111	0.000	379±126	309±109	0.031
Hospital stay (day)	16.8±5	12.9±5	0.000	20.4±9.3	14.29±6.2	0.021

Discussion and Conclusion: The modified CCS represents a practical and easily applicable tool that may help urologists to classify the complications of radical cystectomy and urinary diversion in a more objective and detailed way. In our experience, using this CCS tool, radical cystectomy is associated with a higher morbidity (63%), an 8% reoperation rate and a 1.5% of mortality. Ileal conduit urinary diversion has a higher rate of type I complications. Longer operative time and longer hospital stay are associated with a higher risk of post operative complications.

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UPDATE OF THE SIURO-PRIAS-ITA PROJECT, THE ITALIAN EXPERIENCE IN THE PRIAS INTERNATIONAL COLLABORATIVE STUDY ON ACTIVE SURVEILLANCE

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Introduction and Background: Active Surveillance is being validated worldwide as an alternative to radical treatment (surgery, radiotherapy and brachytherapy) for low risk prostate cancer (PC). The aim of the study is to deal with the issue of overdiagnosis resulting from PSA based opportunistic screening, limit overtreating potentially indolent PC and avoid therapy-induced side-effects. On these assumptions the SIUrO-PRIAS-ITA project started enrolment in PRIAS (Prostate Cancer Research International: Active Surveillance), the international study on observational strategy in low risk prostate cancer patients coordinated by the Erasmus University Medical Center in Rotterdam, in December 2009. *Patients and Methods:* Eligibility criteria for SIUrO-PRIAS-ITA: PSA 10 ng/ml, Gleason Score 6 or Gleason 3+4 in over 69 yr men with <10% positive cores, T1c or T2, PSA density 0.20, max 2 positive bioptic cores (<10% positive cores in case of saturation biopsy), biopsy samples according to the volume (8 for 0-40, 10 for 40-60 and 12 for >60 ml), pathologic review of diagnostic biopsy. At inclusion extensive information on the disease, comorbidities, education, habits are collected and three questionnaires administered: IPSS, IIEF and FACTP. Despite the well known problems of misinterpretation of PSA values, biopsy-induced sequelae and biopsy-resulting false negative/positive reports, follow-up is still based on PSA every 3 months, clinical evaluation every 6 months, evaluation of PSA doubling time (DT), rebiopsy at 12, 48 and 84 months and possible extra biopsy (*i.e.* if PSA DT between 3 and 10 years). Exit criteria: 3 yr PSA-DT, upsizing and/or upgrading at the rebiopsy (Gleason 3+4 is accepted in over 69 yr men with <10% positive cores). *Results:* From December 2009 to March 2012, 255 patients from 8 Italian centers entered the study; mean age was 65.6 years (min 49 max 80); iPSA was <3 ng/mL in 10.6 % patients, between 3 and 6 ng/ml in 54.5%, between 6 and 8 in 27% and >8 in 7.9%. 222 patients are still on protocol with a median follow-up of 16.6 months (min 2 max 39); 33 discontinued active surveillance based on protocol or personal decision. Reasons for discontinuation were upgrading at rebiopsy in 4 cases, upsizing in 9 and upgrading plus upsizing in 5, PSA DT <3 years in 2 cases, other causes in 2 cases (a patient on follow-up for bladder cancer in a center not participating in SIUrO-PRIAS-ITA was erroneously prescribed hormonal therapy; a patient could not stop anticoagulants and repeat biopsy), personal choice in 11 patients. *Discussion and Conclusion:* Active Surveillance is proving an acceptable alternative for patients with low risk PC, which might harbour an indolent PC and thus overtreatment and treatment induced toxicities can be avoided. Unfortunately, the definition of

indolent cancer is still cloudy and there is no test yet able to distinguish between aggressiveness PC, which needs immediate treatment, and low aggressive PC. For this reason Active Surveillance should be carried on within protocols with well defined criteria for inclusion, follow-up management and discontinuation. The very important follow-up phase should be organized according to a precise scheme to guarantee high standard of care and switch to therapy should any modification in the clinical situation occur. Every effort should be made to systematically check adherence to the protocol criteria and limit the number of patients lost at follow-up.

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EPITHELIOID SARCOMA OF THE PENIS: A CASE REPORT

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Introduction: We reported a case of epithelioid sarcoma of the penis initially diagnosed and treated as Peyronie's disease. *Patients and Methods:* May 2010: a 20 years old man came to our outpatient department, referring the onset of a progressive left dorsal penile curvature (about 90°) that started 3 years earlier. The patient was evaluated with 2 US examinations that revealed two sites of tunical thickening with normal hemodynamic evaluation. The physical examination demonstrated a dorsal fibrotic plaque of about 2.5 cm. A new US confirmed presence of a fibrotic plaque determining a dorsal left deviation (39×25×5 millimetres) that prevented sexual intercourse. *Results:* A juvenile form of Peyronie's Disease was diagnosed and the patient was scheduled for surgical treatment (plaque's incision/excision and grafting). The surgical approach resulted difficult with penile degloving hampered by tenacious adherence between superficial layers and albuginea; the great part of the left corpus cavernosum appeared substituted by a very tough tissue which deeply involved the erectile tissue. The intraoperative biopsy was consistent with the possible diagnosis of mesenchymal epithelioid cancer with sarcomatoid differentiation. Because of lack of informed consent for radical excision and in order to wait for the definitive report from the pathologist, we proceed with the original plane, performing a wide excision of the pathological tissue and using buccal mucosa and acellular porcine dermal matrix for grafting. The final histological report confirmed the diagnosis of epitheliod sarcoma; a CT scan (total body) and a MRI abdominal-pelvic were done and were negative. June 2011: after a proper psychotherapeutic counseling, the patient has undergone a new operation. The intraoperatory histological examination of corpora cavernosa, of peri-urethral tissue and of neurovascular bundle, confirmed neoplastic involvement. The cavernosal bodies, the glans, the neurovascular bundle and great part of anterior urethra were excised. A portion of proximal urethra was preserved and covered with penile skin. *Conclusion:* In literature, only 13 cases of epithelioid sarcoma of the penis have been reported, so far. The low incidence, the slow progression of the disease and the aspecific ultrasound aspect, can justify a late diagnosis. In young patients suffering for idiopathic acquired penile curvature, greatest attention must be placed, with possible proposal of immediate biopsy or of explorative surgical intervention.

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THE IMPACT OF THE EXTENT OF LYMPH-NODE DISSECTION DURING RADICAL CYSTECTOMY FOR BLADDER CANCER ON CANCER-SPECIFIC SURVIVAL

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Background: We evaluated the associations between the number of lymph nodes retrieved during radical cystectomy (RC) for bladder cancer (BC) and the cancer-specific survival (CSS). *Patients and Methods:* We evaluated 229 consecutive patients submitted to RC for BC between November 1995 and October 2009 with complete follow-up data. Exclusion criteria were 1) neoadjuvant or adjuvant therapy 2) palliative RC 3) pNx patients 4) incomplete clinical and pathological data. Therefore, we evaluated 167 patients. Patients were divided into two LN-groups according to the number of LNs retrieved: group 1 (n=56, 33%) had 1 to 12 LNs removed; group 2 (n=111, 67%) had 13 or more LNs removed. Primary endpoint was the evaluation of CSS. *Results:* The mean follow-up was 52.6 months (1-172). Overall, among the 167 patients, the CSS rate was 67.1% and 57.7% at 5-ys and 10-ys respectively. Cancer-specific death was observed in 51 (30.5%) patients. The mean number of LNs obtained was 16.5 (143); 23 (10%) patients were N+, with a mean number of positive LN was 5.6 (1-19). Figure 1 shows the Kaplan-Meier curve for CSS with patients stratified by LN-group. At univariate and multivariate Cox analysis for clinical and pathological characteristics correlated with CSS, patients with

lower pathological stage, negative LN, conventional transitional cell carcinoma (TCC) and more LN retrieved had better CSS. *Conclusion:* In our study, patients undergoing a more extensive pelvic lymphnode dissection (PLND) have a better CSS than those undergoing a more limited one.Our data support a possible role of PLND on cancer outcome. Although the extent of PLND may indirectly influence the BCR because of the Will Rogers phenomenon, the inclusion of both node-positive and node-negative patients may partially exclude this bias.

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IMPACT OF RADICAL PROSTATECTOMY IN HIGH RISK PROSTATE CANCER PATIENTS

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Introduction and Objectives: High risk prostate cancer is an aggressive disease with an impaired long term survival prospective. We reviewed our institutional prospective database to assess the impact of radical prostatectomy and of adjuvant/salvage treatments. *Patients and Methods:* The review of a prospective database of 1179 subjects submitted to radical prostatectomy from 1991 to 2011 for clinically localized prostate cancer disclosed that 788 individuals had a complete dataset and 433 had one or more of the subsequent characteristics: preoperative PSA >= 20 ng/mL, pathological stage T3/N0, pathological primary Gleason score of 4 or 5. Excluding 28 subjects who received immediate hormonal therapy, 405 patients remained for the analysis. 401 had a minimum follow-up of 3 months, range 3±188, median 36. 132 (33%) had positive surgical margins *Results:* From March 2007, interquartile range March 2005 - July 2008, 31 (8%) were submitted to adjuvant radiotherapy. 43 (11%) were submitted to salvage radiotherapy at a median time of 31 months (range 7-106), whereas 51 (13%) to salvage hormonal therapy at a median time of 29 months (range 4±103). 11 (2.7%) patients died at a median follow-up of 45 months, range 19±147 months, 4 of prostate cancer and 7 of unrelated causes. A subgroup of 276 (69%) patients who were not submitted to any adjuvant or salvage therapy had a PSA <0.4 ng/mL at a median follow-up of 31 months, range 3±149 months. 262 (95%) were completely continent. 34 out of 123 (27%) evaluable had a satisfactory sexual activity with or without the use of oral drugs. *Conclusion:* High risk prostate cancer treated by radical prostatectomy offered excellent long term survival in our series even if the use of radio or hormonal therapy was limited to a minority of cases. Notably "cured" patients preserve almost always their urinary continence while sexual activity is impaired mainly due to the aggressive surgery performed.

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FEASIBILITY, SAFETY AND 1 YEAR FOLLOW UP OF EN BLOC TRANSURETHRAL RESECTION OF BLADDER TUMOR COMPARED TO A MATCHED COHORT OF PATIENTS SUBMITTED TO STANDARD TUR

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Background: The main limit of the standard TUR of bladder cancer is the fragmentation of the specimen which may hamper accuracy of pathological examination and oncological results. The en bloc TUR overcomes the problem. Unfortunately only small lesions fit for the procedure as the specimen is retrieved through the resectoscope with a standard evacuator. We developed a simple technical modification to retrieve specimens up to 4.5 cm and compared results in a matched cohort of patients submitted to standard TUR. *Objective:* To assess feasibility, safety and 1 year recurrence rate of the technique of modified en bloc TUR (EBTUR). *Design, Setting, Participants:* From March to September 2010, 26 consecutive patients gave their consent and were scheduled for EBTUR of a bladder tumor, 1 patient harboring invasive cancer was excluded from the analysis. Data were matched with a cohort of 50 patients submitted to standard TUR enrolled in a prospective trial with similar clinical and pathological characteristics. *Results:* There was no significant difference in regard to age, male to female ratio, ASA score, proportion of primary/recurrent cases, of single/multiple lesions, Ta/T1 lesions, lesions >3 or <3 cm in the 2 groups. The median dimension of the lesion extracted intact from the bladder in the EBTUR group was 2 cm, range 0.5-4.5 cm. 11 lesions were equal to or greater than 3 cm, and none of them was solid. Median postoperative catheter removal and discharge time was 2 days in both groups. No death or major surgical or medical complications occurred. Overall grade I-II, according to the Clavien Dindo classification, complications rate was 6/26 (28%) compared to 8/50 (16%) of the corresponding cohort (p=0.657). All patients completed 1 year of follow-up.1 year recurrence rate was 11/26 (42%) in the EBTUR group and 24/50 (48%) in the standard group (p=0.818). The main limits of the analysis were 1) the prospective non randomized dataset; 2) the small number of patients enrolled. *Conclusion:* Feasibility, safety and 1 year recurrence rate of EBTUR is comparable to a matched cohort of patients submitted to standard TUR. The objective advantage of an accurate pathological examination (identification of micro focal invasion of lamina propria or of muscular wall, surgical margins assessment) is associated with a substantial safe technique. Long term data and larger dataset of cases are necessary to demonstrate an advantage in terms of recurrence or progression.

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MALIGNANT MESOTHELIOMA OF THE TUNICA VAGINALIS OF THE TESTIS

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Purpose: Mesothelioma is a malignant tumor arising from pleura, peritoneum and pericardium; less than 5% originate from the tunica vaginalis of the testis. We report the case of a 67 years old patient who noticed a progressive volumetric increase of the right scrotum since 2009. In 2009 Ultrasound (US) showed a diffuse thickening both of the albuginea and vaginalis of the right testicle associated to voluminous hydrocele. MRI confirmed a right hydrocele associated with contrast-enhanced excretions and diffuse thickening of the tunica vaginalis. The appearance was diagnosed as a widespread vaginalitis and the patient was followed-up. In May 2011 the patient presented to our outpatient department because of a painful right-sided scrotal swelling; the physical examination demonstrated a voluminous hydrocele of hard consistency that extended in inguinal region. The radiological assessments confirmed the thickening and contrast-enhancement both of the albuginea and the tunica vaginalis. Patient underwent surgical exploration: the tunica vaginalis appeared to include by numerous small nodular masses which extended to the albuginea. Intraoperative biopsy showed a malignant mesenchymal lesion, probably a mesothelioma. So we decided to perform a right radical orchiectomy. The final histological examination confirmed the diagnosis of malignant epithelioid mesothelioma of the tunica vaginalis, with sarcomatoid and rhabdoid differentiation. A post-operative CT showed pulmonary, hepatic, pancreatic and bone multiple metastases. *Conclusion:* Malignant mesothelioma of the tunica vaginalis is an unfrequent and, in general, slow-growing neoplasia; even if prognosis for these mesotheliomas appear to be better than intrathoracic or intraabdominal disease, with a better survival and the clinical and radiological pattern is very similar to that of hydrocele, in doubtful cases fine needle aspiration cytology, biopsy and/or surgical exploration should not be postponed because sometimes the disease can have a highly aggressive course

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A RANDOMIZED PROSPECTIVE TRIAL TO ASSESS IMPACT OF TUR PERFORMED IN NARROW BAND IMAGING MODALITY ON NON MUSCLE INVASIVE BLADDER CANCER RECURRENCE

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Background: Narrow band imaging (NBI) is an optical enhancement technology for endoscopy which consists of filtering the standard white light into 2 bandwidths of illumination centered on 415 nm (blue) and 540 nm (green). NBI cystocopy increases the bladder cancer detection rate and therefore it may influence favorably recurrence rate. *Objective:* To assess impact of TUR performed in NBI modality on non muscle invasive bladder cancer with 1 year recurrence rate. *Design, Setting, Participants:* Consecutive patients with overt or suspected bladder cancer were included in a prospective study designed to disclose a 10% absolute difference of 1 year recurrence rate in favor of cases submitted to NBI TUR. Excluding patients with muscle invasive bladder cancer, negative pathological examination or without follow-up, the study population included 148 subjects randomized from August 2009 to September 2010 to NBI TUR, 76 cases, or standard TUR, 72 cases. Clinical, pathological characteristics and incidence of intravesical instillations in the 2 groups were similar. *Results:* Overall 25 patients (32%) recurred in the NBI group and 37 (51%) in the standard group (Chi square test, p=0.034). In multivariate analysis NBI was a protective factor against recurrence (odds ratio 0.4472, p=0.0297) as well adjuvant topic therapy (odds ratio 0.378, p=0.0309). *Conclusion:* TUR performed in NBI modality was able to reduce significantly and independently the 1 year recurrence rate of non muscle invasive bladder cancer of at least 10% in terms of absolute difference. Trial Registration: NCT0100421.

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INSULIN RESISTANCE (IR) AND PROSTATE CANCER (PCa):THE EFFECT OF NEOADJUVANT ANDROGEN DEPRIVATION THERAPY ON IR IN PATIENTS WITH A DIAGNOSIS OF PCa

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Background: PCa represents the most prevalent neoplasm, with an incidence rate of around 80 cases per 100000 per year, and the most common cause of cancer death in men (1). PCa has a multifactorial etiology and, in recent years, insulin and insulin like growth factor have been suggested to play a role in its development, although the mechanism underlying this effect has not yet been completely clarified (2). Androgen Deprivation Therapy (ADT) is nowadays one of the main tools in the medical treatment of PCa. ADT has been found to be associated with insulin-resistance (IR) and a consequent impairment of metabolic homeostasis (3). The aim of the present study was to evaluate the role of ADT in the development of IR and the correlation between IR index and the markers of PCa. *Patients and Methods:* Nineteen patients with PCa (age 58-74, mean: 66.2±4.1 yrs) were enrolled in the study and randomly divided into two groups: 9 patients were treated with ADT (cyproterone acetate, 400 mg/die) for three months whereas 10 patients remained untreated for the same period before surgical intervention. None of them had diabetes, three were obese, while five had metabolic syndrome according to ATP III classification. The study was performed at baseline and after three months of ADT or no treatment. The evaluation of anthropometric parameters (weight, BMI, waist, hip, waist-hip ratio (WHR)) and insulin-resistance indexes, as well as metabolic and hormonal parameters was performed in all patients at baseline and after 3 months, while at diagnosis biochemical and histological PCa markers (total prostate specific antigen (PSA), free (f) PSA, free on total PSA ratio (f/t), prostate health index (PHI), PCA 3, Gleason score) were also evaluated in all patients. Results WHR at diagnosis was directly correlated with PCA 3 and fPSA (p=0.035 and p=0.034 respectively); no other correlations were found between IR indexes or metabolic parameters and biochemical or histological PCa markers. In patients treated with ADT, HOMA-1 (p=0.01), HOMA-2 (p=0.01), Quicky (p=0.01), McAuley (p=0.01), fasting insulin (p=0.01) and post-glucose load insulin AUC (p=0.01) were significantly increased while testosterone and 17 β-oestradiol were significantly decreased (p=0.008 and p=0.01) after 3-months of therapy. Conversely, no significant change was found in anthropometric, metabolic and hormonal parameters as well as in insulin-resistance indexes in the subgroup of patient not treated with ADT. *Conclusion:* The preliminary results of the present study demonstrate that WHR, but not insulin sensitivity, is correlated with biochemical markers of PCa. Furthermore, ADT, represented by cyproterone acetate for three months, is able to impair insulin sensitivity according to the change in IR indexes. Further evaluations on a large cohort of patients are mandatory to draw a definitive conclusion on the relationship between insulin resistance and pathophysiology and prognosis of PCa.

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IS THERE A DIFFERENCE IN QUALITY OF LIFE BETWEEN INTRAVESICAL CHEMOTHERAPY AND BCG? RESULTS OF A RANDOMIZED PHASE II TRIAL

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Objectives: According to current evidence, BCG is perceived as less torelable than intravescial chemotherapy. Both these treatment options can be used as adjuvant treatment in intermediate-risk NMIBC. This is the first study to prospectively evaluate and compare the quality of life (QoL) of intermediate-risk NMIBC patients treated with chemotherapy or BCG. Gemcitabine, a promising intravesical agent for its efficacy and tolerability, was employed in the chemotherapy arm. *Patients and Methods:* We enrolled 120 intermediate-risk NMIBC patients. 61 were randomized to receive GEM 2000 mg/50 cc weekly for 6 weeks

(maintenance monthly for one year), while 59 BCG Connaught 1/3 dose weekly for 6 weeks (maintenance 3 weekly instillations at 3, 6 and 12 months). QoL was measured by EORTC QLQ-C30 and BLS-24 questionnaires at the following time intervals (T0 baseline, T1 after completion of induction cycle, T2 after 1 year). Adverse events were graded according to the CTCAE version 3.0. *Results:* 88 patients completed the study (47 in BCG-arm and 41 in the GEM-arm). Mean age was 67.4 years. At T1, the GEM-group showed a significant better QoL in cognitive (p=0.01) and emotional (p 0.03) functioning with moderate effect sizes as well as better QoL in urinary symptom distress (p=0.03) and intravesical treatment problems (p=0.01). At T2, the GEM-group showed a significant better QoL in cognitive functioning (p=0.01) with a moderate effect size as well as less symptom distress regarding nausea and vomiting (p=0.001) with a large effect size. No significant differences were recorded in the Global Health Status. Multivariate analyses showed no significant differences between the BCG and GEM group in all QoL dimensions (EORTC-QLQ-C30) including bladder cancer-specific quality of life. Treatment was well-tolerated in both groups, with a higher incidence of adverse events in the BCG-arm. *Conclusion:* Intravesical instillations caused a worsening of patients' QoL, irrespectively of the drug used. Gemcitabine showed a significant better tolerability profile than BCG in few specific items on univariate analysis not clearly attributable to intravesical therapy. Notably these differences were lost on multivariate analysis.

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ATYPICAL SMALL ACINAR PROLIFERATION (ASAP): IS REPEAT BIOPSY STILL WARRANTED?

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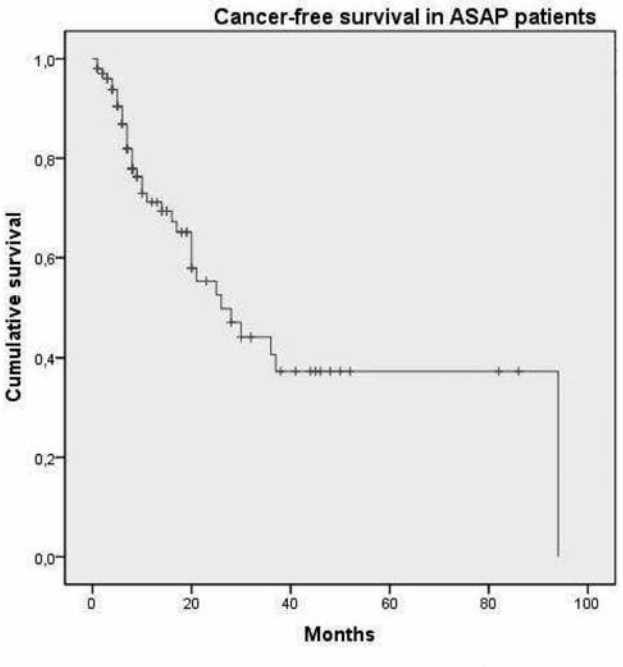
Introduction: Atypical small acinar proliferation (ASAP) indicates a situation of diagnostic uncertainty, highly predictive for prostate cancer (PCa) on subsequent biopsies. The PCa detection rate is estimated around 34-60% after an initial diagnosis of ASAP. According to recent evidence, the presence of ASAP would warrant a repeat biopsy within 3-6 months. Aim of the current study is to evaluate the natural history of ASAP and discuss indications and timing for a repeat biopsy. *Patients and Methods:* We analyzed our database of transperineal prostate biopsies performed in the period 2002-2010. We enrolled in study 101 patients who underwent repeat biopsy at any time after a previous diagnosis of ASAP. We analyzed the PCa detection rate at the rebiopsy and we estimated the PCa-free survival after diagnosis of ASAP using the Kaplan-Meier survival curves. *Results:* Among the 101 patients with ASAP, the PCa detection rate at rebiopsy was 36.6%, being 27.7% at the first rebiopsy (101 cases) and 37.5% at the second rebiopsy (N 24). Mean time from ASAP diagnosis to first rebiopsy was 11.8 months, whereas mean time from first to second rebiopsy was 17.5 months. According to Kaplan-Meier survival curves, mean PCa-free survival in ASAP patients was 45.4 months (standard error 5.69) (Figure 1). *Conclusion:* our 36.6% PCa detection rate at rebiopsy after diagnosis of ASAP, comparable to data reported in the literature, warrants the repetition of prostate biopsy. However, the long time elapsed before development of PCa questions the necessity of an early rebiopsy, suggesting the safe adoption of a longer time interval before repeating this procedure.



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TREATMENT OUTCOME OF PATIENTS WITH METASTATIC RENAL CELL CARCINOMA WITH POOR HISTOLOGICAL FEATURES

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Background: Sarcomatoid dedifferentiation in metastatic renal cell carcinoma (mRCC) is well established to be associated with biological and clinical aggressiveness that negatively impacts response to therapy. We assessed the influence of poor histological differentiation on clinical outcome of treated patients (pts). *Patients and Methods:* A single center database was reviewed to identify pts with mRCC with the following histological features of poor outcome to medical therapy. Pts included in the present study had sarcomatoid or poor differentiated (grade 3 or 4 according to the Fuhrman classification) mRCC histologies. Clinical outcome was evaluated as objective responses and progression-free survival (PFS), determined on the basis of the first-line treatment. *Results:* Twenty pts [14 M, 6 F; median age 62.6 years (range, 47-80 years); ECOG performance status (PS) of 0-1 in 15 pts and PS of 2 in 5 pts] were included in this analysis. Fourteen pts (70%) had a metastatic disease at the time of initial diagnosis and 19 pts underwent nephrectomy prior to medical therapy. Tissue samples for histological characterization were obtained from primitive tumor in these 19 pts. In one case pathological examination was done on the lung metastasis. Histology subtypes of the study population included 13 clear cell, 1 collecting duct and 6 high grade unclassified carcinoma. A sarcomatoid component was found in 9 cases. According to MSKCC prognostic score, risk group distribution was 15% good risk (n=3), 45% intermediate risk (n=9), and 40% poor risk (n=8). All pts began medical treatment during the period of January 2008 to October 2011 at Ospedale Niguarda Ca' Granda, Milan. First-line therapy was sunitinib in 12 pts (60%), temsirolimus in 3 pts (15%), sorafenib in 2 pts (10%) and bevacizumab plus interferon-alpha in 2 pts (10%). One patient was treated with chemotherapy containing adriamycin and ifosfamide. Among 19 pts evaluable for response, progressive disease (PD) was shown in 11 pts (57.9%) partial responses (PR) were observed in 4 pts (20%), while 4 pts (20%) had stable disease (SD) as their best response. In overall study population median PFS was 15.1 weeks [(95% Confidence Interval (CI)=9.3-21)]. No difference in PFS was observed on the basis of the presence or absence of sarcomatoid dedifferentiation [12.8 weeks (95% CI=8.4-17.2) *vs*. 16.8 weeks (95% CI=11-22.6), respectively. Log-rank test: p=0.97]. Instead the 8 pts with disease control rate (PR + SD) as best response had a significant greater PFS when compared with pts with PD [26.3 weeks (95% CI=12.3-40.3) *vs*. 12.4 weeks (95% CI = 8.3-16.5), respectively. Log-rank test: p=0.004]. Among the 19 pts with documented PD, only 8 pts (42%) received second-line treatment, due to the rapid clinical worsening. However none of these 8 pts had radiological response or any degree of tumor shrinkage. Median overall survival has not been reached and the 6-months survival rate was 70%. *Discussion and Conclusion:* In our series pts with poor differentiated mRCC had an unfavorable prognosis, independently of the presence of sarcomatoid component. The response to first-line therapy influenced disease outcome, in terms of greater PFS, conversely subsequent treatments had a marginal impact on clinical course. Due to the absence of definitive data, further studies to characterize tumor biology and develop novel treatment strategies are needed.

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PHASE II STUDY OF PACLITAXEL IN PATIENTS WITH METASTATIC PENILE CANCER

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Background: Previously published preliminary findings showed promising activity of paclitaxel in chemotherapy-pretreated metastatic penile cancer.Our aim was to evaluate the activity and safety of paclitaxel in pretreated metastatic penile cancer. *Patients and Methods:* Twenty-five patients were enrolled in a single-arm phase 2 multicentre study and treated with 175 mg/m^2 paclitaxel at 3-wk intervals until disease progression or irreversible toxicity. The objective response rate was the primary end point. Safety, progression-free survival (PFS), and overall survival (OS) were secondary end points. *Results:* Partial responses were observed in 20% (5 of 25 patients). Grade 1-2 neutropenia, nausea, and oral mucositis were the most common side-effects, noted in 13, 9, and 8 patients, respectively. Grade 3-4 neutropenia was reported in seven patients (28%). Median PFS was 11 wk (95% confidence interval [CI], 7-30); median OS was 23 wk (95% CI, 13-48). Median survival in responders was 32 wk (95% CI, 20-48), (Figures 1 and 2). One limitation of our study was the limited accrual, which did not reach the target of 27 patients, due to the typical slow enrolment of a rare disease. *Conclusion:* Final results of this study demonstrate that paclitaxel is moderately active and well tolerated. Further trials, which may also explore the combination of paclitaxel with other agents, are required to confirm our findings.

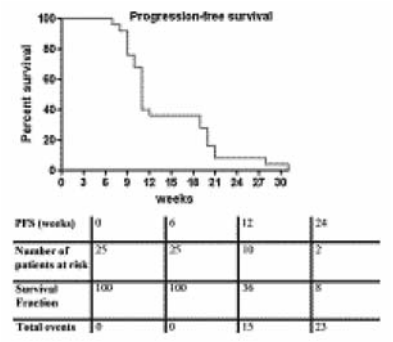

Figure 1

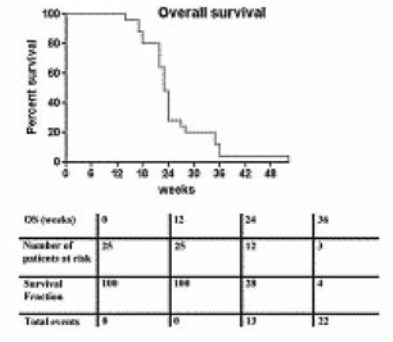

Figure 2

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DOSE-ESCALATED RADIOTHERAPY TREATMENT USING TOMOTHERAPY IN A MODERATELY HYPOFRACTIONATED REGIMEN FOR PROSTATE CANCER: RETROSPECTIVE MONOINSTITUTIONAL EXPERIENCE AT THE RADIOTHERAPY UNIT OF AOU POLICLINICO DI MODENA

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Aim: Curative treatment of patients with prostate cancer comprises surgery, radiotherapy (RT) with or without hormonotherapy. In external beam RT dose escalation is currently investigated to improve outcomes and several studies provide strong evidence for a dose-response relation of local tumor control, biochemical progression free survival and progression free survival. It's commonly known that dose escalation can also be achieved by increasing the dose per fraction above 2 Gy (as in our study) and several studies showed that prostate cancer cells may be strongly susceptible to this regimen due to their low alfa/beta ratio. Dose escalation and hypofractionation may hypothetically increase acute and late genitourinary and gastrointestinal toxicity but the introduction in recent years of IMRT may allow us to deliver higher doses without increasing toxicity. *Patients and Methods:* From February 2008 to December 2011 a total of 64 patients with histologically proven prostate cancer underwent radical radiotherapy treatment using hypofractionated regimen with or without concomitant hormonotherapy; all of them were treated using image guided radiotherapy with Tomotherapy. Median age was 71years (range 57-79 years). Eight of 64 patients had low risk prostate cancer (12.5%), 4 intermediate risk (6.5%) and 52 high risk (81%). All patients underwent rectal ultrasonography, biopsy, abdominal CT scan and pelvis RMN; at the end of the staging protocol 13 patients (20%) had T1 prostate cancer, 7 T2, 10 pts had T3a (15.6%) and 34 pts (53.1%) had T3b; abdominal lynphoadenopathy were found in only 5 pts (N1 stage). Of all patients, 34 received neoadjuvant (53.1%) and/or concomitant hormonotherapy, while 30 pts (46.8%) received even adjuvant hormonotherapy. Analysis of biopsies revealed a Gleason Score less than 7 in 23 pts, equal to 7 in 15 pts and superior in the other 16 patients; median Gleason score was 7. Radiotherapy was delivered to a median dose of 70 Gy (range: 45-74 Gy). Clinical target volume included just prostate in 2 pts, prostate and seminal vescicles in 34 patients (53%), while only in 28 patients (43.7%) pelvic abdominal radiotherapy (with prophilactic intent) was performed due to high risk of lymphatic extension (based on Roach algorithm). *Results:* After a median follow-up of 20 months 57 out of 64 patients are still free from disease (90%), while 5 pts (8%) are alive with locoregional disease and 2 pts (2%) developed metastatic disease. All patients with locoregional or systemic disease were submitted to hormonotherapy with LHRH. Radiotherapy treatment was well tolerated with only 4 patients complaining acute severe urinary toxicity, while 1 pt developed Grade 3 acute rectal side-effect. Late Grade 3 rectal toxicity was reported in 4 patients while Grade 2 urinary toxicity in 3 pts; no grade 3 urinary late toxicity were found. No treatment related deaths were encountered in our population.

