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Referees of Abstracts

1

MICRORNA501 UP-REGULATION MAY INCREASE THE AGGRESSIVENESS OF CLEAR CELL RENAL CARCINOMA THROUGH MTOR ACTIVATION AND P53 DEGRADATION

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Introduction: Many biological processes as gene expression, cell proliferation, differentiation and apoptosis are affected by microRNAs (miR), which are small noncoding RNAs that act at post transcriptional level. In fact, the impaired function of these short RNAs might cause several diseases including cancer (1). We have found a variable expression of miR501 in 63 pairs of normal and clear cell renal carcinoma (ccRCC) tissues, therefore, a possible function of this miR in ccRCC was investigated. *Materials and Methods:* Analysis of miR501 expression was carried out by microarray and real time RT-PCR. MiR501 up or down-regulation was performed by cell transfection with a specific plasmid expressing miR501 sequences (PL-501) and antagomiR, respectively. Apoptosis was analysed through caspase-3 activity, Hoechst method and cell cycle analysis. Cell proliferation was evaluated by direct cell count and with the CellTiter method. Gene expression, protein ubiquitination and kinase activity were analysed by immunological techniques and cell imaging. *Results:* Follow up analysis of 35 ccRCC subjects showed a good prognosis for patients which a lower expression of miR501 in ccRCC tissues compared with normal renal parenchyma. Conversely, about 50% of patients with unchanged or higher levels of miR501 exhibited a poor prognosis. In order to evaluate the role of miR501 in renal cancer, we modified its expression transfecting kidney carcinoma cells KJ29 (2) with a specific antagomiR and with the PL-501 plasmid. MiR501 down-regulation caused a reduction of mTOR activity, the increase of G_0/G_1 phase of cell cycle and induced apoptosis by enhancing the activity of caspase-3. Activation of apoptosis occurred in a p53-dependent manner without affecting the expression of the mTOR-related MDM2 protein, an inhibitor of p53, which results overexpressed in metastatic kidney carcinoma (3). On the other hand, miR501 up-regulation caused mTOR activation that stimulated cell proliferation as well as cell survival. The latter biological processes were associated with an increased expression of MDM2 which induced p53 degradation activating the proteasome by p53 poly-ubiquitination. *Discussion and Conclusion:* MiR501 seems to act as a molecular switch able to turn on or off mTOR signalling. In fact, the down-regulation of miR501 led to sequential mTOR kinase inhibition, p53 activation and increased apoptosis. Conversely, miR501 up-regulation caused mTOR activation, increased expression of MDM2 and p53 degradation, promoting cell survival, as already observed in follow up data. These findings support the role of kingmaker for the miR501 among apoptosis and cell survival in ccRCC patients, therefore miR501 expression could be used to evaluate the prognosis of patients with clear cell renal carcinoma.

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2

USE OF ASPIRIN AND PROGNOSTIC RISK IN PROSTATE CANCER

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Introduction: In recent years the role of inflammation in cancer etiology has gained attention and several studies have suggested that acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) may have chemopreventive activity and reduce the risk of prostate cancer (PCa). We investigated if there is a correlation between prolonged use of aspirin and prognostic risk in PCa. We examined this association in a large population-based cohort of PCa patients. *Patients and Methods:* From January 2002 to December 2007 three experienced surgeons of our department performed 385 radical retropubic prostatectomies (RRP) for localized PCa. Patients were divided randomly and retrospectively in two groups. Group A (GA): 174 patients who have been treated with aspirin 100 mg once a day per 2 years or more, as a preventive and/or curative measure for cardiovascular disease. Group B (GB): 211 patients who have not been treated with NSAIDs, if not occasionally. To evaluate the correlation between aspirin use and prognostic risk of PCa we examined these factors: biochemical recurrence (Br), percentage of positive surgical margins (PSM), pathological stage pTNM (pT), pathological Gleason

score (pGS), percentage of positive lymph nodes (PPL) and preoperative PSA (pPSA). Follow-up was conducted according to the EAU Guidelines on PCa: 3, 6 and 12 months post-RRP during the first years, and every six months in the second year and thereafter with PSA level and digital rectal exam. PSA level >0.2 ng/ml by two subsequent measurements was defined as Br. We used Cox proportional hazards regression to calculate the hazard ratio (HR) and 95% confidence intervals (CI). Tests for linear trend were conducted by assigning the median value in