Conclusion: Hypofractionated dose escalated radiation treatment using IG-IMRT with Tomotherapy seems to be feasible and well tolerated being able to obtain optimal outcomes reducing total treatment time without increasing acute and severe side-effects. Hypofractionation and dose escalation in radical or concomitant (hormonotherapy) setting should be considered in the management of non surgical prostate cancer.

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EVALUATION OF TRANSURETHRAL BLADDER RESECTION COMPLICATIONS: A MODIFIED CLAVIEN CLASSIFICATION SYSTEM ANALYSIS

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Introduction: The modified Clavien classification system (CCS) has been proposed to classify and grade complications in general surgery. It is increasingly becoming popular in urology although has never been used to date in common procedures such as transurethral resection of bladder tumor (TURB). The aim of our study is to evaluate the applicability of the modified CCS in reporting and grading the severity of perioperative complications in patients with bladder tumor treated with TURB. *Patients and Methods:* A consecutive series of patients with bladder lesions who underwent transurethral resection of bladder tumour (TURB) from April 2011 to August 2011 at six academic centres were evaluated for complications occurring up to the end of the first postoperative month. Variables analyzed for each patient were: age, sex, diabetes, hypertension, ischemic heart disease, score, tumor size, number of lesions, grade of tumor, anticoagulation therapy, type of diversion, operation time, preoperative hydronefrosis and BMI. All complications were prospectively recorded and classified according to the modified CCS. Results were presented as complication rates per grade. Chi-square, Kruskal Wallis tests and logistic regression analysis were used for statistical analysis. *Results:* 275 patients were consecutively enrolled. Mean age was 68.26±8.1 years; mean BMI was 28.3±4 Kg/m^2, mean tumour size was 2.38±2.3 cm; mean number of tumour lesions was 2.52±2.3. All patients underwent a monopolar TURB. Mean operative time was 43±28 m. Fifty-six complications were recorded in 51 patients. Overall perioperative morbidity rate was 18.5%. Most of them were not serious (haematuria and clot retention) and were classified as Clavien type I (42 cases; 75%) or II (8 cases, 14%). Higher grade complications were scarce: CCS IIIb in six cases (11%). No TURB related death was reported. Six patients were re-operated due to significant bleeding or clot retention on postoperative days 2-7. No significant association between Age, sex, ASA score, anti-coagulant treatment, BMI, tumor size, number of lesions, diabetes, hypertension, ischemic heart disease and hospital stay with the number of complications were observed. On univariate (73.5±38 *vs.* 36.7±21.6 minutes) and multivariate analysis longer operative time was the only independent parameter associated with a higher risk of CCS type I complications (OR: 1.040 per minute, 95%CI 1.025-1.055, p=0.001). Grade Complications I 42 II 8 IIIb 6 IV 0 V 0. *Conclusion:* The modified CCS

represents a practical and easily applicable tool that may help urologists to classify the complications of TURB in a more objective and detailed way. In our experience, using this CCS tool, TURB is a safe procedure with a low morbidity rate. Post-operative bleeding is the most significant complication that determines a reoperation. A longer operative time is a significant risk factor for not serious post-operative complications.

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HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) IN PROSTATE CANCER IN PATIENTS WITH LOW, INTERMEDIATE OR HIGH-RISK OF PROGRESSION

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Objective: HIFU is a minimally invasive treatment based on thermal ablation of tissues which are warmed up to 85˚C in the focal area. Clinical studies have shown such treatment modalit y to be safe and effective in the management of localised prostate cancer (1) as well as of local recurrences after radical prostatectom y or radiotherapy (2), but there are still few data in patients with high -risk localised prostate cancer: clinical stage > o or =T2c or Gleason score 8-10 or PSA >20 (3). *Patients and Methods:* From May 2 002 to February 2012, 179 patients with no previous treatment for prostate cancer, aged 44 to 86 years (mean 75) underwent 206 HIFU treatments; 27 patients needed a second treatment as the first was incomplete (4 patients) or because of recurrence (23 patients). The prognosis subgroups were defined as low -risk in 29 patients (clinical stage T1-T2a, PSA < or = 10 ng/mL and Gleason score lower than 7), intermediate -risk in 47 patients (clinical stage T2b or PSA 10-20 ng/mL or Gleason score of 7), and high-risk in 103 patients (clinical stage > or = T2c or PSA >20 ng/mL or Gleason score higher than 7). *Results:* At a mean follow -up of 79.3 months, biochemical success rate (PSA constantl y <0.5 ng/ml) was obtained in 82.8% of low and intermediate risk patients and in 42.7% of high risk patients; post -treatment biopsies (6 months after treatment) revealed no residual tumour in 92.1% of low or intermediate risk patients and in 58.2% of high risk patients. *Conclusion:* Radical prostatectomy remains the "gold standard" for localised prostate cancer. However, HIFU seems to be a promising alternative and less invasive treatment modality with an encouraging success rate, at least in the short-term, in patients with low and medium risk of progression, not candidates for radical surgery; in cancers with clinical stage >or=T2c, or PSA >20 ng/m L, or Gleason score higher than 7 seems to get good results in about half of patients.

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NEPHRON SPARING TREATMENT IN THE TRANSITIONAL CELL CANCER OF THE UPPER URINARY TRACT

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Purpose: Nephroureterectomy with excision of a cuff of bladder remains the standard for managing upper tract transitional cell carcinoma, which could, in selected cases, be managed conservatively (1). *Patients and Methods:* In 12 years we have treated 169 reno-ureteral unities (r.u.u.) for urothelial tumors; 107 r.u.u. with low-stage and low-grade disease (96 patients, 11 with bilateral tumor and 4 solitary kidney), were treated by an endoscopic approach; in 62 cases (5 for high grade recurrences after conservative approach) nephroureterectomy was performed. In 107 r.u.u. treated by ureteroscopic approach, we observed 5 high-grade recurrences (nephroureterectomy) and 34 low-grade (G1-G2) recurrences. Each r.u.u. received an average of 2.5 ureteroscopic operative procedures. The patients were followed up for a mean of 49.9 months after initial treatment and currently they are all recurrence free. 11/96 patients with suspect tumor of the upper tract (11.4%) had no carcinoma in the ureteroscopic biopsy.

Conclusion: Ureteroscopic approach of upper urinary tract urothelial tumors in the current literature has been used successfully (2), resulting in recurrence rates ranging from 31% to 65% and disease-free rates of 35% to 86% (1). Progression and metastatic rates are low and correlate with tumor grade.

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PREOPERATIVE P2PSA AND PROSTATE HEALTH INDEX PREDICT PATHOLOGICAL OUTCOMES IN RADICAL PROSTATECTOMY FOR PROSTATE CANCER

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Background: In men with prostate cancer, the clinical parameters used such as PSA, digital rectal examination, or biopsy Gleason sum, fail to accurately predict PCa aggressiveness. Therefore several biomarkers have recently been investigated with promising results.The objective of this study is to evaluate the use of prostate-specificantigen (PSA) isoforms p2PSA, percentage of p2PSA to free PSA (%p2PSA) and the Prostate Health Index (PHI), in predicting PCa characteristics at final pathology after RP. *Patients and Methods:* An observational prospective study was performed in 63 consecutive men diagnosed with clinically localised PCa who underwent RP at our istitution. None of the patients included in the current study receved neoadjuvant –deprivation therapy.We determined the predictive accuracy of p2PSA, %p2PSA, and PHI. The primary end point was to determine the accuracy of these biomarkers in predicting the presence of pT3 disease, pathologic Gleason sum <7, and tumour volume <0.5 ml. *Results:* The mean patients age was 66.3 yr (75-50), preoperative median tPSA, fPSA and fPSA-to-tPSA ratio values were, respectively 7.09 ng/mL, 1.03 ng/mL, and 6.2%. Median p2PSA, %p2PSA, and PHI value were respectively, 27.98 pg/ml, 1.62%, 69.83. Overall 34 patients (68.3%) were diagnosed with pathological grade Gleason Sum >7; 23 patients were diagnosed with pT3 disease. Tumor Volume <0.5 mL was observed in 6 patients. On bivariate analyses, %p2PSA and PHI were accurate predictors of presence of T3 disease, pathological grade Gleason sum >7 and tumor volume <0.5 mL. The p2PSA, %p2PSA and PHI levels were significative higher in patients with pT3 disease. Pathological Gleason sum >7 (all p value<0.001), respectively 30.50 *vs*. 26.53-1.21% *vs*. 1.86% - 77.67 *vs*. 65.23 Conversely in patients with tumor volume <0.5 mL p2PSA and PHI were significantly lower. *Conclusion:* In the current study, we investigated the relationship between p2PSA, PHI and PCa characteristics at final pathology in a group of men treated with RP for clinically localized prostate cancer. The results of the study supported the hypothesis that p2PSA and its derivate PHI, may predict the final pathological outcomes. Further studies are required to externaly validate our finding.

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ABIRATERONE ACETATE, AN EFFICIENT TREATMENT OPTION FOR ELDERLY PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CARCINOMA

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Background: Prostate cancer (PC) is the most common cancer in men in Europe and the United States, and the third leading cause of death from cancer in European men. Survival of PC cells is dependent on the activation of androgen receptors, that are overexpressed in this tumor. Furthermore, nearly 90% of PC patients responding to first-line androgen deprivation therapy (ADT) undergoes rapid progression. This condition is defined as castration-resistant prostate cancer (CRPC). Docetaxel based regimens significantly improve survival in patients with CRPC, and represent the only treatment strategy approved by FDA. Recently, the results of several studies have confirmed that activation of the androgen receptor is the key factor in the continued growth of PC. The landscape for PC treatment has changed with the approval of cabazitaxel, and abiraterone –a drug that significantly reduces androgen production by blocking the enzyme, cytochrome P450 17 alpha-hydroxylase. Blockade of androgen production by non gonadal sources has led to clinical benefit in this setting. Abiraterone (second hormonal therapy) has been shown to improve survival in patients with CRPC who progressed after docetaxel-based chemotherapy. Since cabazitaxel in older men has been shown to exert both high haematologic and extra-haematologic toxicity rates, we have chosen to treat unfit elderly patients with CRPC with abiraterone. The aim of this study was to evaluate the efficacy and tolerability of a treatment with abiraterone in elderly cancer patients with CRPC with disease progression after docetaxel-based chemotherapy. *Patients and Methods:* 27 elderly (>60 years) patients with CRPC were the target of this clinical investigation. They were consecutively treated, from February 2010 to December 2011, within the "compassionate use" program of abiraterone. Their median age was 72 yrs (range 60-81), and they had the following Gleason scores: 11 (1 pts), 9 (5 pts), 8 (5 pts), 7 (3 pts), 6 (1 pts), 4 (3 pts). 35% of the 27 pts received more than 2 lines of therapy, and 30% had visceral sites of metastatic disease. Abiraterone was administrated at standard daily dose of 1000 mg per os/die in parallel with prednisone. The study outcome was the evaluation of: 1) disease control by means of PSA and alkaline phosphatase; 2) clinical benefit by means of ECOG PS, hemoglobin level (Hb), and episodes of pain measured by VAS; 3) toxicity according to EORTC criteria. The median follow-up time was 5 months, and at each follow-up (FUP) visit individual variations (+/–) of PSA, Hb, PS, AP and VAS were evaluated as a percentage of the baseline value. *Results:* The PSA steadily decreased during the FUP, starting at 2-month FUP to reach –53.9% than the baseline value at 4-month FUP, while alkaline phosphatase started to decrease at the 5-month FUP. Regarding clinical benefit, the Hb levels constantly increased since the first FUP to reach +15.2% at 7-month FUP. PS and VAS values showed a positive trend after 1-month FUP. Three pts experienced grade 2 gastrointestinal toxicities, 1 pts grade 1 metabolic toxicity and 1 pts grade 1 cardiovascular toxicity. None of the pts reported grade 3 or 4 toxicity. *Conclusion:* These preliminary data indicate that abiraterone used in the daily routine is associated with a good response rate -in terms of disease control and clinical benefit- with acceptable side-effects also in elderly patients. This observation has encouraging implications for the management of PC patients and its therapeutic role in CRPC deserves attention.

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DIFFERENT PSA KINETICS AFTER BRACHYTHERAPY OR EXTERNAL BEAM RADIATION THERAPY IN LOW-RISK PROSTATE CANCER

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Aim: Due to a slow process of tumor-cell killing, PSA levels after radiotherapy (RT) gradually decrease, and PSA remains detectable until reaching a nadir value in 2-5 years. Aim of the present study is to retrospectively evaluate PSA kinetics in a cohort of low risk prostate cancer patients treated either with brachytherapy (BRT) or external beam radiotherapy (EBRT). *Patients and Methods:* Clinical records of 150 consecutive low-risk (NCCN risk classification) prostate adenocarcinoma patients were selected from our database. Between April 2003 and December 2009, 69 patients underwent BRT and 81 EBRT. Patients treated with androgen-deprivation therapy (ADT) prior to RT, with a minimum follow-up >24 months and/or with >4 PSA measurements after RT were excluded. PSA nadir (nPSA), Time to PSA nadir (TnPSA), bounce PSA (bPSA) and Time to bounce PSA (TbPSA) were evaluated in the 2 groups by using univariate and multivariate analysis. Nadir PSA was defined as the lowest PSA value after RT; bPSA was defined as a post-treatment PSA rise >0.4 ng/ml followed by a spontaneous decrease to pre-bounce level or lower; biochemical failure (BF) was defined as biochemical relapse according to the ASTRO-Phoenix definition or introduction of ADT. *Results:* Median age was 67.4 years (range 53-77) in BRT group and 68.9 years (range 56-80) in EBRT group. Median pre-treatment PSA value was 6 ng/ml in both groups.

A total of 1574 PSA measurements (754 in BRT group and 820 in EBRT group) were recorded after RT. Median follow-up time was 51 months (range 24-101) in BRT arm and 55.6 months (range 24-99.3) in EBRT arm. Biochemical disease-free survival (bDFS) was similar for the 2 arms: at 36 months 96.7% (95% Confidence Interval [CI]: 87.3%99.2%) in BRT arm and 98.8% (95% Confidence Interval [CI]: 91.6%-99.8%) in EBRT arm (p=0.72). The median time to BF was 31 months (range, 31-90) after BRT and 52.92 months (range 11-72) after EBRT. The median nPSA was 0.18 ng/mL (range 0-0.94 ng/mL) in the BRT group and 0.28 ng/mL (range, 0-2.01 ng/mL) in the EBRT group (p<0.001). The median time to the nPSA was longer after BRT than EBRT (38.47 months *vs*. 26.37 months; p<0.01). Twenty-six patients (37.7%) in the BRT group and 11 patients (13.6%) in EBRT group experienced a bounce PSA at any time during follow-up (Chi-square p=0.001). Bounce PSA occurred earlier after BRT (median time to bPSA 22 months; range 10-40 months), than after EBRT (median time to bPSA 31 months; range 9-47 months) (t Student p=0.04). *Discussion and Conclusion:* In low-risk prostate cancer patients, PSA kinetics after BRT or EBRT significantly differs. After BRT, lower nPSA values and longer TnPSA were expected because of the higher dose delivered. Rising PSA levels in the first 24-36 months after BRT should be considered with caution (nearly 40% of patients experienced a PSA bounce, and this phenomenon may cause anxiety and unnecessary start of hormonal therapy). Longer follow-up time and a larger study population are required to identify an optimal nPSA cut-off after each radiation treatment modality.

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SMALL CELL CARCINOMA OF THE BLADDER: A CASE REPORT AND REVIEW OF LITERATURE

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The tumor-small cell represents an extremely rare variant of neuroendocrine tumor of the bladder for which are not standardized therapeutic trials. *Patients and Methods:* Woman 47 yrs, smoker, with repeated episodes of hematuria. TC: "thickening" plaque "of 30 mm of the floor." TURV: "cr undifferentiated urothelial infiltrating the muscularis, with neoplastic invasion of vascular spaces." Cystectomy was performed in March 2011. Histological report: "cr. urothelial cells associated with small cr. urothelial high grade, infiltrating the muscularis full thickness ". After adjuvant chemotherapy: the first line (4 cycles) with gemcitabine 1000 mg/sqm + cisplatin 80 mg/m^2. Second line protocol ACOCEV: adriablastin 30 mg/sqm + cyclophosphamide 400 mg/sqm + vincristine 1.4 mg/m^2 + + carboplatine VePesid 60 mg/m^2. *Results:* The small cell cancer of the bladder is an extremely rare manifestation of neuroendocrine tumors: about 900 cases since 1981. Neurondocrine tumors include carcinoid and neuroendocrine tumors are divided into small cell and large cell neuroendocrine tumor. Unlike the lung bladder rarely gives paraneoplastic syndromes (hypercalcemia, S. Cushing, neuropathy) and is rarely pure. Incidence is approximately 0.7%, three times higher in males than females, 50 to 70% of patients are smokers, mean age 67 years. Diagnosis is usually invasive and shows spread with repetitions instrumentally detectable. Characteristics include gross hematuria (95%), strangury, urethral obstruction, infection and irritative symptoms. The pathological criteria are small, round or oval, scant cytoplasm, high mitotic count, nuclear material finely dispersed, absent or inconspicuous nucleoli. Common finding is necrosis and perivascular tissue. As a neuroendocrine tumor immunostains are essential: chromogranin, synaptophysin (>60%), the leu-7, TTF-1 (40%), Other reported indicators include p53 (75%), c-kit (27%) and EGFR (27%). Comparative studies of genomic hybridization show frequent alterations such as genomic deletions of 10q, 4q, 5q and 13q, and transposition of 8p, 5p, 6p and 13q. Possible metastases may be diagnosed by CT: retroperitoneal lymph nodes, lung, bone and brain. Because of the rarity there are no validated therapeutic trials and review of the literature shows that the most common therapeutic approach is the combination of chemotherapy and radical cystectomy and the latter using the same protocols as for the respiratory system. Radiotherapy is important in the treatment of secondary lesions in the brain, bone pain and neurologic compression. A review of the literature shows that the prognosis is worse for pure carcinomas, compared to the mixed ones. In the study by Nabil Ismaili, patients with disseminated disease treated with chemotherapy alone, median survival was not different from those who performed cystectomy and adjuvant chemotherapy (13.7 months *versus* the 14.8). The worst results were obtained by adopting the radical cystectomy alone, as evidenced by the study of Stev *et al*. (2004). This is confirmed by a retrospective study of 'MD Anderson Cancer Center in 46 patients, in which the five-year survival was increased by 78% in the case of neo-adjuvant chemotherapy and cystectomy, compared to only surgical

approach (survival less than 36%). In a study of the Mayo Clinic, cystectomy and chemotherapy have led to a survival rate of 70% at 2 years and 44% at 5 years.

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ADJUVANT HIGH DOSE RADIOTHERAPY FOR PROSTATE CANCER: A SAFE AND FEASIBLE TREATMENT

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Aim: Local failure after radical prostatectomy (RP) is common in patients with cancer extending beyond the capsule. Two randomized trials demonstrated an advantage for adjuvant radiotherapy (RT) compared with a wait-and-see policy (1, 2). However the optimal dose of external beam radiotherapy remains controversial. This study aimed at evaluating the feasibility of high dose radiotherapy after radical prostatectomy in locally advanced and/or positive resection margin adenocarcinoma of the prostate. *Materials and Methods:* A retrospective analysis was conducted on 119 men treated with adjuvant radiotherapy after radical prostatectomy between 2000 and 2011, because of locally advanced stage (pT2-4, pN0-1 and/or positive surgical margins). The volumes to be treated were defined as follows: pelvic lymph nodes (CTV2), prostatic fossa and the region of seminal vesicles (CTV1). A dose of 45 Gy (1.8 Gy/fx) was given to the PTV2, followed by a boost to the PTV1 to a total dose ranging between 64.8 and 71 Gy. Pelvic irradiation was performed using 3D conformal RT (box technique) in all patients, while boost irradiation was performed using 3D-RT (box 4) or IMRT (step and shoot; 5 coplanar beams 6 MV photons). Acute toxicity was evaluated according to the RTOG scale, while EORTC-RTOG scale was used for late toxicity. Biochemical freedom from failure was defined as the maintenance of a serum PSA level ≤0.2 ng/ml, while freedom from failure was considered as the absence of clinical local recurrence and distant metastases. *Results:* The median age was 64 years (range 46-78). The median follow-up was 44 months (range 4-123). The median pre-operative PSA level was 9.5 ng/ml, while median post-operative PSA was 0,1 ng/ml. All patients completed RT. Pathological stages were distributed as follows: pT2a: 1 (0.9%), pT2b: 3 (2.5%), pT2c: 12 (10.1%), pT3a: 55 (46.2%), pT3b: 43 (36.1%), pT4: 5 (4.2%); pN0: 106 (89%), pN1: 13 (11%); R0: 40 (33.9%), R1: 78 (66.1%). Adjuvant hormonal therapy was prescribed in 78 (65.5%) patients because of high risk of failure. Treatment toxicities were scored according to the EORTC-RTOG scoring scales. Acute Grade 2 gastrointestinal (GI) toxicity was seen in 23/119 (19%) patients, while acute grade 2 genitourinary (GU) toxicity was seen 19/119 patients (15.9%). Three patients showed grade 3 acute GI and four GU toxicity. At median follow-up period of 44 months (range 4-123), two patients (1,6%) had grade 3 late GI toxicity and three (2,5%) had grade 3 late urological toxicity. Despite the retrospective nature of the analysis, our data show an improvement both in overall survival and biochemical free-survival. Indeed, on univariate analysis, the actuarial 5-years overall survival was 95%, while the actuarial 5 years biochemical failure free survival was 85%. *Discussion and Conclusion:* In our experience doses ≥70.2 Gy were administered with acceptable toxicity grade (>2) late gastrointestinal and genitourinary toxicities were observed only in 3.3% of patients. Furthermore, these results confirm the positive impact of the RT ≥70.2 Gy in patients at high risk of disease recurrence after radical prostatectomy, with an increase of biochemical relapse free survival. However, further follow-up is needed to assess the effect on biochemical disease-free survival and overall survival.

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ROLE OF URINARY DIVERSION ON COMPLICATION RATE AFTER RADICAL CYSTECTOMY: RETROSPECTIVE STUDY ON A SINGLE-CENTRE COHORT OF 407 CONSECUTIVE PATIENTS

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Introduction: Radical cystectomy (RC) with urinary diversion (UD) is the urological surgical procedure with the higher rates of morbidity. Aim of this study is to evaluate if the type of UD influences the risk of postoperative complications. *Patients and Methods:* At our institution the type of UD is chosen on the basis of the operative risk and oncological features. Thus, generally, ureterocutaneostomy (UCS) is reserved to high risk patients, neobladder (NB-VIP technique) to low or intermediate risk patients, affected by cancer <=cT2/T3a and not involving the prostatic urethra,

ileal conduit (IC) to all the other patients. The data of the 407 consecutive patients undergone RC between 2001 and 2011 at our institution have been perspectively stored in a dedicated DB. Post-operative complications have been classified according to the Clavien-Dindo system. By a binary logistic regression, it has been evaluated in uni and multivariable analysis, which factors were associated with a complication grade 3 or more. Continuous variables have been reported as mean±standard deviation or median and interquartile range (25-75), as appropriate. *Results:* 73 patients (17.9%) have been submitted to UCS, 223 (54.8%) to IC and 111 (27.3%) to NB, and Table I summarizes their characteristics.

Table I

	UCS	IC	NB	*p*
Age (yrs)	74.3±7.8	70.4±8.1	60.6±8.9	<0.001
Male gender	74.0% (54 pz)	82.1% (183 pz)	81.1% (90 pz)	0.312
Charson-Romano score	2 (1-4)	2 (1-3)	1 (0-2)	0.001
ASA score	3 (3-3)	3 (2-3)	2 (2-3)	<0.001
BMI	26.1±3.7	26.3±4.3	26.3±3.6	<0.001
Operative time (hours)	5.00 (4.50-5.50)	5.75 (5.25-6.50)	6.17 (5.50-7.00)	<0.001
LAD	83.6% (56 pz)	92.7% (200 pz)	88.1% (96 pz)	0.002
pT>=3	66.7% (46 pz)	56.0% (121 pz)	35.2% (37 pz)	<0.001
pN+	25.4% (17 pz)	21.1% (46 pz)	15.7% (17 pz)	0.002
Alimentation (days)	5 (4-7)	7 (6-9)	7 (6-9)	<0.001
Hospital stay (days)	22 (15-35)	20 (16-24)	24 (20-29)	<0.001

Overall, 405 events of complications have been registered in 248 patients (60.9% of the cohort), with a median of 1 event of complication/patient (1-2); the worst complication has been grade 1 in 70 patients (28.2%), 2 in 131 (52.8%), 3a in 16 (6.5%), 3b in 13 (5.2%), 4a in 7 (2.8%), 4b in 3 (1.2%) and 5 in 8 (3.2%). Table II summarizes the results of statistical analysis.

Table II

Factor	*p*	HR (95%CI)	*p*	HR (95%CI)
Age (yrs)	0.002	1.035 (1.013-1.057)	0.386	1.012 (0.985-1.039)
Male gender	0.613	0.758 (0.609-0.944)	-	
Charlson-Romano score	0.003		0.200	
0	referent		referent	
1-3	0.11	1.844 (1.148-2.964)	0.162	1.438 (0.865-2.932)
>=4	0.001	2.817 (1.518-5.228)	0.085	1.829 (0.921-3.635)
ASA score 3-4	<0.001	2.434 (1.585-3.737)	0.005	1.931 (1.214-3.069)
BMI	0.425	1.011 (0.998-1.024)	-	
Operative time (hours)	0.207	0.853 (0.666-1.092)	-	
LAD	0.589	0.817 (0.392-1.703)	-	
pT>=3	0.609	0.838 (0.636-1.104)	-	
UD	<0.001		0.007	
UCS	referent		referent	
IC	<0.001	0.373 (0.215-0.647)	0.004	0.441 (0.251-0.775)
NB	<0.001	0.260 (0.140-0.486)	0.003	0.364 (0.186-0.714)

Discussion and Conclusion: This study confirms that RC is a surgical procedure with a high rate of complications (>60%), severe (grade >=3) in 18.9% of the cases. The factors with an impact on this risk have been a high ASA score (3-4) and the UCS as UD. However, the latter conclusion should be considered cautiously without stating that IC and NB are UDs with a lower risk in all the patients, especially in the ones for whom UCS is usually reserved. Anyway, from these data it is possible to speculate that IC and NB are at least no more morbid than UCS. Finally, we can conclude that the

commonly available clinical data are poor predictor of the risk of complications after RC.

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PROSTATIC CAPSULE AND SEMINAL SPARING CYSTECTOMY: ONCOLOGICAL AND FUNCTIONAL OUTCOME. A TEN YEARS EXPERIENCE

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Introduction: Prostatic Capsule and Seminal Sparing Cystectomy (PCSSC) is a choice for invasive bladder cancer and for high grade, refractory to conservative therapy, multifocal and quickly recurrent superficial bladder cancer, in patients determined to preserve erectile function and early continence recovery. The aim of the study is to evaluate oncological and functional results in our series of patients undergone PCSSC. *Patients and Methods:* We retrospectively reviewed clinical and pathological data of 30 consecutive patients (mean age 59.4, range 44-73 years) undergone PCSSC with VIP orthotopic ileal bladder reconstruction for transitional cell carcinoma (TCC) histopatologically confirmed after transurethral resection (TUR-BT). Overall, 19 patients (63.3%) underwent surgery at first-dignosed, sporadic, T2 high-grade TCC; 11 patients (36.7%) had single to multifocal non-muscle invasive lesions, refractory to intravescical immunotherapy with BCG. Our exclusion criteria were: posterior wall, trigonal, bladder neck or prostatic urethra involvement and suspected prostatic cancer. Preoperative staging included: physical examination, PSA, digital rectal examination, chest X-ray, renal function evaluation, CT-urography. All cases were restaged according to 2009 TNM classification. Potency and continence were evaluated preoperatively and at months 1, 3, 6, 12 with IIEF-5 and ICIQ male questionnaire. *Results:* Mean follow-up was (range) 67.7 (1-132) months. Definitive pathological staging was: 14/30 ≤T1, 8/30 T2 and 8/30 T3. In 1 case a single lymphnode tumoral involvement was found; in 1 patient an incidental small prostate cancer focus (T1a, Gleason 3+3) was found. Two patients died perioperatively due to thrombohembolism, one for colon cancer 44 months after PCSSC and five for metastatic TCC (mean time to progression: 34.6, range 9-72 months; mean cancer specific survival: 34.7, range 6-86 months). Two patients are currently on follow-up after chemotherapy with stable residual disease. Overall 26/28 (92.8%) patients completely fulfilled our continence criteria (no pads) on daytime and 23/28 (82.1%) resulted continent on night-time. Continence rates obtained at catheter removal and at 1,3,6,12 months were 64.2% (18/28), 78.5% (22/28), 87.5% (24/28), 89.2% (25/28) and 92.8% (26/28) respectively. In 21/28 cases we observed spontaneous recovery of erectile function at mean 1.3 months after surgery (range 1-3); two patients required oral medical therapy (*i.e.* phosphodiesterase-5 inhibitors). During follow-up 2 patients developed major complications: 1 urethral stricture discovered and treated by cold endoscopic incision 7 months after PCSSC and 1 pyonephrosis due to ureteral reflux treated by nephrectomy 14 months after surgery. *Conclusion:* In our experience, prostatic capsule and seminal sparing cystectomy can be considered oncogically safe; the saving of prostatic capsule determines an early continence and erectile recovery without increasing the risk of leaving neoplastic tissue *in situ*. The accurate selection of patients represents a crucial phase to reach the best oncological and functional outcome. Our study suggests the need of multicenter randomized trials to define standard indications and an operative algorithm with regards to tumor features, patients' performance status and wishes.

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CLINICAL AND PATHOLOGICAL OUTCOME AFTER RADICAL AND NERVE SPARING ANTEROGRADE PROSTATECTOMY FOR BIOPTIC GLEASON SCORE ≥7 AND PSA ≥10 NG/ML

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Objectives: To evaluate long term clinicopathological outcomes in intermediate to high risk patients but otherwise clinically localized prostate cancer (PCa) and Gleason score (GS) ≥7 disease treated by anterograde radical prostatectomy (ARP), and to analyze the well known predictors of progression in this cohort. *Methods:* We prospectively recruited 183 patients with GS ≥7, preoperative PSA ≥10 ng/ml and clinically localized PCa undergoing ARP from 2000 to 2010, selected from our institutional RP database of 1328 patients. The clinical and pathological features were evaluated. Survival analysis was performed using the Kaplan Meier method. Logistic regression was used to determine predictors of unfavorable disease. *Results:* 51.3% of patients presented a pathological GS 7, while 48.7% resulted 8-10. We obtained a prevalence of 79.8% PCa with extracapsular extension, 20.2% of patients were N0 at final pathological examination. Incidence of positive surgical margins was 20.7% with a prevalence of pT3-4 (86.9%); 7.1% with concomitant lymph node involvement. The mean follow-up was 39.1 months (median 31.5, range 6-119). The progression free survival rate for all patients was 64.8% and 55.1% at 3 and 5 years

respectively. Above all 25.7% of patients had biochemical recurrence (BCR) and mean time to biochemical failure was 13 months (median 11, range 3-56). Of the 102 patients with bioptic GS 7, in 79.4% it was confirmed at the final pathological specimen, while in 20.6% there was a higher pathological GS (8-10). A statistically significant difference was found in BCR-free survival comparing the 5-year survival rates for GS and pTNM. For those with pathologic GS 7 and 8-10,BCR free survival rates were 63.9 and 45.4% respectively (p=0.015), while for those with pT2, pT3a, and pT3b were 78.3, 68.6 and 28.9% respectively (p<0.0001). Overall, Nerve Sparing (NS) technique was performed in 23 patients (12.5%). Mean preoperative PSA in the 23 patients with Bilateral or Monolateral NS RP was 13.3 ng/ml (median 13, range 10.0-47.76), mean age was 63.4 (median 64, range 52-78). Bioptic GS was 7 in 91.3% of them, but after final pathological examination it resulted equal to 7 in 65.2% patients. Prevalence of organ confined disease was observed 43.5%, while it was 56.5% for ECE, with few cases of seminal vesicle invasion (21.1%). Only 3/23 patients (13%) presented BCR with a mean time of 21.3 months (median 24, range 4 – 36). Survival analysis according to NS stratification (Bilateral and Monolateral) didn't show a significative difference compared to the radical approach (p>0.05). Pathological GS (p=0.02), pTNM (p<0.005), surgical margin status (p<0.005) and lymphnode involvement (p=0.02) demonstrated to be predictors of unfavorable disease at univariate logistic regression. On the contrary at the multivariate logistic regression preoperative PSA level, bioptic and pathological GS and surgical margin status had no statistically significant impact on BCR-free survival. The multivariate Cox model showed tumor stage as the only independent prognostic factor for BCR, especially seminal vesicle invasion to be the only independent prognostic factor (p=0.018). *Conclusion:* Cancer specific survival in our study indicated that selected patients with intermediate to high risk PCa who undergo RP can experience a survival benefit, even when NS surgery was adopted though men with unfavorable disease fared poorly.

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PHI AND PCA3 SIGNIFICANTLY IMPROVE DIAGNOSTIC ACCURACY IN PATIENTS UNDERGOING PROSTATE BIOPSY

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Background: Prostate health index (phi) and prostate cancer antigen 3 (PCA3) have been recently proposed as novel biomarkers for prostate cancer (PCa). We assessed the diagnostic performance of these biomarkers, alone or in combination, in men undergoing first prostate biopsy for suspicion of PCa. *Patients and Methods:* One hundred and sixty male subjects were enrolled in this prospective observational study. PSA molecular forms, phi index (Beckman Coulter immunoassay), PCA3 score (Progensa PCA3 assay) and other established biomarkers (tPSA, fPSA and %fPSA) were assessed before patients underwent a 18-core first prostate biopsy. The discriminating ability between PCa-negative and PCa-positive biopsies of Beckman coulter phi and PCA3 score and other established biomarkers were determined. *Results:* One hundred and sixty patients met inclusion criteria. %p2PSA, phi and PCA3 were significantly higher in patients with PCa compared to PCa-negative group (median values: 1.92 *vs*. 1.55, 49.97 *vs*. 36.84 and 50 *vs*. 32 respectively, $p \leq 0.001$). ROC curve analysis showed that %p2PSA, phi and PCA3 are good indicators of malignancy (AUCs=0.68, 0.71 and 0.66, respectively). A multivariable logistic regression model consisting of both the phi index and PCA3 score allowed to reach an overall diagnostic accuracy of 0.77. Decision curve analysis revealed that this "combined" marker achieved the highest net benefit over the examined range of the threshold probability. *Conclusion:* Phi and PCA3 showed no significant difference in the ability to predict PCa diagnosis in men undergoing first prostate biopsy. However, diagnostic performance is significantly improved by combining phi and PCA3.

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EXCAVATED LUNG METASTASES IN METASTATIC RCC (MRCC): PSEUDOPROGRESSION AS A RESPONSE TO SUNITINIB

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Introduction: mRCC is the most common form of kidney cancer. Surgical resection remains the treatment of choice for most patients with mRCC. Although the recent availability of targeted agents has improved outcomes for these patients, it has also increased the complexity of treatments available to clinicians and these targeted therapies have significantly altered the management of pts with mRCC. In current guidelines, in Europe, one of the standards first-line therapy, for the good and intermediate risk group, is sunitinib a TK Inhibitor. In this report we describe the case of an old patient with mRCC who achieved a particular clinical response with TKI therapy: excavated lung lesions. *Patients and Methods:* A 69-year-old man presented with cough. He had hypertension and a Karnofsky performance score of 90. His physical examination was negative for peripheral adenopathy, organomegaly, or abdominal masses. Diagnostic evaluation revealed normal laboratory tests. The CT scan of the chest was positive for metastatic disease and mediastinal nodes. On a CT scan of the abdomen, he had a 6 cm mass in the middle of left kidney, left renal hilar lymphadenopathy, and thrombosis of the vena cava. The pt underwent left radical nephrectomy, surrenectomy and nodes debulking, The pathological stage was characterized as T1bN0M1. The pathology was consistent with Fuhrman grade 4, clear cell renal cell carcinoma with sarcomatoid component. In July 2011, after surgery, his performance score declined to 70. On physical examination, he had decreased breath sounds in the lung, and LDH level was slightly elevated. The CT scans of the chest and abdomen revealed an increase adenopathy in the mediastinum, an increase of metastatic lung lesions, but no pleural effusion. In August the patient began therapy with sunitinib 50 mg daily, 4 weeks on, 2 weeks off. In November after 2 cycles of treatment the pt showed very persistent cough without fever or other symptoms. He had an examination by pneumologist and he began a course of antibiotics for 10 days associated with bronchodilators aerosol drugs. The CT scan of the chest showed an increase of the diameter of lung excavated metastases (1 lesion increased in diameter from 23 to 37 mm but with excavation in the middle of 29 mm) and an overall reduction of metastasis by 10%. We delayed the treatment by week because of neutropenia G2/3 until recovery and then we reduced the dose of sunititib to 37.5 mg/day, 4 weeks on and 2 weeks of. After 1 month of treatment, at the end of third cycle, cough disappeared and patient improved his PS. After 4th cycle the CT scan showed a reduction in number and size of all lung nodules, and the response was greater than 30%, the biggest lesion was 20 mm. His best response appeared after only 2 cycles as psedoprogression and his performance score improved. He had mild adverse events characterized by grade 1 fatigue, grade 2/3 neutropenia, and grade 1 anemia. He responded to therapy and had a reduction in the tumor burden, and the response was maintained after the dose. reduction *Conclusion:* This case shows that is it necessary to continue therapy at the maximum dose if the toxicity is not important, and the presence of excavated lesions at the first CT is an obvious sign of drug activity. Sunitiib is a very active drug in mRCC and a positive correlation between dose- toxicity and response is shown.

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CORRELATION BETWEEN PCA3 AND PAYHOLOGICAL FEATURES OF RADICAL PROSTATECTOMY SPECIMENS

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Introduction: Prostate cancer is one of the most common malignant diseases in men. The PSA testing has increased the diagnosis of prostate cancer, but many men with low-risk cancer are still treated actively and exposed to potential complications such as incontinece and erectile dysfunction. The aim of this work is to assess the correlations between Prostate Cancer gene 3 (PCA3) levels and pathological features of radical prostatectomy (RP) specimens, which define cancer aggressiveness. *Patients and Methods:* The analysis included 63 men with localized prostate cancer, who underwent radical prostatectomy, with a mean age of 64.3 y (52-75 yr). After digital rectal examination (DRE), first-catch urine was collected from all patients. The PCA3 score was calculated using the Gene Probe Progensa(™) assay. After RP, the PCA3 scores were correlated to the pathological features of the RP specimens. *Results:*The mean PCA3 score was 85.06 (3-554), In this group the mean PCA3 score was statistically significant

lower in men with RP Gleason score <7 *vs*. >7 (60.79 *vs*. 105.76) $p<0.001$, also the PCA3 score was statistically lower in men with pT2a- T2c *vs*. pT3a-T3b cancer, respectively 66.22 *vs*. 117.82 $p<0.001$. PCA3 scores correlated significantly with tumour volume, the mean score in tumor <0.5 mL was 26 *vs*. 91 with $p<0.01$. *Conclusion:* The present study shows that the median PCA3 score was stastistically significantly lower in men with characteristics of indolent prostate cancer. The study also shows, in according with other studies, the relationship between the PCA3 score and prostate cancer significance. PCA3 scores correlate to numerous histoprognostic factors, specifically tumour volume and positive surgical margins. These results may have a clinical impact in the near future on the selection of patients eligible to undergo active surveillance and nerve-sparing surgery.

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ONCOLOGICAL OUTCOMES OF LAPAROSCOPIC AND OPEN TREATMENT (NEPHROURETERECTOMY) FOR UROTHELIAL TUMORS OF THE UPPER URINARY TRACT

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Introduction: Currently the treatment of choice in urothelial tumors of upper urinary tract is nephroureterectomy (NU) performed Open (ONU), but the laparoscopic treatment is now routinely performed as a minimally invasive therapy (LNU). LNU has demonstrated oncologic safety at least equivalent to open, but some issues dealing with cancer still remain. *Patients and Methods:* We analyzed data from 36 LNU performed between 2006 and 2010 retrospective compared with the data of 32 ONU performed in 2002-2005 (prelaparoscopy era). The mean follow-up was 23 months in patients undergoing LNU and 42 months for those treated with ONU. We evaluated in particular cancer recurrence, the site of recurrence and survival. *Results:* We observed local recurrence in 3 patients (8.3%) after LNU and 2 after ONU (6.25%). 2 patients undergone LNU (5.5%) died of metastatic disease at 9 and 12 months, 3 patients undergone ONU (9.3%) died of metastasis at 12, 16 and 23 months. Bladder recurrence was observed in 3 patients after ONU and 4 after LNU. The most frequent sites of cancer recurrence were: local recurrence (3 LUN 2 ONU), 1 laparoscopic port recurrence, 3 regional lymph node recurrences (2 LNU, 1ONU, bladder recurrences (3 LNU, 4 ONU). *Conclusion:* There were no significant differences in disease recurrence and even survival rates at 1 and 3 years were not very different between the two techniques. The grade and stage of cancer affecting the incidence of metastatic disease, as well as the localization of early disease (pelvis-ureter-both) was a negative prognostic factor, rather than the surgical technique used. There was no evidence so that the control was compromised in cancer patients treated with LNU rather than with ONU.

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PREPARATION OF THE URETHRA, BLADDER-URETHRAL ANASTOMOSIS, AND FUNCTIONAL AND ONCOLOGICAL RESULTS IN RADICAL RETROPUBIC PROSTATECTOMY

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Introduction: We retrospectively analyzed oncological and functional results in a series of 530 patients in our open retro pubic radical prostatectomy. *Patients and Methods:* From April 2002 to December 2011, 590 patients underwent RRP for clinically localized prostate cancer. The mean age of the patients was 64 years (47-74), PSA 1.9 to 46.7 ng / ml. Our surgical technique involves the saving of the pubo-prostatic ligaments, careful preparation of the urethra with its muscle-aponeurotic structures, which is sectioned prostatic apex, careful preparation of the bundle for nerve-sparing technique, saving the bladder neck at the time of vesico-prostatic junction section and eversion of the mucosa,calibrating diameter of bladder neck on urethra, anastomosis with 5-6 loop suture of 3-0 Caprosyn on 22 Ch Foley catheter, encapsulating all musculoskeletal structures aponeurotic. The bladder catheter is usually removed at 12° day. From January 2010 we have introduced, for the realization of the bladder-urethral anastomosis, the technique described by Van Velthoven, performed with a double monofilament absorbable suture in 3/0.The catheter is removed in the 5-7 day *Results:* The mean follow-up was 54.3 months, pathological stage pT2 83%, pT3a 13%, pT3b 7%, Gleason score = or <7 in 78.5%, >7 in 21.5%.Positive surgical margins were detected in 8.4%, negative in 91.6%. 493/530 patients (93%) were completely continent (no pads), 27 (5%) had mild incontinence (1-2 pads daily), 5 (1.8%) were incontinent (>2 pads daily). Continence was assessed at the catheter removal and 1, 3, 6 and 12 months and was 59%, 76%, 88.5%, 91%. In the group Van Velthoven we have observed better results (continence at 1, 3, 6, 12 months respectively was 65%, 79%, 86% 94%). Only 9 patients (1.7%) developed a vesico-urethral junction sclerosis in about 6 months after surgery (nobody in the Van Velthoven group), then treated with endoscopic resection. *Conclusion:* Our technique allows an accurate preparation of prostate apex and urethra, preserving the striated sphincter, the urethral support structures and preserving the maximum length of the urethra. Moreover, the preparation of neurovascular bundles, and the preparation of the bladder neck allows to obtain functional optimal results. Furthermore, the introduction of the technique of Van Velthoven, in the face of operating time comparable with surgical technique to loop suture, allows anticipating the removal of the catheter, a better and earlier continence.

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ROBOTIC RETROPERITONEAL PARTIAL NEPHRECTOMY FOR RENAL CELL CARCINOMA

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Introduction: Robot-assisted partial nephrectomy (RAPN) is becoming popular, especially at referral institution for robotic surgery. However, even if open partial nephrectomy is performed *via* a lumbotomic retroperitoneal access by the majority of surgeons, RAPN is generally made *via* an anterior transperitoneal access, since the vast majority of laparoscopic and robotic surgeons are much more confident with it. Here we present a case of RAPN conducted *via* a retroperitoneal access. *Patients and Methods:* Male, 54 years old, with a BMI of 39.3, who previously underwent open bilio-pancreatic diversion (Scopinaro's technique) due to pathologic obesity. During the assessments performed to investigate a right renal cholic caused by an ureteral stone which required ureteral stenting, a renal mass, 3.1cm in diameter, partially exophytic and located in the posterior face of the lower third of the left kidney was discovered (RENAL 8P, PADUA 9PM). The patient has been submitted to a retroperitoneal RAPN with a conventional technique: open retroperitoneal blunt access, positioning of 3 robotic trocars along a subcostal line and one 12-mm assistant trocar; docking of the robotic system DaVinci Si; dissection of the psoas muscle; isolation and suspension of the main renal artery; isolation of the kidney from its fat and exposition of the tumor; clamping of the renal artery with a dedicated robotic bulldog (ScanLan); enucleoresection of the tumor; renal renorraphy and closure of the parenchymal defect by sliding clips technique; de-clamping; drainage. *Results:* The operative console time was 160 minutes; the post-operative course has been uneventful with mobilization in day 1, alimentation in day 1 and discharge in day 6. Histology was consistent with a clear cell renal cell carcinoma with negative margins, 2.8 cm in diameter, pT1a Nx M0 G2. *Discussion and Conclusion:* RAPN is gaining popularity, at least in referral robotic centers, and is generally performed *via* a transperitoneal access. However, open surgery has been historically generally performed *via* a retroperitoneal lumbar access, due to its clear advantages mainly regarding the more direct approach to the renal artery. Moreover, without entering in the peritoneal cavity and keeping close the retroperitoneum,

the risks of bowel, liver and spleen injury are virtually absent during the procedure, as are all the possible consequences coming from local complications (hematoma, urinoma, infection) of the post-operative course. The majority of laparoscopic surgeons are not confident with retroperitoneal access since they are less intuitive and because this is a virtual space that needs to be developed during the first steps of the operation. Coming from our experience in conventional laparoscopic renal surgery, in the case here presented of a pure posterior renal tumor, a retroperitoneal RAPN gave a significant advantage in the suturing, as confirmed by the relatively short time of ischemia, but also in the accessibility to the kidney and to the tumour, also taken into account the high BMI of the patient and its history of complex abdominal surgery. In a centre with experience in retroperitoneal conventional laparoscopy, retroperitoneal RAPN is feasible and effective.

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PCA3 SCORE VALUE IS SIGNIFICANTLY RELATED TO GLEASON'S SCORE ON REPEAT PROSTATE BIOPSY AND RADICAL PROSTATECTOMY SPECIMENS

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PCA3 score represents the amplification rate of PCA3 gene measured by mRNA copies in prostate cells collected from voided urine after digital rectal examination. On a series of up to 1200 cases (Bollito *et al*., Anal Quant Cytol Histol, 2012, in press) we have recently demonstrated a good diagnostic accuracy of this test when applied to patients who had a prior negative prostate biopsy, in order to assess the opportunity of a repeat biopsy. However, some issues are still debated, such as the correlation between PCA3 value and grading of cancer found in subsequent biopsies and radical prostatectomy. In fact, some Authors reported a significant correspondence (van Poppel H *et al*., BJU Int *109(3)*: 360-366, 2012), while others (van Gils, Prostate *68(11)*: 1215-1222, 2008) did not confirm the relationship between PCA3-score value and other prognostic parameters including grading. Among the whole series we analyzed a subset of patients who had already been submitted to repeat prostate biopsy after PCA3 test (n=70) and eventually to radical prostatectomy (n=47). Relevant patients' characteristics are reported in Table I. Data on PSA, %freePSA and PCA3-score at repeat biopsy and at radical prostatectomy (RP) according to variation in Gleason grades are reported in Table II. PCA3 scores and Gleason score were strongly associated in the biopsy done after PCA3 test (70 pts, $p<0.001$). Meanwhile, the same PCA3 scores were correlated to the Gleason's score at RP (47 pts, $p=0.031$). In conclusion, these preliminary data indicate that PCA3 scores are higher in high Gleason grade patients both at repeat biopsy and RP and may therefore assist in the identification of indolent *versus* aggressive prostate cancer cases.

Table I. *Main patients' characteristics*.

Age (median-range)	67 yrs (51-84)		
Cancer familiarity (positive)	22/209 pts (10.5%)		
First biopsy (done)	227/227 pts (100%)		
Final biopsy (positive)	70/227 pts (30.8%)		
Gleason score at repeat biopsy	5-7a(3+4): 7b (4+3)-10:	50/70 (71.4%) 20/70 (28.6%)	
Gleason score at Radical Prostatetomy	5-7a(3+4): 7b (4+3)-10:	26/47 (55.4%) 21/47 (44.6%)	
	Final biopsy Negative	Final biopsy Positive	<0.001
PCA3 score (<35)	122 (87.1%)	18 (12.9%)	
PCA3 score (>35)	35 (40.2%)	52 (59.8%)	

Fisher's exact test

Table II. *Patients characteristics by Gleason score at final Bx and at RP (median-range)*.

	Bx GS ≤7 (3+4)	Bx GS ≥7 (4+3)	*p**	RP GS ≤7 (3+4)	RP GS ≥7 (4+3)	*p**
PSA	6.01 ng/ml (2.00-15.30)	7.76 ng/ml (3.60-23.00)	0.075	5.56 ng/ml (2.00-14.00)	6.90 ng/ml (3.60-23.00)	0.309
%fPSA	14.00 (6.00-24.00)	18.00 (6.00-31.00)	0.298	12.00 (6.00-24.00)	14.00 (6.00-21.00)	0.949
PCA3 score	55 (5-160)	145 (48-254)	<0.001	62 (11-160)	97 (9-254)	0.031

*Mann-Whitney test.

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WHOLE PELVIS RADIOTHERAPY IN PATIENTS WITH HIGH-RISK PROSTATE CANCER

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Introduction and Aim: Intensity-modulated radiotherapy (IMRT) seems to reduce the risk of radiationrelated toxicities in whole pelvic radiotherapy (WPRT) but not all patients can benefit to be treated with IMRT. The role of WPRT in the management of prostate cancer continues to be an area of controversy. The Radiation Therapy Oncology Group (RTOG) 9413 Trial (1) showed a progression-free survival benefit with WPRT in patients with high risk of lymph node involvement but it is also true that WPRT has been associated with high risk of gastrointestinal (GI) and genitourinary (GU) toxicity. This study aimed at analyzing effects and toxicity of three-dimensional conformal WPRT in patients with high-risk prostate cancer. *Patients and Methods:* Seventy-nine patients with high risk localized prostate cancer and >15% risk of lymph node involvement (based on Roach *et al*., 2) were treated with WPRT at the Radiotherapy Department in Foggia between October 2006 and February 2011. All patients did not undergo surgery and 92.4% of them received hormonal therapy (total androgen deprivation or bicalutamide alone 150 mg/die). For all patients Clinical Target Volume (CTV) and Planning Target Volume (PTV) were delineated. CTV1 included the entire prostate and seminal vescicles with a margin of 6-10 mm to obtain PTV1, while CTV2 included bilateral obturator, external iliac, internal iliac and presacral nodal regions with a margin of 7-10 mm to obtain PTV2. The median dose to PTV2 was 44 Gy (range between 44 and 50) with a daily dose of 1.8-2 Gy. The median dose to PTV1 was 72 Gy (range between 68 and 80). The organs at risk (bladder, rectum, femoral heads and bowel) were contoured and evaluated with respect to dose constraints. The acute and late GI (rectal and bowel) and GU toxicities were scored according to the EORTC/RTOG scales. Biochemical relapse rate, metastasis rate, Disease Free Survival (DFS) and Overall Survival (OS) were calculated. Biochemical relapse was defined as a nadir PSA value ≥2 ng/ml at least six months after radiotherapy (ASTRO Consensus Conference 2006). *Results:* Last controls were performed in December 2011. Median follow-up was 36 months. Whole-pelvis radiotherapy was well tolerated and all patients received the prescribed dose except for one patient that interrupted his treatment at 28 Gy. Acute toxicity included rectal (G0, 77.6%; G1, 21%; G2, 1.4%), bowel (G0, 87.3%; G1, 12.7%; G2, 0%) and urinary events (G0, 46.6%; G1, 40.8%; G2, 12.6%). No patients had rectal late toxicity and only one patient had an intestinal obstruction after one year from the end of radiotherapy. Urinary events were observed in 14% of patients (G1 for 12.6% and G2 for 1.4%). Median PSA value was 0.1 ng/ml. Thirty-five (49.3%) were still treated with hormonal therapy at last control. Two patients (2.8%) experienced biochemical relapse and one had bone metastasis. The three-year DFS was 81.2%. The three-year overall survival was 100% since all men were alive at last control. *Conclusion:* Several studies have shown a survival benefit for high-risk prostate cancer patients but whole pelvis radiotherapy continues to be hotly debated. IMRT seems to be associated with a lower frequency and severity of side-effects, but our study suggests that also conventional three-dimensional conformal techniques are well tolerated and can offer good results in terms of Biochemical Failure Rate, DFS and OS with a reasonable acute and late toxicities.

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MULTIDISCIPLINARY APPROACH IN METASTATIC RENAL CELL CANCER (mRCC) WITH SARCOMATOID DIFFERENTIATION: A CASE REPORT

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Introduction: Metastatic renal cell cancer (mRCC) with sarcomatoid differentiation is an aggressive disease characterized by a relatively high incidence of lung and

bone metastases at diagnosis. Median overall survival for these patients is 3-10 months. There is no standard treatment for this histological subtype, which is associated with poor outcomes to chemotherapy, immunotherapy and targeted therapy. *Patients and Methods:* We present a case of a 72-year-old male with diagnosis, on September 2010, of left kidney RCC, Fuhrman grade 3-4, with sarcomatoid and rhabdoid differentiation, and metastatic to bone, lung, thoracic and abdominal lymphnodes. He was clinically managed by our multidisciplinary uro-oncologic team, represented by Oncologists, Urologists, Pathologists, Radiotherapists, Orthopaedists. *Results:* After multidisciplinary clinical analysis and discussion, the patient was first managed by Surgeons, with orthopaedic surgery to right ulna for unique bone metastasis, then submitted to radical cytoreductive left nephrectomy by Urologists. Afterwards, he had radiotherapy to right ulna (total 20 Gy). Subsequently, he was submitted by Oncologists to targeted therapies and to bisphosphonates (Zoledronic Acid 4 mg every 28 days), after jaw osteonecrosis prophylaxis. Concerning systemic treatment, he had first line therapy with Sunitinib 50 mg/die for 4 weeks every 6 (6 months of therapy, with partial response on lymphnodes), second line therapy with Sorafenib 800 mg/die (4 months of therapy, with progressive disease), and third line therapy with Everolimus 10 mg/die (still ongoing since 5 months, with stable disease). Overall survival of this patient is 18 months, longer than initially expected (3-10 months). *Discussion and Conclusion:* Since diagnosis of mRCC on September 2010, several therapeutic strategies were applied for this patient, who is still assuming third line targeted therapy, with stable disease, tolerable toxicity and good quality of life. Prospective randomised clinical trials are necessary to establish the standard treatment for mRCC with sarcomatoid differentiation. As suggested by this case report and by our daily clinical activity as a uro-oncologic team, the multidisciplinary approach can offer more chances of treatment to patients, possibly affecting positively either their response to treatments and their survival.

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SPONTANEUS REGRESSION OF THORACIC METASTASES FROM CLEAR CELL RENAL CELL CARCINOMA AFTER CYTOREDUCTIVE NEPHRECTOMY: CASE REPORT

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Introduction: Spontaneous regression of metastatic renal cell cancer (mRCC) has been reported in some anecdotal experiences in the literature. The first reported case of spontaneous regression of mRCC was described by Bumpus in 1928. Many of the cases are associated with surgical removal of the primary tumor, but regression can also occur in association to radiation or embolization of the primary tumor. We present herein a case of spontaneous partial regression of untreated thoracic metastases from RCC, occurring after cytoreductive radical nephrectomy. *Patients and Methods:* A 73 year old man, with excellent performance status and without relevant medical history, presented at his first urological visit for abdomen ultrasound (US) and computed tomography (CT) scan evidence of a left kidney tissue mass (65 mm), arising from the middle of the kidney and consistent with primary renal cancer, and a suspicious left adrenal adenoma (12 mm). Urologists indicated staging completion with chest CT scan, which revealed several bilateral lung millimetric nodules (maximum diameter 7 mm), right pleural thickenings (maximum diameter 16 mm) with right diaphragm infiltration, and pathological left pulmonary hilar lymphnode (20 mm). On December 22 2011, the patient underwent laparoscopic cytoreductive radical left nephrectomy and left adrenalectomy. Histology revealed clear cell RCC, Fuhrman grade 3, uninjured ureteral margin and left adrenal gland. No systemic treatment was started by oncologists until post-surgical re-staging with thorax-abdomen CT scan. *Results:* On February 6 2012, 1 month and a half after nephrectomy, post-surgical CT scan revealed a spontaneous partial response of bilateral lung nodules (with reduction of the maximum diameter from 7 to 3.5 mm), a complete regression of all pleural thickenings except for the lesion which infiltrated right diaphragm and which decreased from 16 to 7 mm, and a relevant decrease of the pathological left pulmonary hilar lymphnode (from 20 to 8 mm). The Uro-Oncological team decided to defer the start of systemic treatment, planning a subsequent CT scan after 2 months. *Discussion and Conclusion:* The rarity and the heterogeneity

of anedoctal cases of spontaneous regression of metastases by RCC after nephrectomy do not provide the opportunity to identify the pathophysiologic mechanisms of this phenomenon. It has been speculated that the resection of the primary tumor may result in removal of growth factors released by the tumor, and even in stimulating the immune system to control residual disease. It is important to recognize the existence of spontaneous regression of metastases in RCC, in order to properly consider surgical intervention and, subsequently, the appropriate moment to start systemic treatment.

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ZERO ISCHEMIA LAPAROSCOPIC PARTIAL NEPHRECTOMY. PRELIMINARY EXPERIENCE

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Introduction: Laparoscopic partial nephrectomy (LPN) remains a technically challenging procedure that requires advanced laparoscopic skill. Bleeding is one of the most fearful complication of LPN. Warm ischemia time is a mainstay issue that could impact on renal function. We report our preliminary experience with zero ischemia laparoscopic partial nephrectomy. *Patients and Methods:* A transperitoneal approach was performed; medialization of colon and identification of renal vessels. A self made tourniquet was usually passed around artery without clamping. Renal tumour was identified using Ligasure™ device. In 6 patients we performed identification of selective vascular branches that supply tumour blood; selective arterial and venous branches were clipped with HemOlok™ and then cut. In the remaining 4 patients a controlled hypotension was realized to reduce bleeding without clamping. The renal lesion was excised using Ligasure™ and cold endoshears. Medullary was repaired with Vicryl™ sutures arrested with absorbable clips. Suture of cortex was completed with other stitches secured with Hem-O-lok™ clips. Surgicell™ booster were usually applied on resection area that was also covered by application of Floseal™ or Tachosil™. *Results:* 10 patients underwent laparoscopic partial nephrectomy (4 right, 6 left) without clamping for renal tumour (8 patients) and for renal lithiasis (2 patients). Mean age of the patients was 50.9 years (±18.7). Mean tumour size was 3.7 cm (±1.5). Operative time was 175 (±50.4) minutes; blood loss was 435 (±280) ml. Two patients required blood transfusion. Mean hospitalization was 7.3 (2.8) days. In one patient postoperative urine leakage required placing of ureteral stent. Histological evaluation revealed a Renal Cell Carcinoma in 5 patients, an oncocytoma in 2 patients, an angiomyolipoma in 1 patient. All surgical margins were negative for cancer. *Conclusion:* Zero-ischemia laparoscopic partial nephrectomy without hilar clamping is feasible and safe. Eliminating global renal ischemia now appears achievable. It allows both preservation from ischemic renal damage and an excellent control of bleeding.

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PHOTODYNAMIC DIAGNOSIS OF NON MUSCLE INVASIVE BLADDER CANCER: PRELIMINARY EXPERIENCE

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Introduction: Bladder cancer (BC) is the most common tumour of the urinary tract. White light cystoscopy (WLC) is the standard investigation for the diagnosis of bladder tumors. Recent studies suggest that using exogenous fluorescence (PDD) can improve the diagnostic sensitivity and specificity of cystoscopy as well as the radicality of transurethral tumor resection (TURB). We report our preliminary experience with PPD, comparing Hexaminolevulinate fluorescence cystoscopy with white light cystoscopy for detecting papillary and flat lesions in patients with bladder cancer. *Patients and Methods:* Patients with known or suspected bladder cancer underwent bladder instillation with Hexaminolevulinate (Hexvix) (85 mg) for 1 hour. Cystoscopy was then performed using standard white light followed by blue light cystoscopy (PPD). Lesions or suspicious areas identified under the 2 illumination systems were mapped and biopsied for histological examination (cold biopsy or TURB). *Results:* A total of 68 patients (55 male, 13 female) underwent combined cystoscopy (WL + PPD). 42 patients had primitive known or suspected bladder cancer (group 1), while 26 underwent PPD-Returb for previous T1HG bladder cancer (group 2). Of group 1 patients, 6 had no lesions, 20 had single and 16 had multiple tumours, respectively. Histological evaluation revealed: inflammation (4

patients), dysplasia (3 patients), TaG1 (14 patients), T1G1 (2 patients), T1G2 (1 patient), T1G3 (5 patients), T1G3 + CIS (2 patients), CIS (1 patient), T2G3 (4 patients). PPD cystoscopy revealed 17 suspected areas in 14 patients: inflammation (4), dysplasia (5), TaG1 (4), T1G3 (1), CIS (3). Of 26 ReTurb patients (group 2), 19 presented no lesions, 2 dysplasia, 1 TaG1, 1 TaG3, 2 T1G3, 1 CIS. PPD cystoscopy revealed 9 suspected areas in 6 patients: 1 inflammation, 3 dysplasia, 4 T1G3, 1 CIS. *Conclusion:* Hexaminolevulinate fluorescence cystoscopy can be used in conjunction with white light cystoscopy to aid in the diagnosis of bladder cancer. In our preliminary experience HAL fluorescence cystoscopy detected at least 1 more tumor than white light cystoscopy in approximately a third of the patients. Whether this would translate to better outcomes in terms of recurrence and progression free survival has yet to be determined.

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ANALYSIS OF OUTCOMES OF PROSTATE ADENOCARCINOMA WITH SEMINAL VESICLE INVASION (pT3b) AFTER PURE LAPAROSCOPIC/ ROBOT-ASSISTED RADICAL PROSTATECTOMY

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Introduction: The prostate specific antigen era has led to an earlier detection and stage migration, but seminal vesicle invasion is still reported in pathological analysis and remains a poor prognostic factor. In this study we investigated features of disease and outcomes in men with pT3b disease treated in our center. *Patients and Methods:* From October 2001 to November 2011 we studied 70 patients who underwent laparoscopic or robot-assisted radical prostatectomy for prostate cancer with a pathological diagnosis of seminal vesicle invasion (stage pT3b). Follow up visits were scheduled at 1, 3, 6 and 12 months. Biochemical- and disease-free survival were evaluated with post-operative PSA, bone scan and abdominal CT. *Results:* The median follow-up was 52 (4-118) months. Mean age of the patients was 63.9 (50-76) years with a mean preoperative PSA of 12.7 (3.7-54) ng/ml. The 35.7% of our population had a positive digital rectal examination. Median bioptic Gleason Score was 7 (4-9) as the pathological Gleason Score (69). Positive surgical margins were found in 47% of patients, with 68% of them with a >3 mm length and 46% at the apex. Three cases of neuroendocrine and one of ductal prostatic adenocarcinoma were found. Lymph-node dissection was performed in 71% of patients and a positive nodes rate of 40% were registered. A small percentage of patients underwent neoadjuvant therapy (14.2%), while 64.3% of patients was subjected to adjuvant radio- and hormono-therapy. The biochemical free survival rate was 76% and the disease free survival rate was 82.3%. Two cancer-specific deaths were registered during the follow-up. *Conclusion:* We disclose the limits of the study such as the retrospective design and the low number of enrolled patients. Our results of laparoscopic and robotic surgery are comparable with those of open surgery. We think that pure laparoscopic/ robot-assisted radical prostatectomy may offer good results in pT3b prostate cancer, being understood that multimodal therapy is basic in this setting.

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METASTATIC COLON CANCER OF THE URINARY BLADDER: A CASE REPORT

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Background: The urinary bladder may be directly invaded by tumors of the rectum, prostate, and female genital tract, while metastases from adjacent or distant organs, *via* the hematic or lymphatic stream, are rare. Adenocarcinoma as primary bladder cancer is only found in 0.5-2% of all primary bladder cancers so any adenocarcinoma of the bladder should raise the suspicion of a distant primary cancer. We report a rare case of solitary urinary bladder metastasis from a large bowel cancer, presenting a urologic symptom. *Case Report:* A 69-year-old man was admitted for intermittent gross hematuria. His medical history included a right colectomy for cancer of the ascending colon. Cystoscopy detected a semi-pedunculated, non papillary, white-gray mass with focal hemorrhagic areas, grossly spherical in shape, 3.5-4 cm in diameter, situated above the front wall of the bladder. A transurethral resection of the neoplastic tissue and of its base was performed subsequently. The histology showed tubular and pseudoglandular adenocarcinoma type strucures. The malignant cells were very similar to the original colon cancer, and showed positive staining for CK20+ and Cdx-2+. The postoperative course was uneventful. The patient is currently doing well, with no signs of recurrence, at 24 months after the transurethral resection. *Discussion:* Abdominal or extra-abdominal malignancies very rarely involve the bladder wall as isolated metastases. The mechanism of metastasis to the urinary bladder, as well as the factors promoting this process, are obscure, although hematogenous and/or lymphatic spreads should always be taken into account. Involvement of the bladder can be assessed by ultrasonography, CT scan, MRI,

and cystoendoscopy. Detection of an adenocarcinoma in the bladder should raise the suspicion of a metastatic cancer either from a gastrointestinal focus or from the upper urinary tract. A thorough differentiation between the primary enteric type adenocarcinoma of the bladder and secondary colorectal adenocarcinoma involving the bladder should be performed, because these two conditions are morphologically indistinguishable. An immunohistochemical panel including CK7, CK20, villin, and β-catenin can help the diagnosis, because most lesions of colorectal origin have a CK7 negative profile while showing a CK20-, villin-, and β-catenin-positive immunoprofile. Locally advanced cancer directly involving the bladder wall can be successfully treated by an en bloc partial or total cystectomy. The treatment of secondary adenocarcinomas, depending on the stage of the primary tumor and on its location, extent, and number of bladder metastases, can be performed by an open or transurethral resection, and/or by a combination of chemo- and radiotherapy. *Conclusion:* The possibility of metastases should be considered in patients with a history of colonic adenocarcinoma and an adenocarcinoma of the bladder. The use of an immunohistochemical panel is recommended to differentiate between primary and metastatic tumors. Solitary metastases as observed in this case may only require local resection.

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TRANSRECTAL ULTRASOUND-GUIDED PROSTATE BIOPSIES IN PATIENTS TAKING ASPIRIN FOR CARDIOVASCULAR DISEASE: A META-ANALYSIS

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Introduction: The management of anti-platelet therapy in the peri-operative period is a source of great concern. The dilemma is between whether to stop these agents peri-operatively in order to reduce the risk of bleeding complications, or to continue them in order not to compromise the protection they afford against the risk of cardiovascular events. *Patients and Methods:* The aim of this systematic review and meta-analysis was to understand whether continued aspirin therapy is a risk factor for bleeding complications after ultrasound-guided biopsy of the prostate. A bibliographic search covering the period from January 1990 to May 2011 was conducted in PubMed, MEDLINE and EMBASE. We also included our own series in the analysis. *Results:* A total of 3218 participants were included. Haematuria was statistically more frequent (p=0.001) among patients taking aspirin than in the control group with an odds ratio estimate of 1.36 [1.13; 1.64]. This increased risk was, however, due to minor bleeding. The occurrence of rectal bleeding and haematospermia was not statistically increased (p=0.33 and p=0.24, respectively) in patients taking aspirin compared to the control group with odds ratios estimate of 1.24 [0.80; 1.93] and 1.52 [0.75; 3.08], respectively. *Discussion:* There is limited information of the relationship between continued use of aspirin and haemorrhagic complications after transrectal ultrasound-guided biopsy of the prostate. This is the first comprehensive analysis on this topic. *Conclusion:* Continued use of aspirin does not increase the risk of overall bleeding or moderate and severe haematuria after prostatic biopsy, and thus stopping aspirin before such biopsies is unnecessary.

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SURGICAL MARGIN STATUS AFTER LAPAROSCOPIC RADICAL PROSTATECTOMY: EXPERIENCE AFTER MORE THAN 400 PROCEDURES

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Introduction: The aim of this study was to analyze the surgical margins status of prostatic glands, resected by laparoscopic radical prostatectomy (RP) for prostate cancer, and to correlate it with biochemical free survival rate (BFSR). *Patients and Methods:* The population was selected from the database of 405 patients who underwent RP from July 2000 to December 2009 at our Urology Department with regular follow-up. To isolate the effect of surgical margins on BFSR, the patients undergoing neoadjuvant or adjuvant therapy were excluded from the study. Three-hundred patients matched all the criteria, 232 of these (77.3%) had negative surgical margins (NSM) and 68 (22.7%) positive surgical margins (PSM). The median follow-up was 68 (24-118) months. We investigated the prognostic value of PSM regarding the BFSR and regarding the tumour-specific and non specific mortality. Biochemical recurrence was defined as increase in PSA values above the threshold of 0.2 ng/ml. PSM were then classified: by extension, in <3 mm (77.8%) and >3 mm

(38.9%); by location, in apical (44.1%) and not apical (55.9%); by number in monofocal (77.9%) and multifocal (22.1%). These data were then entered into a multivariate analysis to assess the weight of each independent prognostic factor for biochemical recurrence, along with age, preoperative PSA, pathological Gleason Score, pT stage, prostate and tumour volume. *Results:* The BFSR rate was 67.6% for PSM and 88.8% for NSM. A statistically significant difference between the two groups was identified by univariate survival analysis ($p<0.001$) and multivariate analysis (hazard ratio or HR 3.78, 95% CI 1.91-7.51, $p=0.0001$). Patients with PSM also showed a worse tumour-specific and nonspecific survival compared with NSM, but this was not statistically significant. According to the extension, BFSR was 77.8% in <3 mm PSM and 38.9% in >3 mm PSM ($p=0.003$ - univariate survival analysis). In multivariate analysis, the HR of 5.46 (95% CI 1.42-21.07, $p=0.0137$) indicates that a PSM >3 mm is the most important risk factor for biochemical recurrence in our series, comparing it with pT (HR 4.54, 95% CI 1.02-20.16, $p=0.047$) and PSA (HR 3.82, 95% CI 1.11-13.16, $p=0.0335$). As for the PSM location, in our study an apical margin has been demonstrated at greater risk of biochemical recurrence in the univariate analysis. BFSR was 59% in apical PSM and 77% in not apical PSM ($p=0.038$). This risk lost statistical significance in multivariate analysis ($p=0.06$). Regarding the number, the increased risk due to multifocality, demonstrated by the univariate analysis (BFSR was 73% in monofocal PSM and 53% in multifocal PSM, $p=0.014$), was not confirmed in multivariate analysis ($p=0.38$). *Conclusion:* We recommend careful evaluation of patients with positive surgical margins with regard to possible adjuvant therapy after radical surgery. The suggestion is stronger if the margin is more than 3 mm.

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THE DIAGNOSTIC ROLE OF CA 15-3, CA 125 AND BETA2-MICROGLOBULIN IN RENAL CELL CARCINOMA

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Introduction: During recent years, there has been increasing interest in tumor markers for detecting, and monitoring tumor growth. There is currently no clinically useful serum marker for Renal Cell Carcinoma (RCC). In the present study we assessed the role of three different serum proteins (CA 15-3, CA 125 and 2-microglobulin) as biomarkers for RCC as well as any association between tumor marker levels and clinical-pathological parameters. *Patients and Methods:* Serum CA 15-3 (0-25 U/ml), CA 125 (0-35 U/ml) and 2-microglobulin (0-2.6 mg/dl) were measured preoperatively in 212 patients who underwent radical or partial nephrectomy for RCC. Mean age was 61 (21-86). The patients were classified according to 2009 TNM (pT1 n=146; pT2 n=24; pT3 n=42). Fuhrman grade was <2 in 138 patients, and >2 in 74 patients; 12 patients had lymph node metastases and in 10 cases there were visceral metastases. The mean follow-up was 13 months (1-38). Statistical calculations were performed with MedCalc 9.2.0.1 software. *Results:* Mean pathological tumor size was 5.51 cm (1-20); 66 patients had a pathological tumor size above 7 cm. Mean level of CA 15-3 was 26,90 U/ml (5.36-139.80), mean level of CA 125 was 18.37 U/ml (2,60223,30) and mean level of 2-microglobulin was 3,72 mg/dl (1.10-41.70). Preoperatively 34,9% (n=74) of the patients had abnormal CA 15-3 level, 7.5% (n=16) of the patients had abnormal CA125 level and 25.5% (n=54) of the patients had abnormal 2-microglobulin. No significant difference between CA 125 and 2-microglobulin values *versus* tumor size and Fuhrman grade was observed. About CA 15-3, statistical significant differences resulted for tumor size (<7 *vs.* > 7 cm; $p<0.0001$), for Fuhrman grade (<2 *vs.* > 2; $p<0.0001$); for the presence of lymph node metastases ($p=0.0026$); and visceral metastases ($p=0.0001$). These results were confirmed by Pearson's correlation coefficient for tumor size (r=0.4790; $p<0.0001$) and for Fuhrman grade (r=0.3956; $p<0.0001$). The Kaplan-Maier curves showed that Fuhrman grade ($p=0.0021$), tumor stage ($p=0.0072$) and visceral metastases ($p<0.0001$) were statistically significant prognostic factors for progression-free survival (PFS). Significant differences in PFS of patients with elevated serum levels of CA 15-3 ($p=0.0003$), CA 125 ($p<0.0001$) and 2-microglobulina ($p=0.0080$), compared with patients who had values below the upper reference interval limit were also observed. ROC analysis showed a higher value for CA 15-3 *versus* CA 125 and 2-microglobulin as predictor for progression (CA 15-3 AUC=0.947 *vs.* CA 125 AUC=0.763 *vs.* 2-microglobulin AUC=0.758) ($p=0.02$). *Conclusion:* We found that CA 15-3, CA 125 and 2-microglobulin are increased to abnormal levels in some patients preoperatively. For CA-15-3, elevated serum levels were correlated to clinical stage and tumour grade. Moreover, for patients with elevated CA 15-3 levels, PFS was significantly shorter than for patients with normal CA 15-3 values. Studies based on larger series are needed to confirm the utility of this biomarker.

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IS SIMULTANEOUS TRANS-URETHRAL RESECTION OF THE BLADDER AND PROSTATE ONCOLOGICALLY SAFE? A META-ANALYSIS ON 1234 PATIENTS

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Introduction: It is not unusual to encounter the clinical scenario of a male patient undergoing endoscopic treatment for bladder cancer (TURBT) who also needs transurethral resection of prostate (TURP). The aims of this meta-analysis were to understand if it is oncologically safe or advantageous to combine the two procedures in terms of subsequent overall recurrences with particular interest to that in the prostatic fossa and to understand if some characteristics of the bladder tumors can influence the recurrence rate. *Methods:* A bibliographic search covering the period from January 1950 to December 2011 was conducted in PubMed, MEDLINE and EMBASE. Meta-analysis approach was applied comparing prostatic fossa recurrences and total recurrences in simultaneous TURBT and TURP and control. Also prostatic fossa recurrences and tumors' grading and multifocality in patients treated with simultaneous TURBT and TURP were analyzed. To investigate to what extent observational time influenced relapses, a random effect meta-regression logistic model based approach was applied. All statistical evaluations were performed using SAS version 9.2. and by RevMan 5.0. A α level of 0.05 was considered as statistically significant. *Results:* Overall, there were 1234 participants in the eight studies considered. The study group consisted of 634 patients and the control group of 600. Mean age was 67.88 and 61.64 years respectively in the study and control groups. In the study group, on a total of 634 patients, 65 recurrences in the prostatic fossa appeared. In the control group, on a total of 600 patients, 58 recurrence in the prostatic fossa occurred. Data did not show a statistically significant difference of recurrence in the prostatic fossa between patients treated simultaneously with TURB and TURP and the control group. Meta-analysis did not show a statistically significant difference of recurrence in the prostatic fossa with the increased grading of the neoplasms. But there was a statistically significant increased recurrence in patients with multifocal tumors. There was a statistically significant reduction of recurrence between patients treated simultaneously with TURB and TURP and the control group but there was no reduction of the recurrence rate in time. *Conclusion:* This meta-analysis emphasized that the two operations could be performed during the same session without any negative oncologic results. The resolution during the same session of bladder outlet obstruction would improve the patients' quality of life and performing the procedures in the same session sparing the patients from a further anesthesiological maneuvers and the need for a further hospitalization for the surgical resolution of the prostatic obstruction.

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INVERTED PAPILLOMA OF THE BLADDER: A REVIEW AND AN ANALYSIS OF THE RECENT LITERATURE OF 365 PATIENTS

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Objectives: Until the 1970s inverted urothelial papilloma (IUP) of the bladder had generally been regarded as a benign neoplasm. However, in the 1980s several reported cases suggested their malignant potential including those indicating malignant evidence, those showing recurrence and those underlining the association with synchronous or metachronous transitional cell carcinoma. The aim of this systematic review and analysis of the literature from 1990 to date was to contribute to the uncertain questions regarding biological behavior and prognosis of this neoplasm in order to establish some key points in the clinical and surgical management of these lesions. *Patients and Methods:* Database searches yielded 109 references. Exclusion of irrelevant references left ten references describing studies that fulfilled the predefined inclusion criteria. *Results:* A problem regarding these neoplasms was the difficulty of obtaining a correct histopathological diagnosis. The major differential diagnosis was endophytic urothelial neoplasia including papillary urothelial neoplasia of low malignant potential or urothelial carcinoma of low or high grade, while other significantly rarer neoplasias included nephrogenic adenoma, paraganglioma, carcinoid tumour, cystitis cystica, cystitis glandularis, and Brunn's cell nests. The size of the lesions ranged from 1 to 50 mm (mean 12.8 mm). Most cases occured in the fifth and sixth decade of life. The mean age of patients was 59.3 years (range 20-88 years). From the analysis of the literature we can find a strong male predominance with a male/female ratio of 5.8:1. The most common sites reported of IUP were the bladder neck region and trigone. Of 285 cases included in 8 studies, 11 cases (3.86%) had multiplicity. Out of the total 348 patients,

six patients (1.72%) had previous history of transitional cell carcinoma of the urinary bladder, five patients (1.43%) had synchronous transitional cell carcinoma of the urinary bladder and four patients (1.15%) had subsequent transitional cell carcinoma of the urinary The time before recurrence was not more than 45 months (range 5-45 months, mean 27.7 months) after surgery. *Conclusion:* Inverted papilloma could be considered a risk factor and it is clinically prudent to exclude transitional cell cancer when it is diagnosed and a follow-up is needed if the histological diagnosis is definitive or doubtful. We recommend a 4-monthly flexible cystoscopy for the first year and then every six months for the subsequent three years. Routine surveillance of the upper urinary tract following inverted papilloma of the lower tract is deemed not necessary.

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PURE *VERSUS* ROBOTIC ASSISTED LAPAROSCOPIC PROSTATECTOMY: IS THERE A DIFFERENCE IN TERMS OF POSITIVE SURGICAL MARGINS DURING THE "LEARNING CURVE"?

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Aim: The aim of this study was to compare oncological results in terms of positive surgical margin (PSM) rate between robotic assisted laparoscopic radical prostatectomy (RARP) and pure laparoscopic prostatectomy (LRP). *Patients and Methods:* We retrospectively analyzed our radical prostatectomy database. We extracted data of the first 250 LRP (July 2000-June 2006) and the first 250 RARP (September 2008-February 2012), performed at our Institution by a single surgeon (FP). Pre-operative data (BMI, PSA at diagnosis, bioptic Gleason score –GS-), peri-operative data, histopathological data (prostate volume, tumor volume, percentuage of volume tumor/volume prostate, number of removed lymphnodes) and TNM staging data of the two groups were compared. Furthermore, rates of overall and stage II PSM were compared. Finally, we divided the patients of each group in three subgroups (procedures #1-100, #101-200, #201-250) to analyze of PSM and compare this between the two groups. *Results:* As regards pre-operative data, PSA at diagnosis was higher in LRP group (7.6 *vs*. 9.7, RARP *vs*. LRP; $p<0.001$) and patients with GS at biopsy <7 were 88% in RARP group and 94.4% in LRP ($p=0.01$). LN dissections were 17.6% in RARP group and 32.8% in LRP group $p<0.001$). pT2 stage were comparable between the two groups (67.2% *vs*. 61.2%,RARP *vs*. LRP; $p=0.16$). GS >7 at histopatological analysis was found in 10% of patients after RARP and in 6% of patients after LRP ($p=0.09$). Overall PSM rate was 28.4% in RARP group *vs*. 29.2% in LRP group ($p=0.84$). PSM rate in stage II tumours was 34/168 (20.2%) in RALP group and 22/153 (14.4%) in LRP group ($p=0.16$). The Table shows the results of the comparison between the different subgroups.

	RARP(%)	LRP(%)	*p*-value
From 1-100	36	35	0.88
From 101 to 200	27	21	0.32
From 201 to 251	14	28	0.08

Conclusion: Overall, PSM rate in the two groups was comparable even if the robotic procedures were performed with a significant laparoscopic experience. Not surprisingly the number of PSM decreased progressively with the experience of the surgeon. Our data do not support the hypothesis that RARP allows better oncological results than pure laparoscopy (at least in terms of PSM) in the initial learning curve. Limitations of this study include the retrospective design.

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DISTRIBUTION OF PODOPLANIN (D2-40) IMMUNOSTAINING IN PROSTATE GLAND AND ITS POTENTIAL DIAGNOSTIC UTILITY

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Background: Podoplanin is a transmembrane mucoprotein strongly and selectively expressed by lymphatic endothelial cells (1). The monoclonal antibody D2-40, directed against human podoplanin, has proved to be useful in detecting lymphovascular invasion by neoplasms and in quantifying lymphatic vessel density in different tumors (1). It represents an excellent marker of vascular neoplasms with lymphatic differentiation, mesothelial and germ cell tumors, but it results always negative in adenocarcinomas. Podoplanin expression was also demonstrated in normal cells, such as osteocytes,

chondrocytes, follicular dendritic cells, type I alveolar cells, myoepithelial cells of the breast (1) and basal cells in the prostate (2-3). The aim of this study was to investigate the distribution and features of D2-40 immunoreactivity in tissues from different prostatic specimens and its potential diagnostic utility. *Patients and Methods:* After routine diagnostic histopathology examination and reporting, significant paraffin blocks from 45 selected patients, who underwent needle core biopsy (18 cases), trans-urethral resection (6 cases), simple prostatectomy (6 cases) and radical prostatectomy (15 cases), were cut to obtain additional slides immunostained with a monoclonal antibody against human podoplanin (clone D2-40, DAKO A/S, Glostrup, Denmark). Selected cases included tissue from the different zones of the gland and the main prostatic diseases, such as adenocarcinoma, PIN, prostatitis, adenosis, hyperplasia and glandular atrophy. *Results:* A strong cytoplasmic immunoreactivity of lymphatic endotelial cells was observed in all cases and used as an internal positive control. Prostatic basal cells were also constantly positive, but with a slightly less intensity than that observed in endothelial cells. A weak positive signal characterized perineurial and Schwann cells of the peripheral nerves, as well as ganglion cells within intra- and extraprostatic nervous ganglia. Smooth muscle fibers and stromal fibroblasts showed mild immunoreactivity. Basal cells of seminal vesicle epithelium showed moderate positivity, with a patchy pattern of expression. Blood vessels endothelium, normal and hyperplastic luminal cells, as well as PIN and adenocarcinoma cells were constantly negative. *Discussion and Conclusion:* As a specific marker of lymphatic endothelium (1), podoplanin has been used for detecting lymphovascular invasion and quantifying lymphatic vessels density in prostate carcinoma. Recent contributions underlined its utility as a basal cell marker, to avoid potential pitfalls in misinterpretation of lympatic invasion (2) and in evaluating atypical small acinar proliferation (3). Our results confirm the value of D2-40 in highlighting lympatics and basal cells, and its role as a negative marker of adenocarcinoma and other glandular lesions. The use of D2-40 in combination with other basal cell markers may be indicated to identify a wider spectrum of basal cells. The positivity of peripheral nerves and nervous ganglia may be useful in highlighting the invasion of these structures by adenocarcinoma cells and in distinguishing intraprostatic ganglion cells from neoplastic cells. The patchy positivity of basal cells in the seminal vesicle may be of help to detect portions of seminal vesicle that may be present in a core biopsy and to distinguish between normal epithelium of seminal vesicles and infiltration of the latter by adenocarcinoma glands in radical prostatectomies. In conclusion, D2-40 immunostaining in prostate specimens helps to identify different cells and structures and may be useful in routine diagnosis, particularly in the limited material available in core biopsies.

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ISOLATED SPERMATIC CORD METASTASIS FROM GASTRIC ADENOCARCINOMA PRESENTING AS AN INGUINAL MASS

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Introduction: Metastatic tumors of the spermatic cord and the paratesticular region are extremely rare (1) with only 22 cases reported in the literature. They usually originate from primary tumors of the abdomino-pelvic district and are characterized by a poor prognosis (1-3). We report a case of isolated metastasis in the spermatic cord in a patient undergone total gastrectomy for carcinoma 2 years before. *Patients and Methods:* A 60-year-old man presented with a right inguinal nodule. Ultrasonography displayed a 22×14 mm hypoechogenic mass and a total-body computed tomography scanning confirmed the finding in the absence of further alterations. Past medical history revealed poliomyelitis at the age of 16 months, left nephrectomy for urolithiasis when he was 27, and a total gastrectomy 27 months before, because of a poorly differentiated adenocarcinoma, pT2pN1pMX, treated with postoperative radiotherapy and chemotherapy. Incisional biopsy of the inguinal nodule allowed the intraoperative histological diagnosis of adenocarcinoma and was followed by

right orchifuniculectomy. *Results:* Surgical specimen consisted of a testis measuring 6×3.8×3.2 cm with a spermatic cord measuring 12 cm in length. Histological examination of the formalin-fixed specimen showed infiltration of the spermatic cord by a poorly differentiated adenocarcinoma, with angiolymphatic invasion, without extension to the epididymis and testis. Neoplastic cells were PAS-positive/diastase-resistant, immunoreactive for cytokeratin 7 and EMA and negative for cytokeratin 20, CA125, PSA, β-HCG and AFP. The patient underwent additional chemotherapy with transient benefit, but died of the disease 34 months later (61 months after gastrectomy). *Discussion and Conclusion:* Primary neoplasms of the spermatic cord are relatively uncommon and in the majority of cases they are of mesenchymal origin. The occurrence of spermatic cord metastases is an extremely rare issue, with primary sites usually represented by prostate, kidney, colon, stomach and pancreas (1, 2). Gastric carcinoma represents the most frequent primary site in the japanese literature (3). Our case may be considered rare because of two main reasons: the spermatic cord localization as the only sign of relapse and the prolonged survival of the patient, as the mean survival after diagnosis in this peculiar condition was 9 months (1). The latter may be partially explained by the absence of other secondary localizations at the time of diagnosis and by the effectiveness of radiotherapy and chemotherapy.

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PROSTATE CANCER DETECTION ON REPEATED BIOPSY AFTER HGPIN AND ASAP

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Introduction: Repeated prostatic biopsy is usually recommended following a diagnosis of high-grade prostatic intraepithelial neoplasm (HGPIN) or atypical small acinar proliferation (ASAP). We reviewed the outcomes of patients undergoing a second and a third biopsy, following an initial diagnosis of HGPIN or ASAP. *Patients and Methods:* Patients diagnosed with HGPIN (group 1) and ASAP (group 2) on the primary biopsy, routinely underwent a further bioptic procedure. We evaluated prostate cancer detection rate on rebiopsy of 112 patients with HGPIN and 74 patients with ASAP on initial biopsy. We also evaluated predictor factors of Pca on rebiopsy: age, PSA, prostate volume, PSA density, number of cores, number of positive cores, time to re-biopsy. *Results:* Of 112 patients with HGPIN, 22.3% and 32% presented PCa on second and third biopsy, respectively. Of 74 patients with ASAP, 31% and 40% presented PCa on second and third biopsy, respectviely. Predictor factors of Pca after HGPIN were PSA and number of cores at first biopsy. Predictor factors of Pca after ASAP were number of cores at first biopsy and re-biopsy. *Conclusion:* HGPIN and ASAP are frequent histopathological findings; in these patients a repeated biopsy is usually recommended. Considering that our prostatic cancer detection rate was 29% after HGPIN and 36% after ASAP. No extended initial biopsy is a predictor factor of cancer after HGPIN. No extended initial biopsy and no saturation biopsy on re-biopsy are predictor factors of cancer after ASAP.

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HEMATURIA ONE STOP CLINIC: FIRST EXPERIENCE IN ITALY WITH 255 CASES

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Objectives: Starting from the UK experience, we decided to test both the feasibility and the advantages of this diagnostic pathway now established in an Italian hospital. We analyzed the outcomes in detecting transitional cell carcinoma (TCC) of the bladder, and other malignant and non-malignant conditions. *Patients and Methods:* Between April 2010 and February 2012, 255 patients presenting with hematuria were referred to the Hematuria One Stop Clinic (HOSC) at our Institution. Each patient underwent a visit, a Urinary Tract Ultrasound, a Cystoscopy and CT IVP in selected cases (evidence of alterations or lesions of the renal parenchyma, presence of stones of the urinary tract, evidence of doubtful or positive urinary cytology). Where a TCC of the bladder was diagnosed, the patient underwent TUR-BT. In other cases (stones, BPH etc.) the appropriate therapeutic pathway was

followed. *Results:* 24.32% of patients with hematuria were found to have a bladder cancer; 20.78% had a urinary stone; 1.18% had prostate cancer; 1.18% had a renal cell carcinoma; 0.39 had a urachus neoplasm. The mean age was 68.6 yrs. 5.8% of the patients (24.2% on patients with TCC of the bladder) had a G3 disease. The mean time from admission to the HOSC until the operation day, in case of TCC of the bladder, was 11.1 days. The mean access time to HOSC since the event of haematuria was 3.88 days. The patient average satisfaction level, for those referred to the HOSC, was 4.5 (on a scale from 1 to 5). *Conclusion:* The Italian experience of the One Stop Clinic confirms a high rate of bladder cancer detection. Furthermore, a high rate of non-malignant conditions was detected, stressing the importance of the HOSC not only as a cancer clinic but as a complete general urological clinic. We report a shorter waiting time to operation, especially for bladder TCC G3 patients. It should be a mission of all urologists who manage this disease to ensure that timely and evidence-based treatment is available to all patients; this should include education of referring providers within their community about bladder cancer awareness and the importance of timely referral for evaluation of haematuria.

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SERUM LEVELS OF ANGIOGENETIC CANCER BIOMARKERS IN MEN UNDERGOING PROSTATE BIOPSY. PRELIMINARY DATA

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Background: The reduction of the number of negative prostate biopsies in patients with elevated serum PSA represents a major challenge. Several angiogenetic biomarkers are involved in carcinogenesis and cancer progression. The aim of our preliminary study was to investigate if their serum levels might be related to prostate cancer detection. *Patients and Methods:* Angiopoietin 2, Follistatin, G-CSF, HGF, IL-8, Leptin, PDGF-BB, PECAM-1, VEGF, PTH were the selected biomarkers for our research. They were measured by BioPlex immunoassay. As a preliminary step, consecutive unselected patients undergoing prostate biopsy for palpable prostate nodule and/or elevated PSA levels were entered. A 12-core transrectal biopsy was planned. The serum levels of the above mentioned biomarkers were related with the histological result of the biopsy. ROC curve analysis was exploited to test the diagnostic accuracy of each biomarker by AUC calculation. A potential cut-off level was computed for each biomarker. *Results:* Thirty-five consecutive patients were entered in this preliminary study. The median PSA was 6.3 ng/ml (mean: 19.4, range 0.41-364). An altered prostate was found at digital rectal examination in 13 (37%) patients. Transrectal ultrasound gave a median prostate volume of 44.5 cc (mean 48.7; range 15-105cc). Seven patients (20%) had a previous negative biopsy and 5 were receiving dutasteride or finasteride. A median number of 12 biopsy cores was obtained (mean: 12 range 4-24). Prostate cancer was detected in 21 (60%) men. ASAP and PIN were detected in 2 more patients respectively. Among the 9 considered angiogenetic biomarkers, only leptin preliminarily shows an interesting diagnostic accuracy with an AUC of 0,714 (Table 1). At a cut-off value of 2166 pg/ml, leptin demonstrates a sensitivity of 74% and a specificity of 75% with a positive predictive value of 85%. *Conclusion:* Only leptin, among the 9 studied biomarkers, showed promising diagnostic accuracy for the detection of prostate cancer, suggesting the usefulness of further research.

Table I. *ROC curve analysis (AUC).*

Angiogenetic biomarker	AUC
Angiopoietin_2	0.511
Follistatin	0.676
G-CSF	0.658
HGF	0.636
IL-8	0.524
Leptin	0.714
PDGF-BB	0.638
PECAM-1	0.596
VEGF	0.589

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RADICAL PROSTATECTOMY FOR PATIENTS WITH CLINICALLY LOCALLY ADVANCED PROSTATE CANCER: RESULTS OF A SINGLE INSTITUTIONAL STUDY

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Introduction: Aim of this study was to report the outcomes of a single institution study on 98 pts with clinically locally advanced prostate cancer (PCa) and prostate specific antigen

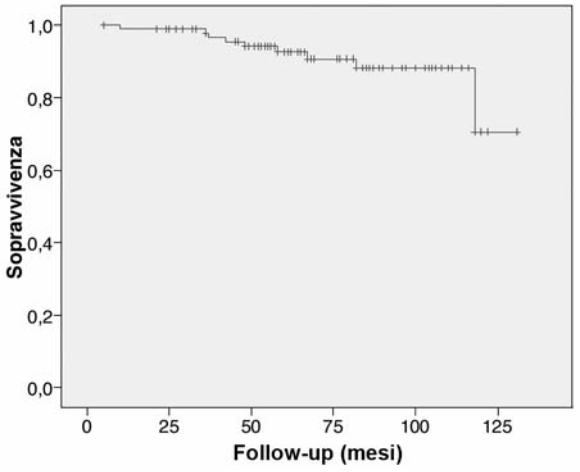

Figure 1. *Cancer specific survival*.

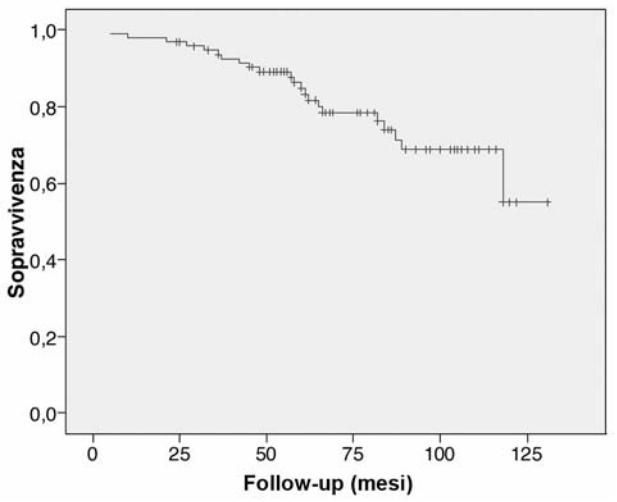

Figure 2. *Over all survival*.

(PSA) ≥20 ng/ml who underwent radical prostatectomy (RP) and pelvic lymphadenectomy (PNLD). *Materials and Methods:* We performed a retrospective review of PCa patients who had initial PSA values above 20 ng/ml and were treated with surgery between 2000 and 2005. Biochemical recurrence was defined as a double rise in PSA levels over 0.2 ng/ml after RP. Adjuvant or salvage radiotherapy (RT) or hormonal therapy (HT) were indicated according to institutional protocols. Overall (OS), cancer specific (CSS), clinical progression free (CPFS), and biochemical progression free survival (BPFS) were calculated for the entire cohort and select subgroups using the Kaplan-Meier method with log rank test and Cox multivariate analysis. *Results:* Mean age was 66 years (range IQR 61.8-71). Mean PSA was 30.4 ng/ml (range IQR 24.4-45). PCa was clinically locally advanced in 69% of cases. Pathological staging identified locally advanced disease in 72.4% of cases (27.6% pT3a, 30.6% pT3b, and 14.3% pT4). Positive surgical margins and lymph node involvement were observed in 68% and 23% of cases, respectively. Mean follow-up was 65.3 months (range IQR 46.0-96.5). Adjuvant RT and HT were administered in 51% and 69% of cases. OS, CSS and BRFS at 5 (and 10) years were 85% (55%), 93% (71%) and 53% (36%), respectively (Figures 1, 2). *Conclusion:* RP is an effective first step in a multimodality approach for locally advanced PCa, with convincing cancer-related outcomes. Patients with PSA ≥20 ng/ml should be considered for an aggressive approach, starting with radical surgery. Most patients need adjuvant HT or RT. This study confirms that RP should be considered as the first step in a multimodality approach for clinically locally advanced PCa.

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WHOLE PELVIS *VERSUS* PROSTATE ONLY 3D-CONFORMAL RADIOTHERAPY IN PATIENTS WITH PROSTATE CANCER: A RETROSPECTIVE COMPARISON

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Aim: The role of elective irradiation of pelvic lymph nodes is an issue that continues to be hotly debated in the radiotherapy treatment of prostate cancer. Our retrospective study aims to compare whole pelvis radiotherapy (WPRT) and prostate only radiotherapy (PORT) as regards prognostic factors, toxicities and dosimetric aspects. *Patients and Methods:* From October 2006 to February 2011, 220 men affected by prostate cancer underwent radical radiotherapy at the Radiotherapy Department in Foggia. They were treated with multiple 10-18MV beams and three-dimensional conformal techniques. PORT included the entire prostate with or without seminal vescicles. WPRT included also bilateral obturator, external

iliac, internal iliac and presacral nodal regions. PORT doses ranged between 68 and 80Gy. WPRT doses ranged between 44 and 50Gy and were followed by a boost on the prostate volume. For each patient, age, pre-treatment PSA, Gleason score and radiation doses were recorded. Toxicity was assessed according to the time of onset (acute or late toxicity) and the organs at risk involved (genitourinary or rectal and intestinal toxicity); the EORT/RTOG scales were used. *Results:* Median and minimum follow-up were 36 and 12 months, respectively. Regardless of risk classification, 159 patients (pts) underwent PORT and 61 WPRT. There was a strong association between class of risk and irradiated volumes ($p<0.01$) and a very significant difference of Gleason score and pre-treatment PSA values between PORT and WPRT groups ($p<0.01$): PSA and Gleason score were important risk factors guiding radiation oncologists to WPRT. On the contrary, there was no age difference in PORT and WPRT groups ($p=0.5$): age at diagnosis did not show to be a variable according to which pts were referred for WPRT or PORT. As regards total radiation doses, a difference between the two groups was outlined ($p=0.01$): when tissues have already received a considerable proportion of dose during irradiation of the pelvis, it is more difficult to deliver high doses to the prostate remaining within tolerance constraints for organs at risk. By analyzing the various types of toxicity, it was noted that 59% of pts undergoing PORT had acute toxicity *vs*. 64% of pts undergoing WPRT ($p=0.51$), 11% of pts who underwent PORT manifested late toxicity *vs*. 10% of pts receiving WPRT ($p=0.75$), 49% of pts undergoing PORT complained disorders of the urinary sphere *vs*. 47% of pts that received WPRT ($p=0.84$), 17% of pts receiving PORT reported rectal or intestinal side-effects *vs*. 31% of pts that received WPRT ($p=0.02$): this association between intestinal toxicity and WPRT can be easily explained by the greater portion of bowel exposed to radiation during WPRT ($p<0.01$). Because of the long natural history of disease and the short follow-up, our series does not allow to draw results about the effectiveness of WPRT *vs*. PORT. *Discussion and Conclusion:* Arguments exist for and against the use of prophilactic irradiation of pelvic lymph nodes in prostate cancer management. Our series shows that WPRT and PORT are two therapeutic alternatives routinely used in the radiation treatment of pts with intermediate-high risk prostate cancer. However the final answer on WPRT is not known and requires further studies. Meanwhile, on the one hand radiation oncologist should consider the ease of execution of PORT, the lower intestinal toxicity expected from PORT and its possibility of delivering a higher dose to the prostate when a 3D-conformal technique is used; on the other hand WPRT should be taken into account with the worsening of prognostic factors, especially pre-treatment PSA and Gleason score. A large and homogeneous randomized trial will clarify the usefulness of pelvic irradiation in selected patients with clinically localized prostate cancer.

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PSA DECREASE IN PATIENTS WITH CASTRATE RESISTANT PROSTATE CANCER TREATED WITH DEGARELIX

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Introduction: Patients with metastatic prostate cancer no longer responsive to treatment with LH/RH agonist (or second-line therapies such as estramustine, estrogens, or ketoconazole) are often treated with docetaxel-based chemotherapy. Recently, the introduction of LH/RH antagonists seems to offer a further line of therapy in patients with low levels of testosterone but with PSA progression, before chemotherapy. At the Radiotherapy Unit of Cremona, Degarelix is prescribed in patients with castration-resistant prostate cancer refusing chemotherapy with taxotere. *Patients and Methods:* From June 2011 to 2/2012 seventeen patients with metastatic and castration resistant prostate cancer (refusing chemotherapy, were treated with Degarelix. Ten patients had previously undergone three therapeutic lines (total androgen blockade -BAT-, estramustine and ketoconazole), four with two lines (BAT and estramustine) and three with only one line (BAT). All patients had detectable testosterone values, but below 50 ng/dl, limit of castration. The patients underwent treatment with monthly injection, for a minimum period of 2 months, up to PSA progression. *Results:* The therapy was generally well tolerated with the appearance of asthenia in four patients, two of which even with lack of appetite. Ten patients (52.9%) had a progression of PSA after 2 doses of degarelix, therefore the treatment was discontinued. Three patients (17.6%) showed stabilization of PSA values (decrease lower than 30%), with a median response of 2 months. Five patients (29.5%) showed a significant fall of the PSA (>30% of initial value) with a median response of 4.5 months (range 3-7 months). *Discussion and Conclusion:* GnRH antagonists induce castration by a different mechanism to that of GnRH agonists, blocking GnRH receptors and causing an immediate blockade of LH and FSH secretion. Because of these different modes of action, degarelix could be active following previous hormone treatments, as we can see when bicalutamide/cyproterone acetate shift is performed. Miller reports 17% of responders to degarelix, when it is used after LH/RH agonists. In our series responders after BAT and other hormone treatments were about 30% (47% with disease stabilization). At the time, the percentage of response appeared high enough to consider degarelix among the possible treatments. In view of the cost of the drug, further studies are needed to identify the subgroup with good probability of response to treatment among the patients with castration-resistant disease, before chemotherapy.

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ROBOTIC-ASSISTED LAPAROSCOPIC *VS.* OPEN PROSTATECTOMY IN A CENTER WITH LOW VOLUME OF CASES: THE EXPERIENCE OF A SINGLE SURGEON

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Introduction: We assessed the outcomes of robotic-assisted laparoscopic prostatectomy (RALP), including the learning curve, compared with those of open retropubic radical prostatectomy (RRP) in the peculiar setting of a single center with a low caseload. *Patients and Methods:* 52 consecutive patients underwent RALP between September 2007 and January 2012, carried out by a single experienced open surgeon with no experience of pure laparoscopic prostatectomy. We compared these cases to 52 patient who underwent RRP in the same period, performed by the same surgeon, in the same center. The baseline characteristics of the two groups were equivalent. We prospectively evaluated the tumour's characteristics, perioperative parameters and early surgical, functional and oncological outcomes of both groups. *Results:* Mean follow-up was 27 months. Table I shows baseline patients' characteristics while Table II shows pathological results and oncological and funtional outcomes. *Discussion:* Our data confirm comparable functional and oncological outcomes with only significant difference in operative time, post-operative haemoglobin values, hospitalization time and catetherization time. The learning curve and the low volume of cases do not affect functional outcomes. The main advantage of RALP is, as previously reported, reduction in blood loss, catetherization time and hospital stay. Moreover there are no differences in positive margins rate, continence rate and time to continence. Approximatively 25% of patients having a nerve sparing surgery will gain full or partial potency with only oral therapy in both groups after one year. *Conclusion:* Notwithstanding a very low caseload and the inclusion of the learning curve cases, RALP allowed to achieve acceptably good oncological and functional outcomes with improved blood loss, hospital stay, catetherization time but a longer operative time as a main draw back.

Table I

	RRP	RALP	*p*
Age (mean±DS) years	65.9±6.2	63.4±5.8	0.03*
PSA (mean±DS) ng/dL	7.4±4	6.9±3.4	0.5*
By optical Gleason score (mean±DS)	6.36±1.7	6.1±1.7	0.5*
Pre-operative Hb (mean±DS) g/dL	15±1.23	15±1.15	0.8*

Table II

	RRP	RALP	*p*
Nerve sparing			
No	41%	55.7%	0.228˚
Monolateral	35%	21.2%	
Bilateral	24%	23.1%	
Lymphadenectomy			
Yes	61.5%	23.1%	<0.01˚
No	38.5%	76.9%	
Operative time (mean±DS) minutes	172±34	276±36	<0.001*
Post-operative Hb (mean±DS) g/dL	11.6±1.4	12.2±1.5	0.03*
Hospital stay (mean±DS) days	8.4±3.5	6.9±2.5	0.01*
Catetherization time (mean±DS) days	15.8±4.3	10.3±5.7	<0.001*
Pathological stage			
organ confined	61.5%	65.4%	0.68˚
not organ confined	38.5%	34.6%	
Pathological Gleason score (mean±DS)	7±0.5	7±0.6	0.8*
Number of node removed (mean±DS)	18±8.7	12.2±7.1	0.04*
Positive surgical margins	28.8%	23.1%	0.5˚
Continence rates at 27 months	87.8%	87.2%	0.9˚
Time to continence (mean±DS) months	3.9±5.4	3.8±4.3	0.9*
Potency rate at 27 months			
(nerve sparing surgery only)	29%	21.7%	0.5˚
Adiuvant or salvage therapy need	23%	15.4%	0.3˚

*Not paired T-Test; ˚Chi-Square.

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VITAMIN D RECEPTOR GENE POLYMORPHISM IN PROSTATE CANCER AND BENIGN PROSTATIC HYPERPLASIA

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Background: The prostate cancer (CaP) is among the most commonly diagnosed cancers, accounting for about 20% of all

newly diagnosed cancers. Subject of recent studies is the role of vitamin D in the pathogenesis of CaP. Literature data speculated a role of vitamin D in the progression of Cap. In addition, several studies have shown an association between VDR gene polymorphism FokI and CaP especially in the Asian population. *Objective:* The aim of this study was to compare two populations: CaP *vs*. benign prostatic hyperplasia (BPH), to study both the potential role of serum 25-OH vitamin D ($25(OH)D_3$) and assess the relationship between serum $25(OH)D_3$ and VDR gene polymorphisms FokI and TaqI and between polymorphic sites and the risk of developing cancer. Material and method. Two hundred patients (aged 41 to 83 years) in whom biopsies revealed CaP or BHP were enrolled in the present study. The concentration of $25(OH)D_3$ was measured by chemiluminescence immunoassay and polymorphisms were detected by PCR-restriction fragment length polymorphism (RFLP). *Results:* The results showed a significant association (p=0.002) between the genotype FF FokI polymorphism, responsible for the translation of a shorter protein and therefore more functional than normal, in the BPH population compared to CaP, as well as the genotypes of the TaqI polymorphism (p=0.009). Serum $25(OH)D_3$ did not show significant correlation with respect to polymorphisms and compared to disease, although the concentration was low (<30 ng/mL) in 97% of the analyzed samples of the two populations. *Conclusion:* Concluding the CaP is associated with a less functional VDR variation due to a lower frequency of the genotype FF and for the first time there was evidence that the tt genotype of TaqI polymorphism (synonymous polymorphism) is associated negatively to the disease.

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SOFT COMPUTING FOR PREDICTING HIGH GRADE PROSTATE CANCER

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Introduction and Objectives: Fuzzy system and neural network are complementary technologies in the design of adaptive intelligent system. Artificial neural network (ANN) learns from scratch by adjusting the interconnections between layers. A Neuro-fuzzy system is simply a fuzzy inference system trained by a neural network-learning algorithm. The aim of our work was to develop a Neuro-Fuzzy system to predict high-grade prostate cancer (Gleason sum of 7 or more) (HG PCa). *Materials and Methods:* We retrospectively reviewed 1521 patients who underwent prostate biopsy. All men had a PSA level of 50 ng/ml or less. Of the 1521 men, 473 (31%) were diagnosed with prostate cancer on biopsy, and 262 (17.2%) had HG Pca. A neuro-fuzzy system was developed using a coactive neuro-fuzzy inference system model. The model was composed of an input layer with four neurons (PSA, percent free PSA, PSA density and age), and an output neuron representing the risk of HG PCa. The fuzzy control method was the TakagiSugeno-Kang and each input was specified to consist of 4 bell membership functions. The number of training epochs was 1000. The cases were random divided in train-test group (1000 cases) and validation group (521 cases). *Results:* In the validation group the area under the curve (AUC) for the neuro-fuzzy system output was 0.751 +/0.032 (95% confidence interval 0.712 to 0.788), for PSA was 0.594±0.035 (95% confidence interval 0.550 to 0.636) and for percent free PSA was 0.690±0.028 (95% confidence interval 0.672 to 0.752). Furthermore, pairwise comparison of AUCs evidenced differences among PSA, percent free PSA and PSA density *versus* neuro-fuzzy system (PSA *versus* neuro-fuzzy system's output, p=0.001; percent free PSA *versus* neuro-fuzzy system's output, p=0.005). *Conclusion:* We constructed a neuro-fuzzy system based on both serum data and clinical data (age, total PSA, %free PSA, and PSA density) to identify men at risk of harboring high grade prostate cancer. It may assist patients and clinicians in deciding whether further prostatic evaluations are necessary.

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PERCUTANEOUS MICROWAVE TREATMENT OF SMALL RENAL TUMOURS: CLINICAL AND PATHOLOGICAL ASPECTS

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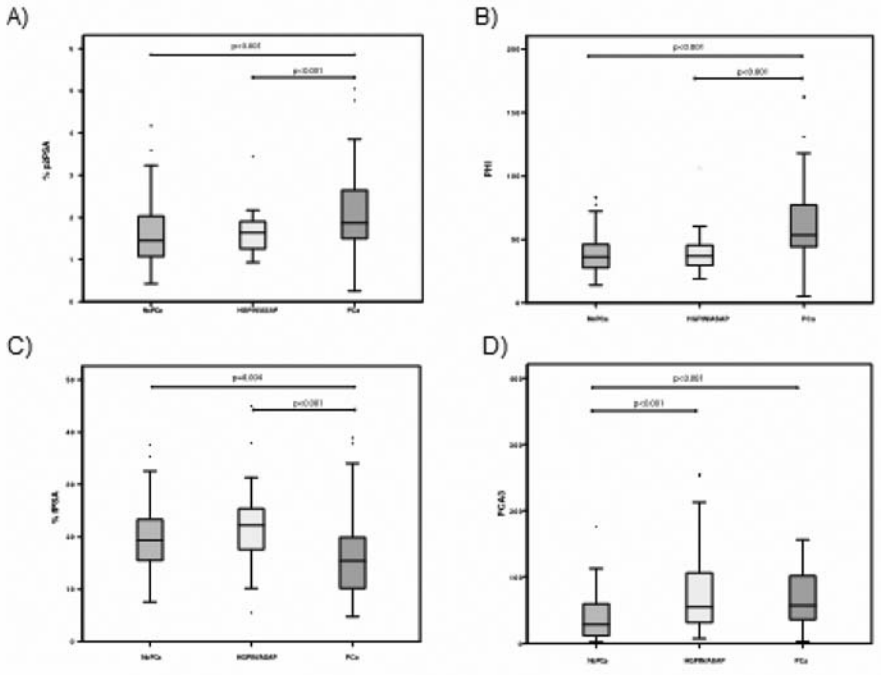
Aim: In this study we evaluated the safety and effectiveness, based on a clinical and pathological follow-up, of the



treatment with percutaneous microwave of small renal tumors in selected patients (with comorbid disease or advanced age). *Patients and Methods:* From January 2010 to December 2011, 12 patients (11 men, 1 woman) with renal cancer, confirmed by previous biopsy, were treated with percutaneous microwave ablation. Under ultrasound guidance, with local anesthesia, 13 G antenna, with a radiating section lenght of 3.7 cm, was placed inside the tumor. Applications of MW ablation at 45 Watt for 10 minutes through one antenna were used. The therapeutic effectiveness was evaluated with a control TC and biopsy 6 months after the surgery and with the next regular uro-oncological follow-up. *Results:* The median diameter of tumors treated was 3 cm (range 2.5-6), the follow-up of 18 months (range 2-26 months) and the mean age 76 years (range (65-82). The mean operative time was 10 minutes and in 8/12 patients one cycle of thermal ablation was performed. In 4/12 patients 2 cycles were performed. All operations were performed under local anesthesia without significant complications. 9/12 patients underwent CT scan at 6 months and in 2/9 cases of persistent doubt, active neoplastic tissue was found. The patients were subjected to post-treatment rebiopsy that in no case showed absence tumor tissue. At follow-up 10 patients are currently alive and disease free, 1 patient died from other causes, 1 patient died 5 months after treatment from progressive disease (patient already metastatic at diagnosis). *Discussion:* Our results, albeit with a small group of patients and a limited follow-up, show the possible efficacy of percutaneous microwave ablation of small renal tumors in selected patients. The radiological assessment alone may not be sufficient to evaluate the effectiveness of minimally invasive techniques in the treatment of renal tumors.

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PREDICTING PROSTATE BIOPSY OUTCOME: PROSTATE HEALTH INDEX (PHI) AND PROSTATE CANCER ANTIGEN 3 (PCA3) ARE USEFUL BIOMARKERS

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Background: The indication for first biopsy is actually based on prostate specific antigen (PSA) serum level and digital-rectal examination (DRE). These tools remained the cornerstones in diagnosis of prostate cancer (PCa), despite their low predictive values. Several new markers have been proposed to improve cancer detection. Recently phi and PCA3 have been demonstrated as good indicators of biopsy outcome. The aim of this study was to compare the ability of phi and PCA3 in predicting biopsy outcome. *Patients and Methods:* Two hundred and fifty men were referred to our prostate clinic to undergo their first prostate biopsy. Among these, 151 met inclusion criteria: age over 50 years, no prior prostate surgery and biopsy, no bacterial acute or chronic prostatitis, no use of 5-α reductase inhibitors in the previous six months, PSA values between 2 and 20 ng/ml, negative digital rectal examination (DRE), availability of serum and urine samples and corresponding clinical data. PSA molecular forms, phi index (Beckman coulter immunoassay), PCA3 score (Progensa PCA3 assay) and other established biomarkers (tPSA, fPSA and %fPSA) were assessed before patients underwent a 18-core prostate biopsy. *Results:* Values of %p2PSA and phi were significantly higher in patients with PCa compared with PCa-negative group (median values: 1.86 *vs*. 1.45 and 53.38 *vs*. 36.21 respectively, $p<0.001$) and also compared with HGPIN/ASAP (1.86 *vs*. 1.64 and 53.38 *vs*. 36.82 respectively, $p<0.001$). PCA3 score values were significantly higher in PCa compared with no PCa (57 *vs*. 28, $p<0.001$) and in HGPIN/ASAP *vs*. no PCa (54.5 *vs*. 28, $p<0.001$); Figure 1. ROC curve analysis showed that %p2PSA, phi and PCA3 are good indicators of malignancy (AUCs=0.73, 0.77 and 0.71, respectively). Values of PSA, p2PSA, %p2PSA, phi and PCA3 were significantly higher and %fPSA significantly lower in patients with Gleason score ≥7. *Conclusion:* %p2PSA, phi and PCA3 carry a comparable ability to predict a diagnosis of PCa in men undergoing their first prostate biopsy. PCA3 score is more useful in discriminating between HGPIN/ASAP and non-cancer. %p2PSA, phi and PCA3 also show a comparable ability to predict a diagnosis of high-grade PCa.

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VALUE OF LONGITUDINAL PERCENT FREE PSA

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Introduction and Objectives: There are limited data on the predictive value of longitudinal percent free PSA measurements for subsequent prostate cancer detection. To evaluate the clinical importance of percent free PSA kinetics before 12 core prostate biopsy, we compared longitudinal percent free PSA in prostate cancer patients and in controls. *Methods:* A prospective, institutional review board approved database of 2208 12 core prostate biopsy, performed at our institution from February 2002 to January 2009, was searched for patients with 4 or more total and free PSA done in 1 or more years before biopsy. The percentage of freePSA slope was calculated with linear regression analysis. *Results:* 256 men entered the study. A total of 79 cancers (30.8%) were found at the ultrasound guided prostate biopsies. The median PSA before the biopsy was 7.05 (range 1.4 to 52.7 micro/L, median age was 62 years (range 36 to 84). Median percent free PSA was 16.67% (range 1.48 to 50.7). Median PSA density was 0.14 (range 0.03 to 0.99). Median PSADT was 4.49 (range -2101 to 554). Median percent free PSA slope was –0.45 for prostate cancer patients and 0.28 for controls ($p<0.001$). On univariate and multivariate analysis percent free PSA, lnPSA slope and percent free PSA slope showed a significant ability to predict the outcome of a 12 - cores prostate biopsy. At ROC analysis the area under the curve (AUC) of PSA was 0.555 (95% confidence interval 0.492 to 0.617) and the AUC of percent free PSA slope was 0.659 (95% confidence interval 0.597 to 0.717) with a significant statistical difference ($p=0.041$). A value of Percent free PSA slope equal to zero corresponded to a sensitivity of 65% and a specificity of 60%. *Conclusion:* We found that percent free PSA slope was an independent predictor of prostate cancer at 12 core prostate biopsy.

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PREDICTORS OF UPGRADING/UPSIZING AFTER 1-YEAR RE-BIOPSY IN MEN PARTICIPATING IN A PROSPECTIVE ACTIVE SURVEILLANCE PROGRAM

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Introduction: Since 2005, we have been proposing active surveillance (AS) in low-risk prostate cancer (PCa). AS protocols include repeat biopsy at pre-defined follow-up intervals. We here consider the outcome of the first re-biopsy (1 yr after AS beginning) and analyse its possible correlation with diagnosis variables. *Methods:* AS institutional protocol (SAINT) started in March 2005 and was accepted by 121 pts. Entry criteria were: iPSA≤10ng/ml, Tstage≤T2a, GPS≤3+3, positive biopsy-cores≤20%, max core length containing cancer≤50%. Pts drop out was: PSADT≤3yrs, PSA>10ng/ml, upgrading/upsizing at re-biopsy or personal choice. In November 2007 PRIAS protocol was embraced: 222 pts were enrolled (February 2012). PRIAS *vs*. SAINT differs on: maximum 2 positive cores and PSA density<0.2ng/ml/cc. Age, iPSA, PSA density, number of positive cores, % of positive cores, max core length containing cancer, average core length containing cancer, number of negative cores at diagnosis, total number of cores at diagnosis, total number of cores at 1yr-rebiopsy, prostate volume, PCa histology and DRE were considered as factors potentially influencing upgrading/upsizing. GPS was not considered (all pts had GPS=3+3). Three separate endpoints were considered: (1) upgrading OR upsizing; (2) upgrading and (3) upsizing. Multivariable logistic regression (MVLR) was used to analyze correlations between variables and endpoints at first re-biopsy. *Results:* Statistical analysis was performed on 255 pts with complete records (1 yr min f-up). 40% pts had a negative 1-yr biopsy (0 positive cores), 45/255(17.7%) pts had upgrading/upsizing after re-biopsy, switching to radical treatment. Backward and forward MVLR resulted in a two variable best fit model for endpoint "upgrading or upsizing" (overall p=0.02, AUC=0.63): number of negative cores>5 (protective factor, OR=0.43, p=0.19) and prostate volume>60cc (protective factor, OR=0.27, p=0.04). When upgrading (27/255 pts) was considered separately, a four-variable best fit model was determined (overall p=0.018, AUC=0.71): age>60yrs (OR=3.4, p=0.12), PSA density (continuous variable, OR=1.04, p=0.16), number of negative cores at diagnosis (protective factor, discrete variable, OR=1.07, p=0.19) and prostate volume>60cc (protective factor, OR=0.17, p=0.1) Taking upsizing (18/255 pts) as the endpoint, MLVR resulted in a five-variable model (overall p=0.03, AUC=0.73) including: DRE (T2a *vs*. T1c, OR=3.03, p=0.16), : number of negative cores>5 (protective factor, OR=0.32, p=0.30), total number of cores at 1-yr re-biopsy (discrete variable, OR=1.14, p=0.18), age>60yrs (OR=0.48, p=0.23) and max core length containing cancer>10% (OR=3.4, p=0.03). *Conclusion:* The present analysis suggests that upgrading and upsizing at 1-yr re-biopsy are independent events which are correlated to different patient's characteristics. Summarizing, upsizing is strongly related to "volume" variables (DRE, max core length containing cancer and number of negative cores which is a surrogate for millimeters of non-cancer) while upgrading is more related to PSA density and number of negative cores. Age has an opposite effect on the two endpoints (protective for upsizing and risk factor for upgrading). Other variables are included for both endpoints which are a sort of surrogate for adequacy of biopsy sampling. Supported by Fondazione Monzino

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MODEL TO BIOPSY ONLY SIGNIFICANT PROSTATE CANCER

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Introduction: Many patients diagnosed with low grade prostate cancer may have indolent disease that may not benefit from immediate therapy. Our objective was to create a nomogram using PSA kinetics to predict high-grade prostate cancer (Gleason sum of 7 or more) (HG PCa). *Materials and Methods:* From a prospective database of twelve core prostate biopsies, we identified 630 men with at least 3 consecutive PSA measurements over a 2 year interval prior to biopsy. Least squares regression was used to calculate "PSA acceleration" (logPSA slope). Logistic regression was then used to predict HG PCa at biopsy using age, digital rectal

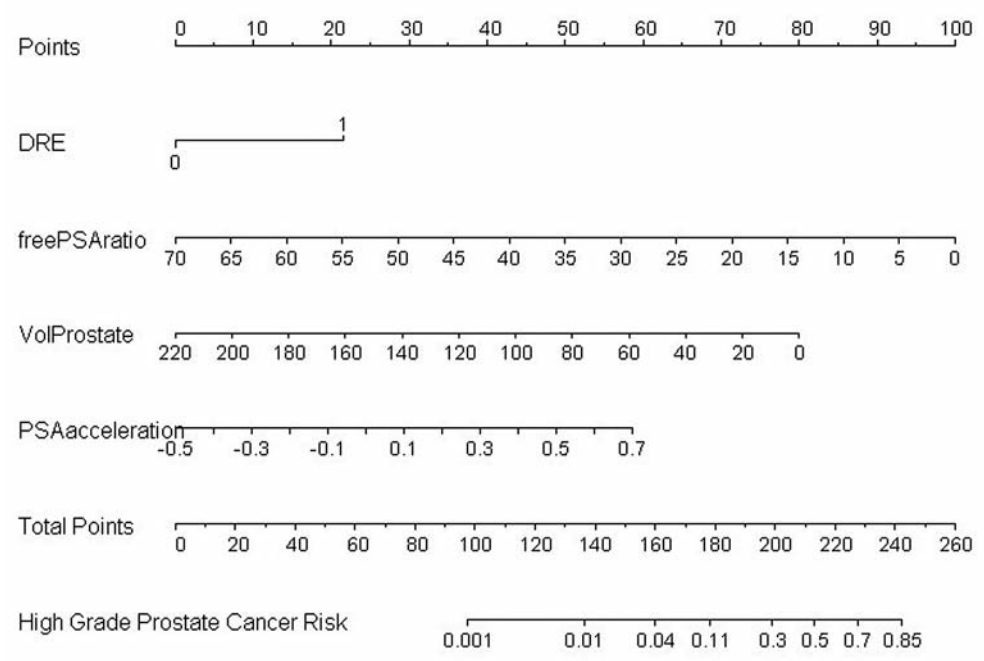

Figure 1 *(abstract 156)*.

examination findings (DRE), PSA, free to total PSA ratio (%fPSA), prostate volume and PSA acceleration. The population was randomly divided into two groups. A nomogram was developed in the training set and was then evaluated in the validation cohort. *Results:* Of the 630 men, 189 (30%) were diagnosed with prostate cancer on biopsy, and 75 (11.9%) had HG PCa. We applied backwards variable elimination to the full model, with the intent of identifying the most parsimonious and accurate model. In this model, all variables except age and PSA were significant predictors of HG PCa, and were included in the nomogram (Figure 1). In the validation population, the nomogram based on the parsimonious model had superior discrimination (AUC=0.817) compared to PSA, %fPSA, PSA density or PSA acceleration alone. Using a cutpoint of 17, the nomogram had a sensitivity of 85.7% and specificity of 69.3% for HGPCa. *Conclusion:* The identification of clinically significant prostate cancer is essential to avoid overdiagnosis. We successfully developed a model to predict HG PCa including %fPSA, DRE findings, prostate volume and "PSA acceleration". Although the nomogram performed well in the internal validation, additional studies are warranted in external populations to confirm the clinical utility of this predictive tool.

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HOW TO REBIOPSY ONLY MEN WITH HIGH GRADE PROSTATE CANCER, AFTER A PREVIOUS NEGATIVE BIOPSY

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Introduction: Several studies have demonstrated a significant association between PSA kinetics and clinically significant prostate cancer. Thus, the aim of the current study was to develop a model to predict high-grade prostate cancer (HG PCa) on repeated prostate biopsy, incorporating "PSA acceleration". *Materials and Methods:* A logistic regression model was constructed to predict HGPCa (Gleason score 7 or more) at repeated biopsy, using age, family history, digital rectal examination findings (DRE), PSA, percent free PSA (%fPSA), PSA density and PSA acceleration from 362 men, who underwent a repeated prostate biopsy with at least 3 prior PSA measurements from which to calculate "PSA acceleration". *Results:* On repeated biopsy, 105 (29%) men were diagnosed with prostate cancer, of which 45 (13%) had a Gleason sum of 7 or more. In the backward stepwise logistic regression model, %fPSA, DRE, family history, PSA density and PSA acceleration provided the most parsimonious model to predict HGPCa after a negative initial biopsy, and were included in the nomogram. The nomogram was well-calibrated and had an area under the ROC curve of 0.774, which exceeded that of any single risk factor. *Conclusion:* We

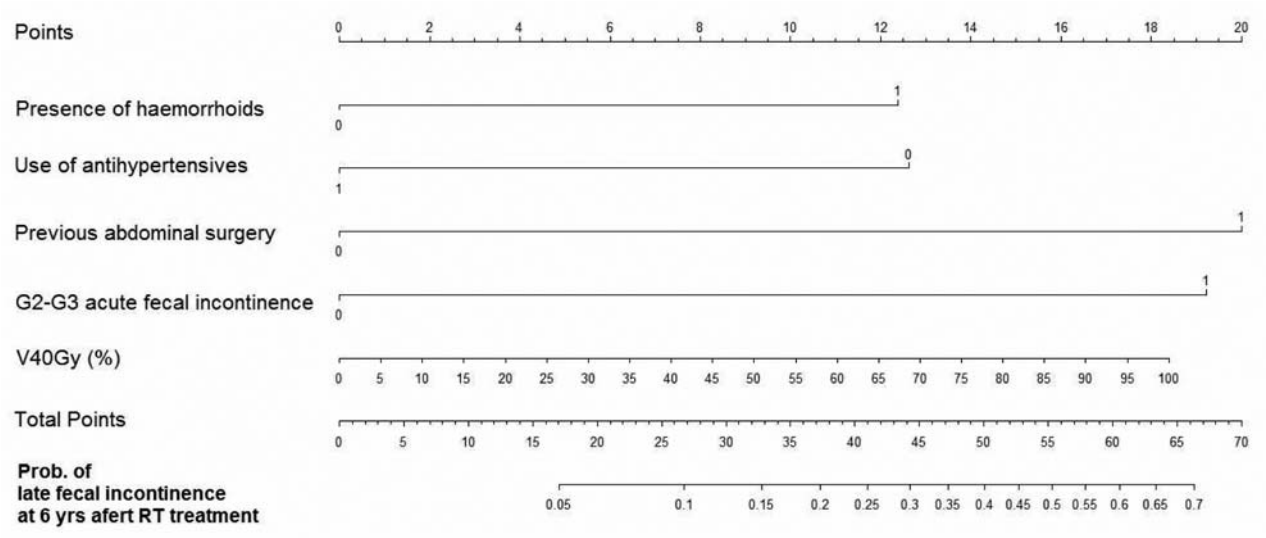

Figure 1 *(abstract 158)*.

successfully developed a model to predict HGPCa on repeat prostate biopsy including %fPSA, DRE findings, family history, PSA density and "PSA acceleration".

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RECTAL TOXICITY 7 YEARS AFTER HIGH-DOSE RADIATION FOR PROSTATE CANCER: CLINICAL AND DOSIMETRIC PREDICTORS

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Purpose: To evaluate long term prevalence of late rectal bleeding (lrb) and of late fecal incontinence (linc) after high-dose radiotherapy (RT) in prostate cancer patients (pts) accrued in AIROPROS 0102 trial (RT doses: 70-80Gy, 1.8-2Gy/fr) and to model the relationship between lrb/linc and clinical/dosimetric factors. *Patients and Methods:* Self-reported questionnaires of 515 pts with a minimum follow-up of 6 yrs (median follow-up 7 years) were analyzed with respect to lbr and linc. G1 lrb was defined as lrb less than 2 times/week, G2 if lrb more than twice/week, G3 if daily lrb was present or if any number of blood transfusion and/or laser coagulation was necessary. G1 linc was scored if unintentional stool discharge was "sometimes" experienced, G2 linc if unintentional stool discharge was "often" experienced or if pts sporadically used sanitary pads; G3 if pts reported daily unintentional stool discharge or use of sanitary pad >2 times/week. The correlation between pre-treatment morbidities, hormonal therapy, drug prescription, presence of diabetes or hypertension, abdominal surgery prior to RT, presence of RTOG greater than 1 toxicity, presence of G2-G3 acute fecal incontinence, pelvic nodes and seminal vesicles irradiation, mean rectal dose, dose-volume histograms constraints (from V20Gy to V75Gy) and lrb/linc was investigated by uni- and multivariate (MVA) logistic analyses. 347/515 pts had at least 3 toxicity questionnaires in the first 36 mos after the end of RT. Correlation between the mean score of fecal incontinence in the first 36 mos and linc at 7 yrs was also investigated. *Results:* 32/515 G1, 2/515 G2 and 3/515 G3 lrb were registered. 50/515 G1, 3/515 G2 and 3/515 G3 linc were reported. Lrb was only correlated to V75Gy (continuous variable): $p=0.02$, OR=1.07. The prevalence of lrb≥1 at 7 yrs was significantly correlated with incidence of G2-G3 lrb in the first 3 yrs after RT treatment: 42.3% in pts with G2-G3 bleeding in the first 3 yrs *vs*. 5.6% in non-lrb pts ($p<0.0001$, chi-squared). Linc was correlated to multiple variables. In MVA (overall $p<0.0001$, AUC=0-77) V40Gy (continuous variable, $p=0.09$, OR=1.015), use of antihypertensives (protective factors, $p=0.005$, OR=0.38), presence of abdominal surgery before RT ($p=0.004$, OR=4.7), presence of haemorrhoids ($p=0.008$, OR=2.6) and presence of G2-G3 acute incontinence ($p=0.007$, OR=4.4) resulted to be correlated to linc. The figure shows the nomogram which was

developed starting from MVA results. Linc at 7 yrs was also correlated to the mean incontinence scores in the first 36 mos ($p<0.0001$): pts without linc at 7 yrs had a mean score of 0.1 during the first 36 mos, while pts with G1 and with G2-G3 linc at 7 yrs had a mean score of 0.5 and 0.78 during the first 36 mos, respectively. The prevalence of linc≥1 at 7 yrs was significantly correlated with the mean incontinence scores in the first 3 yrs after RT treatment: 37.3% in pts with mean score ≥0.5 *vs*. 10% in pts with mean score <0.5 ($p<0.0001$, chi-squared). *Conclusion:* A fraction of pts is still experiencing rectal toxicity symptoms 7 yrs after RT: 7.2% lrb and 10.9% linc. Prevalence of toxicity at 7 yrs is significantly correlated to incidence in the first 3 yrs after RT treatment. This is an indication of a chronic occurrence of symptoms, with late fecal incontinence playing the major role. Mean score for incontinence during the first 36 mos after RT can be used as a surrogate endpoint for late (>6yrs) fecal incontinence. A nomogram for linc prediction at 7 yrs was developed. Linc is correlated to clinical and dosimetric risk factors and individualised toxicity prediction can be performed through the proposed nomogram.

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PREDICTING LATE FAECAL INCONTINENCE AFTER HIGH-DOSE RADIOTHERAPY FOR PROSTATE CANCER: APPLICATION OF ARTIFICIAL NEURAL NETWORK CLASSIFICATION ON A NEW LONGITUDINAL DEFINITION

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Objectives: To study the application of artificial neural network (ANN) classification for the prediction of late faecal incontinence following high-dose prostate cancer radiotherapy (RT). To this aim, a new longitudinal score of incontinence (*i.e*., the mean late incontinence score) was introduced starting from the four-grade scale adopted for the AIROPROS (prostate working group of the Italian Association of Radiation Oncology) 0102 trial. *Materials and Methods:* AIROPROS 0102 trial information 586 men recruited in the AIROPROS 0102 trial, which included the prospective evaluation of acute and late faecal incontinence through self-assessed questionnaires, were analyzed. Incontinence was scored as follows: Grade 1, unintentional stool discharge "sometimes" experienced; Grade 2, unintentional stool discharge "often" experienced or sporadically use of sanitary pads; and Grade 3, daily unintentional stool discharge or use of sanitary pads >2 times/week reported. For the present analysis, a new longitudinal definition of late faecal incontinence expressed as the average score of late incontinence using the four-grade scale was considered. Information was recorded on co-morbidity (with particular attention to hypertension, cardiovascular history, diabetes mellitus, auto-immune diseases), previous abdominal surgery (rectum-sigma resection, kidney resection, cholecystectomy, appendectomy), and use of drugs (anticoagulants or antiaggregants, antihypertensives, hypoglycaemic or insulin). Rectal dose-volume histograms of the whole treatment were recorded for all patients and the percent volume of rectum receiving more than 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70 Gy (named V20Gy→V70Gy) were considered. *ANN analysis:* The overall population was split into a train and a test set. The train group was used to optimize the inner weights and biases of the ANN by means of back propagation and conjugated gradients training algorithms. To avoid data over fitting, the number of inputs and hidden neurons in the ANN was limited and the training iterative process was stopped after a predetermined number of epochs was reached. The test set was used as an independent set to verify the generalization capabilities of the model. A value of longitudinal late faecal incontinence equal or greater than one was arbitrarily considered as the endpoint, because this score selected those patients with persistent symptoms. *Results:* Of the 586 patients, 36 had an incontinence score greater than 0 on the baseline pre-treatment questionnaire and were excluded from the analysis. Thus, the number of patients available for the analysis was 550 (22 positive cases), which were split in 366 (15 positive) and 184 (7 positive) cases for train and test set, respectively. Among the previously described large amount of possible ANN input data, a suitable subset of variables able to better predict late faecal incontinence was selected. Five variables were identified, *i.e*. the V40Gy (continuous variable), surgery (yes/no), seminal vesicles irradiation (yes/no), use of anticoagulants (yes/no), and presence of haemorrhoids (yes/no). The resulting ANN classifier (4 hidden neurons) was able to correctly predict late faecal incontinence with

sensitivity and specificity values of 80% and 68%, respectively for the overall population. Following ROC analysis, area under the ROC curve was 0.84. Adding the acute incontinence information as a further ANN input variable, sensitivity and specificity increased to 80% and 95%, respectively. Following ROC analysis, area under the ROC curve increased to 0.92.

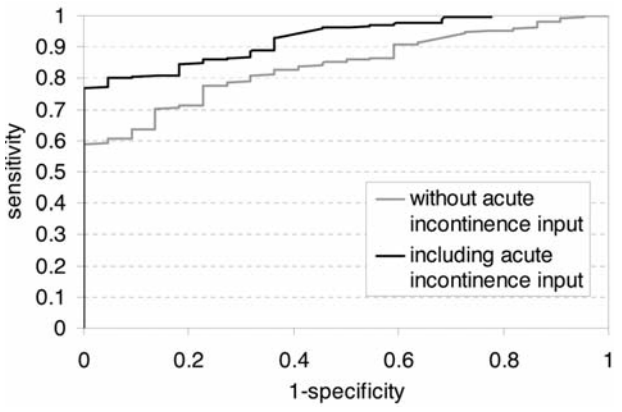

Figure 1. *ROC curves for late faecal incontinence classification with ANN. Results were obtained omitting and including the acute incontinence information as input to the ANN.*

Conclusion: ANN analysis combined to the selection of significant input variables and a longitudinal definition of faecal incontinence resulted to be a powerful tool to predict late rectal morbidity in patients treated for prostate cancer. Models like the one described in this study might help radiation oncologists to predict and possibly avoid an unnecessary worsening of quality of life of a single patient, introducing treatment's corrections to better tailor the treatment to patient's characteristics.

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PROPHYLACTIC BLADDER INSTILLATIONS WITH IALURIL® MAY REDUCE SYMPTOMS OF ACUTE RADIATION CYSTITIS IN PATIENTS UNDERGOING RADIOTHERAPY FOR PELVIC TUMOURS

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Introduction: Acute radiation cystitis (RC) is a common and debilitating problem in patients undergoing radiotherapy for urogenital malignancies. Acute RC symptoms include painful micturition, urgency, frequency, and nicturia We studied the feasibility and efficacy of intravesical instillations with Ialuril® (sodium hyaluronate and chondroitin sulfate sterile solution) to reduce acute radiation cystitis in men and women undergoing pelvic radiotherapy. *Materials and Methods:* The single-arm study was performed between September 2010 and June 2011 and included 15 patients who met the following criteria: primary or adjuvant radiotherapy for pelvic cancer. Exclusion criteria were: bladder cancer, LUTS, overactive bladder syndrome. Symptoms of haematuria, frequency of voiding and the visual analogue scale of pelvic pain (range 0-10) were evaluated before and after the treatment with follow-up of 6 months. During radiotherapy, all patients received weekly bladder instillations of 50 ml of sterile sodium HA 1.6% and CS 2.0% solution (IALURIL®). *Results:* A reduction of degree symptoms of haematuria occurred in 13 of 15 patients ($p<0.001$). reduction of frequency of voiding and of visual analogue scale score were significantly lower than baseline at the 6-months ($p<0.001$, p 0.002, respectively). *Discussion and Conclusion:* Bladder instillations with Ialuril® seems to reduce acute post-irradiation cystitis symptoms in patients treated for pelvic malignancies. Further studies are needed to obtain more robust evidence.

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CENTRALIZED REVISION OF DIAGNOSTIC PATHOLOGIC SLIDES FOR PROSTATE CANCER PATIENTS ON ACTIVE SURVEILLANCE: IS IT JUST TIME AND RESOURCE CONSUMING OR DO WE REALLY NEED IT?

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Introduction and Objectives: Active Surveillance (AS) is offered to prostate cancer (PCa) patients (pts) with very low risk disease, with well defined diagnostic biopsy details coupled to clinical stage criteria and PSA≤10 ng/ml. For this reason, in order to standardize diagnostic inclusion criteria, we requested pathologic review before AS enrollment. We here report on second opinion of prostate needle biopsies to determine how often the expert opinion of a uro-pathologist resulted in a different diagnosis, in the group of pts who were proposed for AS. *Patients and Methods:* AS institutional protocol (SAINT) started in March 2005. Entry criteria were: initial PSA≤10 ng/ml, Tstage≤T2a, GPS≤3+3, positive biopsy-cores≤20%, max core length containing cancer≤50%. In November 2007 PRIAS protocol was embraced. PRIAS *vs*. SAINT differs on: maximum 2 positive cores and PSA density<0.2 ng/ml/cc. From October 2005 through July 2010, a second opinion on biopsy diagnosis was requested in 248 cases, due to outside diagnosis. We analyzed differences between outside diagnosis and institutional expert opinion. For this purpose we considered two different classes of differences: minor differences (changes which did not prevent AS enrollment) and significant changes (differences which resulted in a change in prognosis and closed the possibility of AS enrollment). *Results:* Overall 40/248 (16.1%) cases had minor differences (18 referred to SAINT pts and 22 to PRIAS pts). In the SAINT group, 12/18 (66.7%) biopsies were increased in the max core length containing cancer (but still≤50%) and 6/18 (33.3%) had a change in the number of positive cores (3 reductions and 3 increases, but still≤20% of total cores). In the PRIAS group 10/22 (45.5%) changes were related to upsizing (from 1 to 2 positive cores) and 5/12 (22.7%) to downsizing (from 2 to 1 positive core). 7/22 (31.8%) changes were related to differences in core length containing cancer (from below to above 50%). Significant differences were observed in 30/248 (12.1%): 20/30 (66.7%) changes were related to upgrading (18 to GPS=3+4, 1 to GPS=4+3 and 1 to GPS=4+4). 10/30 (33.3%) pts had an upsizing: 1 SAINT pt exceeded 20% of positive cores, 5 SAINT pts exceeded 50% of max tumor length of positive cores, while 4 PRIAS pts increased from 2 to 3 or 4 positive cores. Among significant differences, there were 20 changes (8.1% of total revisions) that led to an upgrading of the pt's risk class (19/20 moved from Low-Risk to Intermediate-Risk and 1/20 from Low-Risk to High-Risk class). *Conclusion:* Central pathology review reduces population heterogeneity in the specific setting of AS programs. Significant reclassification of risk category involved 12% of pts. Current clinical consequences of central review cannot be determined.

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USE OF ICIQ QUESTIONNAIRE FOR THE EVALUATION OF PELVIC FLOOR MUSCLE TRAINING AFTER RADICAL PROSTATECTOMY OR CYSTECTOMY WITH BLADDER RECONSTRUCTION

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Background: Perioperative and postoperative pelvic floor muscle training have shown to hasten the recovery of urinary continence after radical prostatectomy. Even if pelvic floor muscle training is recommended by EAU guidelines and is widespread used, this treatment has not yet been standardized. In the present study we evaluated the use of three ICIQ questionnaires on a population of prostate and bladder cancer patients undergoing pelvic floor muscle training in order to check the improvement of urinary continence and other symptoms during this treatment. *Patients and Methods:* Between September 2010 and August 2011, all patients referring to pelvic floor physiokinesiotherapy ambulatory of our department were proposed to fill-in the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI ShortForm) and the International Consultation on Incontinence Questionnaire Urinary Incontinence Quality of Life Module (ICIQLUTSqol). All male patients were also required to fill-in International Consultation on Incontinence Questionnaire Male Sexual Matters Associated with Lower Urinary Tract Symptoms Module (ICIQMLUTSsex). All patients were waiting for a major pelvic surgical procedure (radical prostatectomy or radical cystectomy plus bladder reconstruction). Questionnaires

were administered before surgery, after catheter removal, and 3, 6, 9 and 12 months after surgery. All patients received multiple supervised pelvic floor training session from a dedicated nurse before surgery and immediately after catheter removal and repeated for some weeks, and oral and written instructions on pelvic floor muscle contractions and a structured programme of exercises to be performed at home while lying, sitting and standing. Data about erectile dysfunction treatment were also collected. *Results:* A total of 43 patients agreed to fill-in the questionnaires. 33 patients underwent traditional retropubic radical prostatectomy, 6 a robotic-assisted radical prostatectomy and 4 a radical cystectomy with bladder reconstruction (Y-neobladder). Among these last 4 patients, 3 were male and 1 female. Mean age was 65.42 years ± 6.26. The comparison between the questionnaires before surgery and after catheter removal showed a clear worsening of all parameters in all the 3 forms ($p<0.05$). At 6 months questionnaires we recorded statistically significant improvements at most of the questions of ICIQLUTSqol (2a-8a, 10a, 16a, 16b, 18a-19a, 21) and at the whole ICIQ-UI short form ($p<0.05$). At 9 and 12 months questionnaires improvements recorded at 6 months are confirmed and some further statistically significantly improvement is recorded in ICIQ-LUTSqol (9° month: 13a, 14a; 12° month: 8b and 10b) ($p<0.05$). As far as ICIQ-MLUTSsex for the 42 male patients is concerned, no statistically significant improvement was recorded during follow-up. *Discussion and Conclusion:* Pelvic floor muscle training is extensively used after radical prostatectomy and radical cystectomy with bladder reconstruction in order to recover an early continence. Nevertheless, the results and the improvements are difficult to monitor during and after the treatment, and many questionnaires have been proposed and used. International Consultation on Incontinence provides many modular questionnaires that are extensively used for various kind of incontinence. The 3 questionnaires that we have evaluated proved to be effective and easy to use in this context, especially for ICIQ-UI short form.

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Y- NEOBLADDER: AN UPDATE OF A MULTI-INSTITUTIONAL RETROSPECTIVE STUDY

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Background: In the last 90's, we proposed a new kind of ileal orthotopic reservoir: the Y-neobladder proved to be easy and fast to create, to provide good functional results and to have a very low incidence of strictures of ureteral-neobladder anastomosis. In order to confirm those first results, we conducted a retrospective multi-institutional study. *Patients and Methods:* Eight different Urologic Departments from 8 Italian hospitals provided the data of all their patients who underwent radical cystectomy followed by bladder substitution with Y-neobladder. The main steps of surgical technique used were previously described and published. The following parameters were recorded and retrospectively reviewed: indication for radical cystectomy, surgery notes, early and late complications, data about micturitions, continence and self-catheterism and oncologic follow-up. Continence was defined good if no use of pads was recorded, satisfactory for 1 pad, unsatisfactory >1 p pads. Statistical analysis was performed through a PC software. *Results:* Complete data were available for 227 patients, who underwent the procedure between September 1999 and January 2010. The mean age at radical cystectomy was 65.12±9.08 years. Two hundred and one patients were male, while 26 were female. The mean follow-up was 33.0±27.34 months. The indication to radical cystectomy was given for muscle-invasive bladder cancer in 64% of patients, recurrent non-responsive superficial bladder cancer in 34%, other pelvic cancer in 1% and benign bladder diseases in 1%. As far as functional outcome are concerned, the mean daytime voiding frequency was 5.83 micturitions, while the mean nighttime voiding frequency was 2.47 micturitions. A good or satisfactory daytime continence was obtained in 85% of patients with at least 1 year of follow-up (133/157 patients), and nighttime continence was good or satisfactory in 76% (119/157). The following late complications were recorded: stricture of urethral-neobladder anastomosis in 7.49% of patients (17/227), stricture of ureteral-neobladder anastomosis in 2 patients (2/445 renal units, 0.45%), neobladder stone in 13 patients (5.73%), urinary sepsis in 11 (4.85%), vaginalneobladder fistula in 3 out of 27 female patients (11%). No severe metabolic complication was recorded. *Conclusion:* Even though these data are

retrospectively collected, on several different hospitals and with irregular follow-up, the results of the study suggest that the Y-neobladder provide good functional outcomes with a low rate of late complications. We underline that the incidence of strictures of ureteral-neobladder anastomosis is extremely low (0.45% of renal units) if compared to the results of other ileal reservoirs.

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CONTINUOUS SUBFASCIAL WOUND INFUSION FOLLOWING RADICAL RETRO PUBIC PROSTATECTOMY: A PROSPECTIVE, RANDOMIZED INSTITUTIONAL DOUBLE-BLIND STUDY

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Aim: To evaluate the efficacy of continuous wound infusion of local anaesthetic agent after open radical retro pubic prostatectomy (RRP). *Patients and Methods:* 97 patients (54-75 year old) underwent RRP for prostate cancer and were enrolled in a double –blind prospective study into two groups randomized (1:1) for pain control. All patients were placed both continuous wound infusor (Painfusor Catheter -Baxter) and a venous line connected to elastomeric pump. Group A (49 patients, main age 66,3, main incision length 74 mm) received intravenous morphine 12 mcg/Kg/h released by elastomeric pump and continuous wound infusion of 0.9% saline solution. Group B (48 patients main age 68.2, main incision length 78 mm) received continuous wound infusion of ropivacain 400 mg 5Ml/h and intravenous 0.9% saline solution released by elastomeric pump. Each patient underwent total intravenous anesthesia, was instructed to use a patient controlled analgesic device (PCA Midial pump 586). Outcome measured over 72h were visual analogue scale, simple scale and adverse effects. *Results:* Results are summed in the follow Tables I and II:

Table I

Group	Patients	Pain	VAS	PCA	Morphine
A	13 (26%)	Severe	7/8	5/6 h	7 mg
	22 (44%)	Average	4/5	6/7 h	5 mg
	6 (12%)	mild	1/2	24 h	0.8 mg
B	6 (12%)	mild	1/2	24 h	0.8 mg

Table II

	A	A (%)	B	B(%)
Drowsiness	22	44	-	-
NAUSEA	20	40	-	-
Vomit	10	20	3	6
Delay C.	19	39	-	-
Thrill	6	12	4	8
Hypotension	-	-	-	-

Conclusion: Continuous wounds infusion of local anaesthetics are safe and effective to reduce pain and adverse effects related to postoperative analgesic drugs administrations.

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TRANSITIONAL CELL CARCINOMA (TCC) IN RENAL TRANSPLANT PATIENTS: A 20 YEARS RETROSPECTIVE ANALYSIS

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Background: Transitional Cell Carcinoma (TCC) in renal transplant patients is rare but aggressive. Immunosuppression plays a role in its pathogenesis. The best clinical and surgical management of TCC in this population is unclear due to the low incidence of the disease. Aggressive surgical strategies have been proposed. We report on the management of TCC in renal transplant patients in the Transplant Centre of Torino in the last 20 years. *Patients and Methods:* 2581 renal transplants were performed in the Transplant Center of Torino from 1981 to 2011. We made a retrospective analysis of the last 20 year activity. Clinical reports were reviewed looking for TCC diagnosis, treatment and prognosis. 9 cases of TCC were identified: 8 bladder TCC, 1 upper urinary tract TCC (in the graft renal pelvis). *Results:* 8 patients (4 males and 4 females) were diagnosed with bladder TCC. Medium time from transplant to diagnosis was in media 6-7 years (range from 3 months to 13 years). Average tumor size was 1.2 cm (0.5-2 cm) at diagnosis. There was no predominant location in the bladder and TURB had no complications. Pathological examinations were the following: pTaG1 in 3 cases, pTaG3 in 1 and pT1G3 in 4 (1 associated with CIS). 2 out of 3 pTaG1 patients had a multifocal disease. 6 patients received intravescical chemioprophylaxis (5 mytomicine C, 1 epirubicine). No BCG immunoprophylaxis was used. 3 out of 4 patients with pT1G3 TCC progressed to muscle-invasive bladder cancer: 1 had metastatic disease at pT2 diagnosis, 2 underwent radical cystectomy, native nephroureterectomy and graft urinary diversion but they both died after 1 year. All pTa patients are disease-free at a 7 years (range from 4 to 10 years) median follow-up. 1 pT1G3 patient is disease-free at 1 year follow-up. Cyclosporine + azathioprine + steroid was the most commonly used immunosuppressive treatment. 5 patients changed immunosuppressive regimen after tumor diagnosis. The patient with renal pelvis TCC had a double kidney transplantation. The tumor was diagnosed 4 years after the transplantation because of hematuria. A nephroureterectomy of the involved graft was performed. A pT3G3 TCC was histologically diagnosed. After a two-years follow-up the patient is in good health condition, free from recurrences and progression, but under dialytic treatment. *Conclusion:* Treatment of TCC in transplant patients is challenging. Tumor often develops years after renal transplantation. In our retrospective analysis low-risk tumors had a good long-term prognosis and pTa stage at diagnosis was highly predictive for long-term survival. High-risk tumors, particularly pT1G3 in our series, had on the contrary a very poor prognosis with no long-term survival despite aggressive surgical management. Variations in immunosuppressive regimen and optimization of intravescical prophylaxis should play a role in the treatment of the disease. Large series and meta-analysis are desirable to draw conclusions on this challenging issues.

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SECOND-LINE TREATMENT WITH SORAFENIB IN POOR-RISK ADVANCED RENAL CELL CARCINOMA: A CASE REPORT

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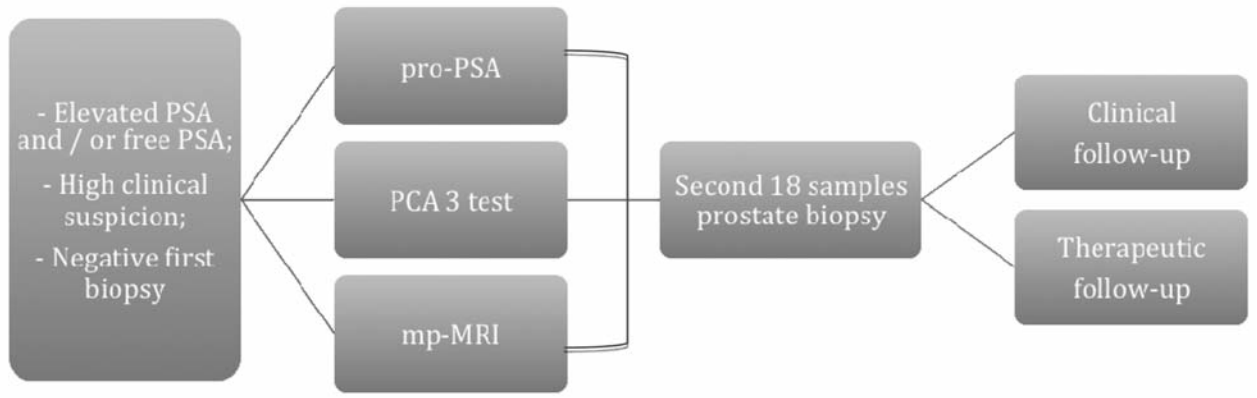
Introduction: In the last few years the development of targeted therapies has significantly improved prognosis of patients with clear cell metastatic renal cell carcinoma (mRCC). Nevertheless, life expectancy of patients with poor-risk mRCC remains less than one year. *Case Report:* We describe a case of a 46-year-old male patient (S.C.), heavy smoker, who underwent nephrectomy at another institute on January 2006 for a histologically confirmed clear cell RCC (Fuhrman nuclear grade III). In September 2008 a CT scan (performed for the onset of asthenia, confusion and detectable hepatomegaly) showed multiple metastatic liver lesions, and a biochemical evaluation showed a severe hypercalcemia. The patient was admitted to our center, his symptoms were settled with rehydration, diuretics and Zoledronate. A skeletal scintigraphy detected multiple bone lesions. The patient was judged to be at poor risk according to Motzer criteria, due to his performance status (Karnofski 50%), severe anaemia, high corrected calcium level and high lactate dehydrogenase level. At this point, in December 2008 treatment with Temsirolimus was started, at a dose of 25 mg once a week. After two weeks the patient exhibited marked clinical improvement and regression of hypercalcemia to normal values. In February 2009 a CT evaluation showed stable disease, and in March 2009 a skeletal scintigraphy revealed complete response of bone metastases. Treatment was well tolerated (with exception of grade I asthenia) and was continued until May 2009, when



patient experienced diffuse bone pain, recurrence of hypercalcemia, severe anaemia and altered liver function tests. Given the severity of symptoms we decided to start a second line of biological therapy without waiting for baseline CT evaluation. In consideration of the patient's fears about Sunitinib-related cardiotoxicity and our willingness to reserve this therapeutic option for an eventual third line therapy, we chose to begin Sorafenib. This treatment (400 mg twice daily) was initiated at the beginning of June 2009. After eight weeks of therapy we observed a significant improvement in clinical condition and laboratory parameters (regression of hypercalcemia, increase of haemoglobin level) The patient didn't submit to scheduled CT scan and asked not to be subjected to further imaging studies because of his poor clinical conditions, so we couldn't achieve a baseline radiological disease evaluation. Since our primary objective was patient's quality of life and in consideration of clinical, haematological and biochemical improvement we decided to continue Sorafenib. After 4 months of treatment the patient interrupted all analgesic therapy and showed further improvement of clinical condition. Biochemical evaluation revealed resolution of anaemia and normalization of liver function tests. Treatment side-effects were grade I asthenia and grade I diarrhoea. In November 2009 he developed poorly tolerated grade II hand-foot syndrome which required a temporary interruption of Sorafenib. Two days after discontinuation of the treatment the patient reported complete resolution of symptoms, so we decided to resume Sorafenib without any dose reduction. In January 2010 a CT indicated stable disease compared to the last examination, which had shown best response to Temsirolimus. In June 2010 the Sorafenib dose was reduced to 600 mg daily because of liver transaminases elevation. This dose reduction led to a rapid normalization of liver function tests. Our patient is still on treatment with Sorafenib (600 mg daily) after more than three years, his Karnofski PS is 100%, liver function tests, calcium and haemoglobin levels are normal and a recent CT scan has confirmed stable disease. *Conclusion:* This case suggests that even in poor-risk mRCC a sequential targeted treatment may determine a relevant benefit in terms of quality of life and, in selected cases, may induce long term survival.

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ASSESSMENT OF THE ROLE OF PSA, PRO-PSA, PCA3 AND PROSTATE MRI IN SELECTING PATIENTS WHO ARE CANDIDATES FOR A SECOND PROSTATE BIOPSY

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Introduction: In patients with persistently elevated PSA and negative biopsy, there is a need for repeated prostate biopsy. The repetition of the biopsy, however, does not increase the detection rate of PCa, which decreases progressively in the next sampling, leading to an increase of side-effects. Additional analyses have been proposed to reduce the number of repeated biopsy (RB) such as pro-PSA, PCA3, and prostate multiparametric Magnetic Resonance Imaging (mp-MRI). Aim of this study was to evaluate the role of these additional analyses using a diagnostic pathway in patients with clinical suspicion of cancer and/or elevated PSA with an initial negative prostate biopsy. *Patients and Methods:* We prospectively included patients with a negative first biopsy (12 samples) and abnormal PSA levels, pathological (as ASAP and/or HG-PIN) or strong clinical suspicion, as shown in Figure 1. Each of them

underwent serum pro-PSA measurement, analysis of urine after prostatic massage for the assessment of genetic markers, urinary PCA3 and MRI performing a conventional study with T1-w, T2-w and diffusion sequences. After precontrast acquisitions, patients were intravenously given gadobutrol. All images were examined by an expert uro-radiologist. All patients were then submitted, according to current European guidelines, to a RB(18 samples), examined by an expert uro-pathologist. We evaluated sensitivity, specificity, positive and negative predictive values, and accuracy of the individual tests and the combination of these to predict the presence of PCa at the repeated (second) biopsy. *Results:* 50 patients were consecutively enrolled in the study, the mean age was 62.5 years, mean PSA at baseline was 7.25 ng/ml. On RB, 15/50 (30.0%) had biopsies positive for cancer.

	PCA3	pro-PSA	MRI	PCA3 + pro-PSA	pro-PSA + MRI	PCA3 + MRI	PCA3 + pro-PSA + MRI
Sens	66.7%	53.3%	93.3%	73.3%	93.3%	100.0%	100.0%
Spec	97.1%	57.1%	91.4%	85.7%	94.3%	94.3%	94.3%
PPV	90.9%	34.8%	82.4%	68.8%	87.5%	88.2%	88.2%
NPV	87.2%	74.1%	97.0%	88.2%	97.1%	100.0%	100.0%
Accuracy	88.0%	56.0%	92.0%	82.0%	94.0%	96.0%	96.0%

Conclusion: We disclose the low number of enrolled patient as a main limit of the study. Our results show that the PCA3 test is the one with the highest PPV, while the highest NPV is obtained with the combination of the mp-MRI and the PCA3. The measurement of pro-PSA does not add useful data to the combination PCA3 + MRI, which is shown to be the best predictive combination for the diagnosis of PCa. We think that these preliminary results are promising even if further cases are necessary to define which patients should be candidate for RB.

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CAN POST-BIOPSY MRI HELP THE SURGEON ON SURGICAL PROCEDURE PLANNING?

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Introduction: Nowadays, in case of laboratory or clinical suspicion of Prostate Carcinoma (PCa), the patient is subjected to random biopsies TRUS-guided. Due to the lack of appropriate techniques for the precise localization of PCa, often treatment is not the most appropriate. Using an imaging examination that allows us to have a correct radio-histological correlation can help the clinician in proper planning of surgery. The aim of our study was to analyze separately each tumor focus to evaluate the diagnostic accuracy of multiparametric Magnetic Resonance Imaging (mp-MRI) in detecting and localizing of PCa. The study was conducted prospectively and as gold standard was considered the pathological findings in patients undergoing Radical Prostatectomy (RP). *Patients and Methods:* The study included 120 patients with high PSA value and biopsy diagnosis of PCa. All patients underwent MRI performing a conventional study with T1-w, T2-w and diffusion sequences. After precontrast acquisitions, patients were intravenously given gadobutrol. All images were examined by an expert uro-radiologist. The sensitivity in identifying lesions was defined as the ratio between the number of true positives (*i.e.* lesions identified histologically recognized as such in MRI) and the total number of lesions histologically recognized. We stratified the sensitivity according to tumor volume, examining changes less than 0.2 cc, between 0.2 cc and 0.5 cc and greater than 0.5 cc. Where defined positive for the presence of neoplastic tissue, hypointense glandular areas in T2-w, with low ADC values (≤1.1 sec/mm^2) and showing an early impregnation peak followed by washout in DCE-MRI. The lesions were considered as positive for Extra-Capsular Extension (ECE) if they had a large degree of contact or if we observed the presence of neoplastic tissue in the periprostatic tissue. It was attributed Seminal Vesicles Invasion (SVI) when a lesion of the base had a margin of contact with the vesicles or if we observed the presence of hypointense tissue on T2-w and contrast impregnation. *Results:* 232 PCa tumor foci were found in histopathological examination. The sensitivity for lesions <0.2 cc was 40.7% (24/59); from 0.2 to 0.5 cc was 42.5% (17/40); >0.5 cc was 91% (121/133). The MRI assessment of ECE has shown sensitivity, specificity, PPV, VPN and accuracy of 88.1%, 91.1%, 68.5%, 97.2% and 90.5%, respectively. The MRI evaluation of SVI has provided values of sensitivity, specificity, PPV, VPN and accuracy 86.7%, 99.1%, 86.7%, 99.1% and 98.3% respectively. *Conclusion:* Our study showed that MRI has high accuracy in staging PCa, more than most of the studies in the literature. MRI has a high sensitivity to localize the lesions with a volume greater than 0.5 cc, which are the most frequent and statistically are more likely to progress. Furthermore it has a high VPN against the ECE and SVI (97.2% and 99.1% respectively). Thanks to these promising results, we can make the best choice in treatment planning.

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ROACH FORMULA AS A GUIDE TO TARGET VOLUME SELECTION IN PROSTATE CANCER RADIOTHERAPY: A SINGLE INSTITUTION EXPERIENCE

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Introduction and Aim: Whole pelvis radiotherapy (WPRT) is controversial in the management of prostate cancer. The estimation of the risk of pelvic lymph node involvement in prostate cancer patients (pts) can help to identify those who will potentially benefit from WPRT. Nomograms and equations based on pre-treatment PSA, Gleason score and/or clinical stage allow clinicians to quickly estimate nodal risk. Among these tools, the formula proposed by Roach (1) is the simplest one. The Radiation Therapy Oncology Group (RTOG) enrolled 9413 pts with an estimated risk of lymph node involvement of at least 15% based on the Roach formula and showed a progression-free survival benefit with WPRT (2). Our study aims to investigate retrospectively the role of the Roach formula in the everyday activities of a department of radiotherapy. *Patients and Methods:* Two hundred and twenty men with prostate cancer were treated with 3D-conformal radiotherapy at the Radiotherapy Department in Foggia, from October 2006 to February 2011: 159 of them received prostate only radiotherapy (PORT), the others were referred for WPRT. All pts did not undergo surgery and 82.7% of them received hormonal therapy. According to prognostic factors (pre-treatment PSA, Gleason score and clinical stage), pts were grouped in classes of risk. For each patient, the value of the Roach formula was calculated with the equation +LN =(2/3) PSA + [(GS – 6) ×10]. Results were analyzed with non-parametric methods. The Roach formula values in fact were not normally distributed (Shapiro-Wilk normality test). The R statistical program was used. *Results:* None of the pts with low-risk cancer received WPRT while more than a half of the pts with highrisk disease underwent WPRT. There is a strong association between class of risk and irradiated volumes ($p<0.01$, Pearson's Chi-squared test). Median values of the Roach formula were 15.3 and 37.0 in the PORT and in the WPRT group, respectively. There is a very significant difference between the values of the Roach formula in the two groups ($p<0.01$, Wilcoxon rank sum test). This is a confirmation that radiation oncologists, with or without the calculation of the formula, were led by risk factors included in the formula while choosing target volumes. It is not surprising that the values of the Roach formula were very different among the three classes of risk ($p<0.01$, Kruskal-Wallis rank sum test) since both Roach formula and risk classification depend on the same prognostic factors. *Conclusion:* The literature from the post-PSA era shows that there may be a benefit from WPRT for pts estimated to be at high risk (>15%) for pelvic lymph node involvement. Even if WPRT remains controversial, Roach formula is a simple tool to assess nodal risk, summarizes the main prognostic factors, reflects and quantifies risk classification and can help radiation oncologists to choose the best target volume for each patient. As suggested by some studies, it is likely that WPRT may not benefit pts with a very high risk of nodal disease and values of the Roach formula beyond a certain cut-off. More trials are needed to identify which pts would benefit from such treatment and to clarify the role of the Roach formula in the radiotherapy practice.

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2 Roach M, De Silvio C, Lawton V *et al*: Phase III trial comparing whole-pelvic *versus* prostate only radiotherapy and neo-adjuvant *versus* adjuvant combined androgen suppression: RTOG 94-13. J Clin Oncol *21*: 1904-1911, 2003.

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COMPUTER AIDED DIAGNOSIS FOR PROSTATE CANCER DETECTION IN THE PERIPHERAL ZONE BY MRI

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Introduction: Prostate carcinoma (PCa) is the most common malignancy in men and represents the third cause of cancer death in industrialized countries. Magnetic resonance imaging (MRI) has been promising in localizing PCa and it is largely exploited in clinical routine to visualize and characterize tumours, thus improving the detection and staging of prostate cancer. An additional value can be given by Computer Aided Diagnosis (CAD) systems in helping radiologists in the diagnosis of prostate cancer. The aim of this study is to develop a CAD system to detect and localize tumour masses, based on T2-w and DCE-MRI images. The CAD will produce the pixel-wise malignancy probability map in a given region of interest (ROI) of the prostate gland. *Patients and Methods:* After an initial phase in which

we built this CAD system and we validated its reliability, we decided to test 10 patients with a biopsy confirmed PCa. All of them underwent MRI performing a conventional study with T1-w, T2-w and diffusion sequences. After precontrast acquisitions, patients were intravenously given gadobutrol and a total of 28 phases were acquired, each lasting 13 seconds. All images were examined by an expert radiologist on the basis of histological information provided after surgery and a total of 13 tumours, all located in the peripheral zone (PZ), were detected. A ROI was drawn around each lesion, on all possible slices to cover the whole tumour extension. When possible a ROI on a healthy region, with dimension comparable to that of the corresponding malignant ROI was also drawn for each patient. Information of pixels belonging to the same ROI were extracted from both T2-w sequence and the 28DCE volume acquisitions, to construct time-intensity curves over time. A filtering operation was performed to reduce noise contribution and signal to noise ratio was estimated to discard low quality data. T2-w images were used to evaluate mean grey value of pixels on selected ROIs, while DCE-MRI points were analyzed applying three different quantitative models (Tofts, Weibull, EU1) and a semiquantitative description (peak location and maximum enhancement, initial slope, curve wash-out, area under the curve). A total of 13 features were collected for each pixel. The initial features set was reduced in order to avoid over-fitting problems and to discard redundant information. Furthermore when a couple of highly correlated features occurred, the parameter of the couple with lower performances rate was discarded. On the basis of these elaboration steps a 6-dimensional vector was generated for all the pixels in which model fitting was successful. Malignancy probabilities were then calculated with the Bayes rule. *Results:* The resulting area under the receiver operating characteristic (ROC) curve was 0.874; sensitivity and specificity were 84.6% and 83.4% respectively. Good separation between malignant and benign points can be observed for the three combination of parameters shown on the Scatter plots of the three quantitative models implemented. *Conclusion:* The CAD scheme presented in this study shows good performance in discriminating between benign and malignant regions in the prostate. This system achieves a high sensitivity and specificity, leading to a better lesion detection rate. Future developments will focus on integrating the dataset with information from diffusion, in order to further improve system performances.

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SIMPLE ENUCLEATION VERSUS RADICAL NEPHRECTOMY IN THE TREATMENT OF pT1a AND pT1b RENAL CELL CARCINOMA

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Introduction and Objectives: Simple enucleation (TE) showed excellent oncological results in large retrospective series. No study has compared oncologic outcomes after TE and radical nephrectomy (RN) for the treatment of pT1 RCC. The aim of the present study is to compare the oncologic outcomes after TE and RN in pT1 RCCs. *Patients and Methods:* We retrospectively analyzed 475 patients who underwent TE or RN for pT1 RCC, N0, M0 between 1995 and 2007. TE was done in 332 patients, while RN in 143. Local recurrence, progression-free survival (PFS) and cancer-specific survival (CSS) were the main outcomes of this study. The Kaplan-Meier method was used to calculate survival functions, and differences were assessed with log-rank statistics. Univariate and multivariate Cox regression models were also used. *Results:* The surgical margin status of tumors that had TE was always negative. The mean follow-up was 72±44 mo after RN and 58±38 mo after TE (p=0.0004). At last follow-up, 393 patients (82.7%) were alive and disease free and 56 (11.8%) had died of other causes. Overall, 26 patients experienced progressive disease (5.4%) and of those 5 were alive but with disease progression (1%) and 21 (4.4%) had died of metastatic disease. No local recurrences were observed in the patients who underwent RN. Overall, 3 patients with pT1a RCC developed isolated renal recurrence after TE and this was always elsewhere in the kidney. Specifically, all patients diagnosed having local recurrences had negative surgical margins. The 5- and 10-yr PFS estimates were 91.3% and 88.7% after RN and 95.3 and 92.8% after TE (p=NS). The 5- and 10-yr CSS estimates were 92.1% and 89.4% after RN and 94.4% (5- and 10-yr CSS) after TE (p=NS). No statistically significant differences between RN and TE were found after adjusting CSS probabilities according to age at surgery (≤65 yr, log-rank p-value: 0.99; or >65 yr, log-rank p-value: 0.14), grade (Fuhrman nuclear grades 1-2, log-rank p-value: 0.48; grade 3, log-rank p-value: 0.89; or grade 4, log-rank p-value: 0.62), stage (pT1a, log-rank p value: 0.46; or pT1b, log-rank p-value: 0.44) or clear cell subtype (log-rank p-value: 0.37). Surgical treatment failed to be a predictor of PFS or CSS both at univariable and multivariable analyses. The potential limitation of the present study includes that the data originate from a retrospective review. *Conclusion:* TE can achieve oncologic results similar to those of RN for the treatment of pT1 RCCs provided tumors are carefully selected based on their safe and complete removal.

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EXTERNAL VALIDATION OF PADUA CLASSIFICATION FOR THE RENAL TUMOR ENUCLEATION TECHNIQUE

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Introduction: To assess the ability of PADUA score to predict the surgical results and the peri-operative complications of open tumor enucleation (TE) technique for renal tumors. *Patients and Methods:* Between July 2006 and March 2011, we prospectively gathered data from 244 consecutive patients treated with open TE with warm ischemia. All clinical and surgical data of patients and tumors were registered. Among the parameters of PADUA score, clinical tumor dimension, polar, face and rim location, and relationship with UCS were prospectively assigned. Instead, the tumor relationship with renal sinus was retrospectively assigned. The relationship between preoperative variables (including PADUA score) and surgical results/perioperative complications was assessed with univariate analysis (Spearman correlation coefficient, unpaired *t*-test, and Pearson's chi square test, as appropriate). A multivariate logistic regression model was done to test the ability of PADUA score, with the other significant variables, to predict overall surgical complications and Clavien grade 3 surgical complications. *Results:* The median PADUA score of renal tumors was 8 (IQR:7-9), and it was ≥10 in 52 (21.3%) patients. The mean WIT was 16.8 min. The mean operative time was 109.4 min and the mean EBL was 183.0 mL. Overall, 47 perioperative complications occurred in 45 patients (45/244=18.4%); of these, 39 (16%) were surgical and 8 (3.3%) medical. Surgical complications included blood loss treated with bedrest in 2 patients (0.8%), with transfusions in 25 (10.2%) and with a second invasive procedure in 5 (2.1%) patients. Urinary fistula occurred in 7 patients (2.9%); it was treated with bedrest and antibiotics in 4 (1.7%), while it needed ureteral stenting in the other 3 cases (1.2%). Two patients had two surgical adverse events each (urinary fistula and blood loss). According to Clavien system, 6 surgical complications were grade I (2.5%), 25 grade II (10.2%), and 8 grade III (3.3%). No grade IV and V surgical complications occurred in this series. At univariate analysis the entirely endophytic tumor growth, the involvement of UCS and renal sinus, the clinical diameter and the PADUA score resulted significantly correlated with WIT and EBL. Only PADUA score and surgical indications resulted as significant predictors of operative time. Significant predictors of overall surgical complications were the entirely endophytic tumor growth (p=0.049), the involvement of UCS (p=0.029) and renal sinus (p=0.036), the tumor diameter (p=0.021) and the PADUA score (p=0.0007). At multivariate analysis, among all the anatomical variables, only PADUA score was found to be an independent predictor of overall surgical complications (p=0.016), and Clavien grade III surgical complications (p=0.008). The surgical indication was also an independent predictor of major surgical complications (p=0.029). *Conclusion:* The PADUA score was significantly associated with the parameters of technical difficulty of TE, and it was an independent predictor of overall and major surgical complications of this technique.

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PREDICTORS OF ACUTE GENITO-URINARY TOXICITY AFTER HIGH-DOSE PROSTATE CANCER RADIOTHERAPY: INITIAL RESULTS OF A PROSPECTIVE STUDY

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Background and Purpose: In April 2010, a prospective observational study (DUE01) aimed at developing quantitative predictive models of genito-urinary (GU) toxicity and erectile dysfunction after high dose (≥70Gy) external radical radiotherapy (RT) for clinically localized prostate cancer was activated. The aim of this first analysis was to assess predictors of GU symptoms during treatment scored by IPSS and ICIQ-SF. *Patients and Methods:* A questionnaire collecting detailed clinical information was filled before RT; four questionnaires on QoL, GU and erectile dysfunction

(QLQ-C30, IPSS, ICIQ-SF, IIEF) had to be completed by patients before RT, at its end, at 3 months and every 6 months up to 5 years after RT. Full 3D planning data were collected and analysed with a dedicated program (Vodca, MSS GmbH, Zurich). The current analysis considered the variation of IPSS and ICIQ-SF scores between baseline and RT conclusion. In particular, an IPSS≥15 at the end of RT was focused on as the main end-point. Logistic uni-variable and stepwise multivariate (MVA) analyses were performed; Spearman and paired samples t-tests were carried out testing continuous variations between baseline and end-RT scores. *Results:* At the time of analysis (Dec 2011), 160 patients had been enrolled by 7 Institutes. 118/160 patients' basal and end-RT questionnaires were analysed. In the group of patients with baseline IPSS≥15, the IPSS score remained unchanged (n=13; average: 17.9 *vs*. 18.8, p=0.80), while it significantly worsened for the others (n=105; 11.6 *vs*. 6.9, p<0.0001). On the other hand, in the group of patients with basal ICIQ-SF≥10, ICIQ-SF improved (n=13, 4.3 *vs*. 10.9, p=0.0002), while it slightly worsened for the others (1.6 *vs*. 0.9, p=0.02); the ICIQ-SF improvement was proportional to the initial ICIQ-SF value (p<0.0001). At MVA (overall p=0.001), the main independent predictors of IPSS≥15 at RT-end were: initial IPSS (OR:1.12, p=0.01), use of hypertensive drugs (OR:4.0, p=0.02) and hypofractionation (2.5-2.65 Gy/fr *vs*. 1.8-2.0 Gy/fr, OR:3.3, p=0.05). Concerning DVH/DSH analysis, data of 85/118 patients were available; in the hypofractionated subgroup (n=45), the fractions of absolute volume/surface receiving more than 72-74 Gy (V72-74Gy, S72-74Gy) were correlated with IPSS≥15 at the end of RT; the best cut-off value assessed by ROC analysis was S74Gy>14cm2 (OR:4.9, p=0.02). *Conclusion:* These preliminary results of the DUE 01 study show initial IPSS, hypertension and hypofractionation as independent predictors of IPSS≥15 at RT-end in a population of patients prospectively followed. Despite the relatively low number of DVH/DSH, the fraction of bladder surface/volume receiving "high-doses" was correlated with IPSS≥15 in the hypofractionation subgroup. These initial results will be better refined after completing the enrolment, expected at the end of this year. The study is supported by a grant from Associazione Italiana Ricerca sul Cancro (AIRC-IG8748)

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LAPAROSCOPIC AND ROBOT-ASSISTED TUMORAL ENUCLEATION FOR TREATMENT OF SMALL RENAL MASSES: PRELIMINARY EXPERIENCE AND EXAMINATION OF POSSIBLE INDICATIONS

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Objectives: Laparoscopic partial nephrectomy (LPN) is oncologically safe for the treatement of renal masses with advantages of mininvasive surgery. Open Tumoral Enucleation (TE) ensures excellent oncological safety allowing maximum preservation of functional kidney tissue. We report our laparoscopic and robot-assisted TE experience (LTE), describing our surgical technique and veryfing the feasibility and the possible indications. *Patients and Methods:* From November 2007 to December 2010, 93 patients underwent LPN. We performed 15 (16%) LTE and 78 LPN. After location of the lesion, the limit between tumour and safe tissue was delineated by a monopolar hook. Then the vascular pedicle was clamped and the mass was enucleated by blunt dissection and by scissors using the aspirator for dissection too. If identified the peritumoral capsule was isolated by blunt dissection using the natural cleavage plane between the peritumoral capsule and normal parenchyma. Then resection bed is sutured by a running suture with Monocryl 3-0. Then resection bed was filled by sealants as FloSeal and oxidize cellulose sheets as Tabotamp and renorraphy was finished by interrupted or double sutures with Vicryl 2-0 across renal capsule or by sliding-clip technique. *Results:* For cortical tumours (CT), LTE and LPN were performed respectively in 5 (5/55; 9%) and 50 (50/55; 91%). For corticomidollar tumours (CMT), LTE and LPN were performed respectively in 10 (10/38; 26%) and 28 (28/38; 74%) cases .Regarding location of the masses, LTE was always performed for peri-hilar tumoral masses (4 cases) and in 11 tumoral masses (11/89; 12%) with other location. The median (range) pathological size of tumours treated by LTE was 2.6 (1.2-5.3) cm and the median operative time was 134 min. The median (range) ischemia time was 21 (12-35) min. The median (range) operative blood loss was 340 (100-1500) cc. We found intaoperative bleeding in 2 (13.3%) cases, both for incomplete clamp with need of hemotransfusions. Then we found 1(6.6%) case of urinary fistula treated by positioning of double j uretheral stent. The medium time of drain removal was 3 (2-10) days. Histopathological analysis revealed no positive surgical margins. We found no local recurrence during a median (range) follow-up of 15 months (1-37). *Conclusion:* LTE is a feasable technique even if not absolutely recommended for pT1a tumours, except for the treatment of peri-hilar masses when LTE let a better preservation of functional renal tissue and near structures. LTE has a low rate of perioperative complications and, as OPN, is not associated with a major risk of positive surgical margins.

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PERITUMORAL PSEUDOCAPSULE INVASION DOES NOT AFFECT THE RISK OF LOCAL RECURRENCE AFTER TUMOR ENUCLEATION IN THE TREATMENT OF RENAL CELL CARCINOMA

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Introduction: Peritumoral pseudocapsule (PS) invasion after tumor enucleation (TE) in the treatment of renal cell carcinoma (RCC) could potentially affect the risk of local recurrence. The aim of the present study is to prospectively evaluate this hypothesis in a consecutive series of patients having TE for RCC. *Methods:* TE was done by blunt dissection in 201 consecutive patients using the natural cleavage plane between the tumor and normal parenchyma. Pseudocapsule penetration, surgical margin (SM) status and routine clinical and pathological variables were recorded. *Results:* Overall, 164 tumors were diagnosed as single sporadic RCCs and thus included in the study. Mean (SD, median, range) tumor greatest dimension was 3.5 (1.7, 3.2, 1.0-12.5) cm. At the pathological examination, the PS was intact and free from invasion on the parenchymal side in 73.2%, while it was penetrated on the parenchymal side in 26.9% of RCCs. In all cases the SM were negative. Even in patients with pseudocapsule penetration and invasion beyond it, neoplastic cells were separated from the surgical margin by a thin layer of normal tissue with signs of lymphoplasmocytic inflammation. The 3-year overall survival was 95.5%. The 3-year cancer-specific and progression-free survival were 100% and 96.6%, respectively. After a mean (range) follow-up of 44 months (25-69), the true local recurrence rate was 0.6%. None of the RCCs with pseudocapsule penetrated on the parenchymal side recurred locally. *Conclusion:* TE is oncologically safe. Peritumoral pseudocapsule invasion does not influence the risk of local recurrence when TE is adopted for the treatment of RCC.

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PATHOLOGICAL CHARACTERISTICS AND PROGNOSTIC IMPACT OF PERITUMORAL CAPSULE PENETRATION IN CLEAR CELL RENAL CELL CARCINOMA AFTER MINIMAL PARTIAL NEPHRECTOMY

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Aim: To evaluate the pathological characteristics of peritumoral capsule and the prognostic impact of capsule penetration on tumor recurrence in patients treated by nephron-sparing surgery (NSS) for clear cell RCC. *Patients and Methods:* Between January 2005 and December 2007, 115 consecutive patients with single sporadic clear cell RCC had NSS. Peritumoral capsule status was carefully analyzed by two dedicated uropathologists. The degree and the side of capsule penetration, if present, were evaluated. *Results:* According to the peritumoral capsule status, in 68 (59.1%) the capsule was intact and free from neoplastic penetration (PC–), while in 47 (40.2%) there were signs of invasion within its layers. Overall, 29.6% had capsular penetration on the parenchymal side (PCK), whereas, 11.3% had peritumoral capsule invasion on the perirenal fat tissue side (PCF). None of the patients had positive surgical margins detected at the pathological examination. Mean (median, range) follow-up was 48 months (46, 25-69). The 5-year cancer-specific and progression-free survival were 91.7% and 89.5%, respectively. The 5-year progression-free survival for tumors PC–, PCK and PCF was 97%, 96.2% and 48.5%, respectively ($p<0.0001$; PC- *vs*. PCF $p<0.0001$; PCK *vs*. PCF $p=0.0002$). The multivariate Cox model showed PCF to be the sole significant independent predictor of progression-free survival. *Conclusion:* PCF is a significant and independent predictor of worse outcome. Patients with clear cell RCC with intact peritumoral capsule, as well as those with PCK, had an excellent prognosis and these pathological features could possibly add to prognostic nomograms if proved statistically significant in larger series with longer follow-up.

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MULTIPARAMETRIC MRI AND SIGNIFICANT PROSTATE CANCER

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Introduction and Objectives: Multi-parametric MRI (mp-MRI) may help rule out clinically significant prostate cancer. To date, studies have been limited by using whole-mount specimens from men with a diagnosis of prostate cancer on TRUS biopsy as the reference standard, incorporating work-up bias. We report on the performance characteristics of mp-MRI using template prostate mapping (TPM) as the reference standard. *Patients and Methods:* Institutional review board exemption was granted by the local research ethics committee. Mp-MRI (T1/T2, dynamic contrast enhancement and diffusion weighting, 1.5Tesla, pelvic phased array) was performed before TPM in men with a raised PSA (n=65), of whom 16 had no previous cancer diagnosis, and 49 had proven cancer on previous TRUS biopsy. Each mp-MRI was reported with knowledge of PSA and patient age, by three uro-radiologists (R1-R3) experts in prostate MRI. Each prostate was divided into 4 regions of interest (ROI) and a score of 1 to 5 assigned to each ROI (1 - 'no cancer', 5 - 'highly suspicious'). TPM was performed under general anaesthesia with 5 mm-spaced sampling using a brachytherapy template grid. Analysis was carried out for all cancers on TPM and two definitions of clinical significance: Definition 1: Gleason grade ≥4+3 and/or ≥6 mm cancer core length (CCL); Definition 2: Gleason grade ≥3+4 and/or ≥4 mm CCL. *Results:* 85 consecutive men (260 ROIs) with a mean age of years 67 (range 40-76) and mean PSA 6.2 μg/L (range 2.1-43) were evaluated. 130/260 (50%) of ROIs were positive for any cancer on TPM. By definition 1 and 2 38/260 (15%) and 69/260 (27%) had positive ROIs, respectively. Accuracy using area under receiver-operator characteristic curve (AUC) improved from 0.66-0.70 for all cancer to 0.71-0.85 and 0.72-0.83 for clinically significant cancer by definition 1 and 2. The negative predictive value of mp-MRI was 0.93-0.97 for definition 1 cancers and 0.85-0.90 for definition 2 cancers, respectively. *Conclusion:* The high negative predictive value for clinically significant cancer defined by two thresholds suggests that mp-MRI may play a role in ruling-out clinically significant prostate cancer. This finding could be used to address the over-diagnosis burden from PSA screening by using mp-MRI as a test to identify men who could avoid a prostate biopsy.

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MULTIPARAMETRIC MRI OF THE PROSTATE AFTER ASAP DIAGNOSIS

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Objectives: Repeat biopsy (re-biopsy) has been advocated following the diagnosis of ASAP found in prostate biopsy specimens. Previous studies of repeat prostate biopsy for ASAP that report cancer detection rates of 40-70%, are based on the sextant biopsy scheme. Currently, extended prostate biopsy schemes that incorporate lateral/anterior peripheral zone are routinely used by most centres because of the associated increased cancer detection rate when compared to sextant biopsy. Our objective was to determine the prognostic value of multiparametric MRI in men who had a diagnosis of ASAP. *Methods:* We retrospectively evaluated 840 transrectal ultrasound guided prostate biopsies between January 2010 and December 2011 in our Urologic departments. All patients who had the initial pathological finding of ASAP were selected to have a MRI and cancer detection rate was determined in follow-up. *Results:* The overall detection rate of isolated ASAP lesions was 2.5% (46 patients). Of 46 patients with isolated ASAP on initial biopsy 44 (98.9%) underwent MRI. In case of positive MRI, a guided biopsy was performed. The total incidence MRI lesion suspicious of cancer rate was 45.4% (20 patients). At the biopsy 18, of them had cancer. The other 24 underwent the same to random biopsy (12 cores) but only 3 had cancer. *Conclusion:* Our results suggest that for patients with a PSA between 4 and 10 ng/ml, whose initial biopsy by ten cores contains ASAP but not cancer, the multiparametric MRI could help to avoid rebiopsy. Timing for re-biopsy, how many sample should be taken on re-biopsy should be performed, and how many times re-biopsy are still problems to solve. MRI could be the answer.

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ANDROGEN DEPRIVATION THERAPY INFLUENCES THE UPTAKE OF 11C-CHOLINE IN PATIENTS WITH RECURRENT PCA: RESULTS OF A SEQUENTIAL PET/CT STUDY IN 22 PATIENTS

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Introduction and Objectives: The influence of androgen deprivation therapy (ADT) on 11C-Choline uptake in patients with recurrent prostate cancer (PCa) has not yet been clarified and there are no recommendations in the literature about whether ADT should be discontinued before 11C-Choline PET/CT. The aim of our study was to investigate this issue by means of sequential 11C-Choline positron emission tomography (PET)/CT in patients with recurrent PCa. *Patients and Methods:* Between September 2003 and September 2011, 1,623 patients were submitted to 11C-Choline PET/CT for PCa

restaging due to biochemical PSA relapse after primary therapy or staging before primary treatment in our center. We identified 22 patients (mean age 69 years, range 54-82) who fulfilled the following criteria: (a) patient submitted to at least two 11C-Choline PET/CT scans within 12 months in the setting of tumour restaging; (b) the first 11C-Choline PET/CT before commencing ADT and the second 11C-Choline PET/CT after 6 months of ADT administration to assess the effectiveness of therapy; (c) confirmation of 11C-Choline PET/CT results by subsequent clinical and imaging follow-up and/or prostatic fossa biopsy; and (d) availability of complete clinical and pathological data for each patient. *Results:* The mean PSA was 14.2±47.3 ng/ml (median 6.4, range 0.25-170) before starting therapy. After at least 6 months of ADT, the PSA value significantly decreased compared to baseline mean (PSA=3.7±3.5 ng/ml, median 0.75, range 0.01-9.5; $p<0.05$). Before starting ADT in 21 of 22 patients we had a positive 11C-Choline PET/CT (bone and/or lymph-node and/or prostatic fossa). After at least 6 months of ADT, 16 patients presented a negative 11C-Choline PET/CT and PSA values significantly decreased. On the other hand, 4 patients showed a rising PSA value during ADT and 11C-Choline PET/CT demonstrated progression of disease. One patient showed both a stable PSA and PET/CT result. Finally, only one patient failed to demonstrate a good correlation between PSA value and PET result in whom a decrease in PSA value and a progression of the disease was observed. These data indicate the presence of a relationship between PSA values and 11C-Choline PET/CT results in ADT responders. *Conclusion:* ADT is able to significantly modify the uptake of 11C-Choline after ADT administration. It is worth noting that the major effect of ADT on 11CCholine PET/CT was recorded in patients with androgen-sensitive PCa, similarly to the effect of ADT on PSA. Thus, it can be assumed that in order to enhance the sensitivity of this imaging technique, ADT should be temporarily interrupted before 11C-Choline PET/CT in recurrent PCa.

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ACTIVE SURVEILLANCE IN PROSTATE CANCER: 7 YEAR EXPERIENCE

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Aim: We here present results on 7 year experience in active surveillance (AS). *Patients and Methods:* Patients in our Institute entered 2 AS protocols: SAINT and PRIAS. The 2 protocols have some common entry criteria: initial PSA≤10 ng/ml, DRE≤T2 and GPS≤3+3. SAINT requires max 20% positive cores and max 50% core involvement, while PRIAS max 2 positive cores and PSA density<0.2 ng/ml/cc. Follow-up includes in both cases PSA every 3mos, DRE every 6mos, re-biopsy after 1yr of AS. When PSA doubling time (DT)=3-10yrs a yearly repeated biopsy is scheduled. Whenever during the follow-up the PSADT<3yrs, clinical stage is >T2, the re-biopsies show more than 2 (or 20%) positive cores or GPS>3+3, change to active treatment is advised. *Results:* 342 pts were enrolled in AS (February 2012): 120 SAINT and 222 PRIAS. 215/342 (62.9%) pts are still in AS (median f-up of 33mos, range 1.5-96.1; median time in AS 22.5 mos, range 1.5-96.1): 6 pts dropped out due to comorbidities, 7 due to personal choice (anxiety), 20 due to off protocol reasons and 1 due to non-PCa death. 93/342 (27.2%) pts dropped out because of disease progression/reclassification: 17 due to PSADT, 76 due to upgrading and/or upsizing at re-biopsy (41/76 at first re-biopsy). The actuarial treatment free survival (ATFS) was 81%, 69% and 58% at 15, 27 and 40 months, respectively. To date, no unfavorable outcome has been observed. Biopsy-related ATFS is related to PSA density <0.10 ng/ml/cc (log-rank test $p=0.004$, ATFS at 27 mos 84% *vs*. 74%), prostate volume >60cc (log-rank test $p=0.001$, ATFS at 27 mos 93% *vs*. 76%) and number of negative cores at diagnosis >5 (log-rank test $p=0.035$, ATFS at 27 mos 94% *vs*. 76%). Best-fit multivariable Cox proportional hazards model for biopsy-related ATFS resulted in a three-variable model (overall $p=0.001$, AUC=0.66), including age (continuous variable, $p=0.08$, HR=1.04), number of negative cores at diagnosis >5 (protective factor, $p=0.16$, HR=0.52) and prostate volume >60cc (protective factor, $p=0.04$, HR=0.31). *Conclusion:* AS is feasible in selected men with early PCa. 1yr re-biopsy is an important check, which can be used as a diagnostic clarification point. Biopsy-related ATFS is correlated to age, number of negative cores at diagnosis >5(protective factor, surrogate of mm of non-cancer) and prostate volume >60cc (protective factor, which may underline the difficulty of an adequate biopsy sampling in patients with high-volume prostate). PSA density is related to ATFS in uni-variable analysis but it resulted to be not included in the multivariable model. Better multivariable models are obtained when more specific endpoints are considered, *e.g*. upgrading and upsizing separately after 1-year re-biopsy (see Abstract 155).

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THE IMPORTANCE OF INTEGRATED MULTIDISCIPLINARY STRATEGY IN THE THERAPEUTIC APPROACH TO METASTATIC RENAL CELL CARCINOMA: IMPACT ON OUTCOME AND QUALITY OF LIFE - A PROSPECTIVE MONOINSTITUTIONAL EXPERIENCE

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Background: In the last ten years the availability of new biological agents introduced deep changes in the global therapeutic approach to metastatic renal cell carcinoma (mRCC). Specifically, the use of tyrosine kinase inhibitors as 1st or 2nd line treatment allows to obtain significant responses with globally manageable toxicities. We have now time and opportunities to plan an 'up-front' sequential strategy approach with several drugs and, in the good-prognosis oligo-metastatic disease, integrate the medical treatment within a network of expertise in order to achieve the best possible response. *Patients and Methods:* We report updated outcome of 35 consecutive metastatic renal cell carcinoma (mRCC) patients (pts) treated at our Institution with sunitinib (scheduling: 50 mg/day, 4 week on/2 off) in 1st (29 pts) 2nd (6 pts) line therapy from 2006. There were 21 males and 15 females, median age 54 years (range 48-80); the most represented metastatic sites were bone (23%), liver (26%), lung (34%), nodes (11%). Histologic subtype was clear cell carcinoma in 80%, papillary carcinoma in 12 and chromophobe in 2. Median time on treatment for all patients was 28 months (range 12-61). Overall survival (OS) and progression-free-survival (PFS) were measured from initial administration of sunitinib until death for any cause or documented disease progression, respectively. With OS data updated at December 1, 2011, the median follow-up was 36 months (range 12-61), OS and TTP were calculated according to the Kaplan-Meyer method. Univariate and multivariate analysis (Log-rank test and Cox proportional hazards model) were performed to identify factors potentially associated with the clinical outcome. Quality of life (QoL) was assessed by FACT-G score every 2 cycles of therapy. *Results:* Twelve partial responses (34%) and 18 stable diseases (51%) lasting >3 months were observed by RECIST criteria, for an overall global clinical benefit of 85%. Treatment-related toxicities were expected and were globally manageable: fatigue (42%), thrombocytopenia (25%), hand foot syndrome (15%), macrocytic anemia (10%) hypertension (8%) and neutropenia (5%). Hypothyroidism took place in 21 pts (60%) and was treated, when symptomatic, with levothyroxine. Dose reduction and/or scheduling modifications were performed, modulating Sunitinib treatment on toxicity degree and patient's compliance over treatment. QoL analysis showed no significant deterioration of the evaluated items. Fifteen patients (9M, 6F) with PR or SD underwent integrated locoregional procedures aiming to optimize the obtained response: thermal ablation for liver metastases in 6 patients, embolization of bone metastases in 5, stereotaxic radiosurgery on lung and brain lesions in 4; 13 of these patients are alive and disease-free at a median of 14 months from the locoregional procedure, 2 are alive with progressive disease, in 2nd line treatment for metastatic disease. *Conclusion:* Our data support the modern global, integrated approach to mRCC, in which the expertise of a multidisciplinary team (urologist, radiotherapist, interventional radiologist, oncologist) allows the patients 'good responders' following an active medical therapy to achieve the best outcome in terms of PFS, QoL and also OS. Another key point of our work is the possibility to modulate sunitinib doses/schedules in the different disease stages, with an easier management of the adverse events and the preservation of a good adherence to long-term therapy, without affecting the drug efficacy. An important endpoint in the global management of the patient with RCC is the achievement of long-lasting disease responses, in view of a sequential and integrated approach with the utilization of the new biological treatments available also in treatment lines following the first.

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THE NUMBER OF ORGANS AFFECTED BY METASTASES IS ONE OF THE MOST INFORMATIVE PREDICTOR OF RENAL CELL CARCINOMA SPECIFIC SURVIVAL IN CANDIDATES TO CYTOREDUCTIVE NEPHRECTOMY

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Background: The natural history of patients with metastatic Renal Cell Carcinoma (mRCC) is extremely heterogeneous. In this context, no study has systematically analysed whether the combination of number of metastatic sites and number of organs affected by metastases affect survival. *Methods:* Between 1987 and 2011, 1847 RCC patients underwent nephrectomy at a single tertiary care institution. Descriptive, univariable and multivariable Cox regression analyses assessed the effect of the number of metastases and the number of organs affected on cancer-specific survival (CSS). Adjustment

was performed for age, symptoms, performance status, tumor size, Fuhrman grade, pathological T stage, lymph nodal status, and presence of necrosis or sarcomatoid features. *Results:* Among 242 (13.1%) mRCC patients, 151 (62.4%), 67 (27.7%) and 24 (10.0%) had 1, 2 or more than 2 distant organs affected. Specifically, metastases were diagnosed in lung (n=141, 58.3%), bone (n=75, 31.0%), adrenal gland (n=44, 18.1%), liver (n=38, 15.7%), brain (n=27, 11.2%) and other sites (n=40, 16.5%). Median survival was 32.0 months *vs*. 9.7 *vs*. 6.8 for patients with 1 *vs*. 2 *vs*. more than 2 organs affected ($p<0.001$). At multivariable analyses, the number of metastatic organs achieved the independent predictor status of CSS (2 *vs*. 1 site: HR 1.68 and >2 *vs*. 1 site: HR 1.62, $p=0.01$). Lung was the location with the highest rate of single organ affected (50.3% *vs*. 35.1% in other sites, $p<0.001$). Considering only patients with a single metastatic organ, no statistically significantly different CSS rates were recorded (log rank pairwise $p>0.3$). *Conclusion:* Among patients with mRCC, the number of organs with metastases is an independent predictor of CSS. Patients with multiple organs affected by multifocal disease have significantly poorer survival. Lung metastases show slightly better survival relative to other metastatic sites. However, when considering only patients with a single organ affected, the location of the metastasis did not affect CSS.

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RENAL AND CARDIOVASCULAR MORBIDITY AFTER PARTIAL OR RADICAL NEPHRECTOMY IN PATIENTS WITH KIDNEY TUMORS UP TO 7 CENTIMETERS: IMPLICATIONS ON OVERALL MORTALITY

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Objectives: To evaluate the impact of radical nephrectomy (RN) or partial nephrectomy (PN) on estimated Glomerular Filtration Rate (eGFR) and cardiovascular morbidity, and whether it could affect overall mortality (OM) in patients treated for renal cell carcinoma (RCC) of up to 7 cm. *Patients and Methods:* From 1987 to 2007, 930 consecutive patients underwent surgery at our institution for sporadic RCC of up to 7 cm of diameter, with a normal contralateral kidney. Renal Function was evaluated by the Estimated Glomerular Filtration Rate (eGFR) pre-operatively and at last folow-up. Renal function worsening was defined as a decrease of eGFR below 60 ml/min/1.73m^2, or as a change of class in renal function. Age was coded as quartile (29-50 yrs; 51-60 yrs; 61-70 yrs and 71-89 yrs). Univariable and multivariable logistic regression analyses addressed the impact of performing RN *vs*. PN on renal function worsening and on cardiovascular morbidity. Cox regression analyses addressed the role of nephron-sparing surgery on cancer-specific mortality (CSM) and OM. *Results:* RN was performed in 443 patients and PN in 487. Median follow-up was 61 months (range: 5-283 mos). Thirty-seven percent of patients who underwent RN had renal function worsening, compared to 16% of patients undergoing PN ($p<0.001$). At multivariable logistic regression analysis, PN ($p<0.001$), younger age ($p<0.001$) and absence of smoking history ($p=0.047$) were associated with a reduced risk of renal function impairment, after adjusting for Charlson Comorbidity Index, gender, presence of hypertension, preoperative eGFR. PN was also an independent predictor of reduced risk of cardiovascular morbidity ($p<0.001$), after adjusting for the other confounders. The type of surgery did not achieve the independent predictor status of CSM or OM, after adjusting for pT, pN, presence of distant metastases, worsening of renal function and cardiovascular morbidity. Nonetheless, worsening of renal function and cardiovascular morbidity were independent predictors of OM ($p=0.07$ and $p=0.08$, respectively). *Conclusion:* PN was significantly associated with a reduced risk of worsening of renal function and a reduced risk of cardiovascular morbidity. PN did not achieve the independent predictor status of OM. However, renal function worsening and cardiovascular morbidity, both influenced by the type of surgery, were associated with a higher risk of OM.

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HOW TO PREDICT CANCER SPECIFIC MORTALITY IN PATIENTS WITH PAPILLARY RENAL CELL CARCINOMA

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Background: Papillary renal cell carcinoma (PRCC) is the second most common subtype among kidney neoplasms. Recently, Klatte *et al*. developed the first tool to predict cancer specific mortality (CSM) in PRCC patients. *Patients and Methods:* Clinical and pathological data were prospectively gathered in 177 patients treated with radical nephrectomy or partial nephrectomy at two academic center, between 1991 and 2010 with a final diagnosis of PRCC. Nomogram predicted survival probability and actual CSM were compared. Discrimination was quantified with the area under the receiver

operating characteristics curve (AUC). Calibration compared the predicted and the observed cancer rates throughout the entire range of predictions. *Results:* At a median 73-month follow-up 24 papillary renal cell carcinoma related deaths had occurred (13.6%). T classification was pT1a, pT1b, pT2ab, pT3abc and pT4 in 66 (37.3%), 53 (29.9%), 24 (13.6%), 33 (18.7%) and 1 (0.6%), respectively. At nephrectomy, lymph node and distant metastases were present in 51 (28.8%) and 13 cases (7.3%), respectively. Grade 1-2 or 3-4 was noted in 137 tumors (77.4%) and 40 (22.6%), respectively. Papillary type 2 was assigned to 64 (36.2%) of PRCCs. Necrosis was present in 69 (39.0%) patients. One, 2, 5 and 10-year cancer specific survival rates were 95.4%, 91.8%, 86.1% and 84.9%, respectively. External independent validation revealed 84.6% predictive accuracy. Overall, the tool showed good calibration with minimal departure from ideal prediction. *Conclusion:* We externally validated a highly accurate tool specifically for papillary renal cell carcinoma using basic clinical and pathological information to predict disease specific survival. This nomogram resulted the most accurate tool to identify papillary renal cell carcinoma with aggressive clinical behavior and may contribute to the ability to individualize postoperative surveillance and therapy.

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DETECTION OF NODAL MICRO METASTASES WITH SERIAL SECTION, IMMUNOHISTOCHEMISTRY AND REAL TIME-POLYMERASE CHAIN REACTION IN INTERMEDIATE AND HIGH RISK PROSTATE CANCER PATIENTS SUBMITTED TO RADICAL PROSTATECTOMY WITH EXTENDED PELVIC LYMPH NODE DISSECTION: A PERSPECTIVE STUDY

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Introduction and Objectives: A consistent rate of patients who are classified as "node-negative" after radical prostatectomy and pelvic lymph-node dissection (PLND) experience a nodal disease relapse. Routine pathological examination can miss micro-metastatic tumor foci in the lymph nodes (LN) of patients with prostate cancer (PCa), resulting in confused tumor staging and clinical decision-making. The aim of the present perspective study was to evaluate the impact of micro-metastasis assessed by serial section (SS), immunohistochemistry (IHC) and real time-Polymerase Chain Reaction (RT-PCR) in patient submitted to radical prostatectomy with extended PLND. *Patients and Methods:* 32 consecutive patients submitted to radical prostatectomy with extended PLND for intermediate (clinical T1c-T2 and PSA:10-20 ng/mL and clinical Gleason Score=7) or high (clinical stage T3 or PSA>20 or clinical Gleason Score=8-10) PCa were enrolled. The average probability of nodal invasion with Briganti pre-operative nomogram (Briganti, Eur Urol 2006) of the whole population was 26.9% (SD=14.4). Extended PLND included obturator, internal/external and distal 2 cm common iliac lymph-nodes (LN). The nodes were processed by one uro-pathologist both according to the routine pathological examination (analysis of the central section for 4 mm nodes or every 2 mm for LN>4 mm), which served as comparative method, both according to SS, IHC with antibodies against PSA and spectrum-cytokeratins (BSCK) and quantitative RT-PCR targeting PSA, PSMA (PS Membrane Antigen) and Glucuronidase-S-Beta (GUSB) mRNA, that are over-expressed in prostatic cancer cells. *Results:* A total of 628 LN were analyzed, with a mean number of LN removed of 19.6 (SD=7.2). Applying the routine pathological examination, 10 (31.2%) patients and 23 (3.9%) LN resulted positive for nodal involvement, with mean positive LN of 2.2 (SD=1.4). After applying the SS and the molecular methods of analysis (IHC and RT-PCR), micro-metastases were found in 11 LN (SS showed micrometases in 3 of them, IHC in 6 of them and RT-PCR in 7 of them) and a total of 3 (9.3%) node negative patients at routine pathological examination showed micrometastasis (in 2 patients with RTPCR and in 1 with IHC). *Conclusion:* Molecular analysis of the LN can detect a not negligible percentage of patient who arbour micrometastatic PCa missed at routine pathological examination and can enhance the accuracy of lymphadenectomy as a staging method. Cost-effective analysis are needed. The significance of the micro-metastasis in PCa and the potential therapeutic role of PLND is not yet clarified but the removal of micro-metastases can reduce the rate of nodal disease relapse

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NON-INVASIVE, EARLY DIAGNOSIS OF SUPERFICIAL BLADDER CANCER: URINE CELL FREE DNA INTEGRITY AND CYTOLOGY

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Background: It is known that the origin of extracellular DNA can be established on the basis of its fragmentation; non-cancer apoptotic cells produce highly fragmented DNA whereas necrotic cancer cells release longer DNA. The aim of our study was to verify the accuracy of urine cell free DNA integrity, alone or in combination with urine cytology, in identifying bladder cancers. *Patients and Methods:* The study was conducted on a series of 129 individuals: 51 cancer patients, 46 symptomatic patients (Lower Urinary Tract Symptoms) with benign diseases, and 32 healthy volunteers. Extracellular DNA was isolated from urine supernatant and free DNA integrity was determined blindly by three quantitative Real Time PCRs on three sequences longer than 250 bp: C-MYC, BCAS1 and HER2. A short fragment called STOX 1 was analyzed to exclude the presence of PCR inhibitors. *Results:* UF DNA integrity analysis highlighted 0.1 ng/µl as the best cut-off value with 0.73 (95% CI 0.61-0.85) sensitivity, 0.84 specificity (95% CI 0.71-0.97) in healthy individuals, and 0.83 (95% CI 0.72-0.94) in symptomatic patients. The areas under the ROC curves were 0.8346 (95% CI 0.7391-0.9300) for healthy individuals and 0.7962 (95% CI 0.7070-0.8855) for symptomatic patients. In our case series UF DNA integrity showed higher sensitivity compared to cytology (0.73 *versus* 0.53) with the highest advantage for low-grade tumors (0.72 *vs*. 0.15). The combination of cytology and UF-DNA analysis increased sensitivity to 0.81(95% CI 0.69-0.93). *Conclusion:* Our preliminary data suggest that urine cell free DNA integrity has the potential to be a good marker for the diagnosis of early, non-invasive bladder cancer. The diagnostic performance of the test did not vary significantly even when symptomatic individuals instead of healthy individuals were considered as reference group. Furthermore, sensitivity of UCF DNA integrity could be further increased by evaluating it in combination with conventionally used urine cytology. Research is ongoing in a larger case series to confirm these results.

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SALVAGE HIGH DOSE RATE BRACHYTHERAPY (HDR-BRT), AFTER PRIMARY EXTERNAL BEAM RADIOTHERAPY (EBRT) FOR PROSTATE CANCER: A CASE REPORT

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Purpose: To assess the feasibility and early toxicity of HDR-BRT dose escalation to biopsy proven and 11C-choline PET-CT visible PC recurrence after EBRT. *Patients and Methods:* In March 2011, a 70 year old patient affected by Prostatic Adenocarcinoma (PC), Gleason score (GS) 7 stage T2bN0M0, treated in 2005 with 74Gy in 37F 3D EBRT for an intermediate risk, underwent salvage treatment with HDR-BRT for a local relapse, reocurred 3 years after the primary treatment by progressive increases of PSA up to 5.5 ng/ml. Bone scan, endorectal US, 11C-choline PET-CT and serial biopsies, evidenced a relapse of PC, GS 8, confined only in the left lobe. MRI was not performed due to a right hip prosthesis. HDR-BRT was performed, under epidural anesthesia, in 2 separate fractions at a distance of 3 weeks, by inserting 17 plastic afterloading catheters using a transperineal transrectal US guided approach. Treatment plan was performed using dedicated software (Oncentra Prostate™). During each fraction, the dose delivered was 9.5Gy to the entire prostate (CTV1) plus 2.5Gy SB to the left lobe (CTV2) where relapse was histologically and biologically demonstrated. Assuming α/β values of 1.5 for PC, these cumulative doses should be biologically equivalent to 59.7Gy for CTV1 and to 92.6Gy for CTV2. Dose constraints were: D90 ≥95% of Target volume, V100 ≥95% of (Prescription Dose) PD, V150 ≤30% of the PD, max dose to the urethra 1CC ≤125% of the PD, max dose to the rectum 1 CC ≤75% of the PD. Prostate symptoms were recorded before and after the BRT using the International Prostate Symptom Score (IPSS). *Results:* CTV1 and CTV2 at the 1^ and 2^ fraction were respectively 44 and 47.4, and 15 and 19 CC, with a 3.5% increase at the 2^ fraction due to postimplant swelling. The predefined dose constraints were respected except for the rectum that received a 9% higher dose to the prescribed D max, to allow a CTV2 good coverage. No complications were recorded during or after BRT procedures. According to the VAS scale, perineal pain was scored as 4 soon after treatment. Two months after BRT, the patient reported occasional urinary urgency and pain (VAS scale 1), while the IPSS-score S was 5 and QLS1. Two months after treatment, PSA was 1.14 ng/mL, while at four and twelve months dosed PSA levels were respectively 0.53 ng/mL and 0.13 ng/mL. One year after treatment patient reports slightly light dysuria. *Conclusion:* HDR-BRT, performed by delivering differentiated doses inside the prostate parenchyma in a patient with local recurrence after EBRT, is feasible and safe. A longer follow-up is necessary to evaluate local control and late effects.

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OBSERVATIONAL DATABASE SERENOA REPENS (DOSSER): OVERVIEW, ANALYSIS AND RESULTS. A MULTICENTRIC SIURO (ITALIAN SOCIETY OF ONCOLOGICAL UROLOGY) PROJECT

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Background: Men affected with Benign Prostate Hyperplasia (BPH) and Lower Urinary Tract Symptoms (LUTS) require an increasing amount of attention from Urologists and Primary-care Physicians. Over the years, common urological medications were based on either α-blockers and/or 5α-reductase inhibitors (1-6). In the last decade there has been an increase in the use of plant-derived drugs for many clinical conditions. Thus the phytotherapeutic drugs are gaining more often a central role in the BPH and LUTS managements. Amongst the various phytotherapeutic agents, the most widely employed is the extract of the dried ripe fruit of *Serenoa repens* (*Sabal serrulata*). In particular, clinical usage of Permixon® (Pierre Fabbre Mèdicament, Castres, France) with a dosage of 320 mg per day, has shown its clinical efficacy and its superiority (7-11). Purpose of this multicentric observational retrospective study was to evaluate all the urological aspects (clinical, biochemical, instrumental and pathological) of patients affected by BPH and LUTS, with a PSA <10 ng/ml, a previous negative prostatic biopsy and in therapy with a daily dose of 320/640 mg of Permixon®. *Patients and Methods:* The study was conducted in 8 different centers throughout Italy from September 2010 to November 2011. Data and information of 298 men with an average of 63 years (mean PSA of 5.4 ng/ml and mean prostate gland volume of 57 cc), affected by non-acute urinary symptoms caused by BPH, a dosed PSA level inferior to 10 ng/ml, a previous negative prostate biopsy and in therapy with *Serenoa repens* alone or associated to an α-blocker, were retrospectively inserted in an extensive on-line SIUrO Database. Comprehensive questionnaires were filled in for each patient at 3 and 6 months of follow-up. Each questionnaire contained various sections, each of them composed by several items: dosed PSA levels, uroflowmetry, urinary symptoms (IPSS), erectile function (IIEF-5), trans-rectal ultrasound (TRUS) patterns, digital rectal examinations (DRE) aspects, previous prostate bioptical results (histology) and side-effects. *Results:* PSA levels weren't subjected to an increase, revealing a stabilizing or downward trend. Percentage of patients with PSA below the level of 4 ng/mL was significantly lower at the end of the study. The overall changes in the uroflowmetry were similar and parallel both in the group with only Permixon® intake and in the group with Permixon® plus α-blocker. The mean medium flow and the mean maximum flow had a slight increase along the observation time. There was a substantial decrease in the amount of patients presenting severe prostatic symptoms. Patients reported through the IIEF-5 score a sexual activity substantially unchanged after 6 months of follow-up. The Permixon® intake resulted in an improvement of the "inflammatory-like reports", in terms of Ultrasound patterns, DRE and bioptical features. *Conclusion: Serenoa repens* demonstrated its efficacy reducing dysuria with minimal side-effects. Further prospective studies might confirm its stabilization or lowering role on PSA levels in this cohort of patients and its possible clinical anti-inflammatory action.

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ACCURACY OF [11C] CHOLINE POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY IN PREOPERATIVE STAGING IN PATIENTS WITH BLADDER CANCER REFERRED TO RADICAL CYSTECTOMY (RC): COMPARISON WITH CONVENTIONAL COMPUTED TOMOGRAPHY (CT)

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Introduction: Lymph node involvement is one of the major prognostic factors in bladder cancer after radical cystectomy, but current imaging techniques are of limited value in the prediction of regional and distant metastatic disease. In the present study we evaluated the diagnostic accuracy of 11C Choline Position Emission Tomography in combination with computed tomography (PET/CT) for LN staging in patients with BCa scheduled for RC in comparison with contrast enhanced CT (CECT). *Patients and Methods:* From April 2011, 15 patients (mean age 70±9.8), with urothelial bladder cancer underwent RC with extended (internal, external, common iliac, presacral and obturator LN) pelvic lymph node dissection (PLND); all patients were preoperatively submitted to CECT and 11C Coline PET with low-dose CT for attenuation correction. At PET/CT the node positivity was defined as the presence of focal uptake in a LN region, while at CECT the size criterium (>1 cm) was considered. Histopathology of resected LN was taken as reference standard and was correlated with the results of 11C Choline PET/CT and CECT in a patient-based analysis. Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy of both the techniques were evaluated. *Results:* Pathological examination of removed specimen showed an organ confined disease in 8 patients (1 CIS, 5 pT1, 2 pT2), while the remaining half of the population harboured a non-confined disease (6 pT3, 1 pT4.) A total of 474 LN were removed (mean 31.6±12.4), and metastases were found in 30 LN (6%) and in 3 of 15 patients (20%). According to patient-based analysis, sensitivity, specificity, PPV, NPV and accuracy, calculated for [11C] choline, were 100%, 92%, 21%, 100% and 93%, respectively, while, for standard CT, the values of these parameters were calculated as 33%, 91%, 8%, 84% and 80%, respectively. By applying a lymph node-based analysis, [11C] choline showed an accuracy of 98% (sens. 10%, spec. 99%, PPV 1%, NPV 99%), while the CT respectively had an accuracy of 93% (sens. 3%, spec. 99%, PPV 99%, NPV 93%). Considering the 3 N+ patients (109 LN removed, mean 36.4±21.5), according to [11C] choline imaging, 4 LN (3%) were found positive for metastatic dissemination, though 2 LN (1%) showed false positivity. As far as our population is concerned, in 11 cases (71%) [11C] choline imaging showed uptake limited to the bladder, while in 4 patients (29%) also LN uptake was detected. *Conclusion:* Alhough this is still an ongoing study, the preliminary data collected show an increase in the accuracy of the preoperative staging of BCa, by performing [11C] PET/CT scan in addition to standard CT in patients referred for RC and PLND.

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(Figures indicate abstract number. *Missing abstracts were withdrawn.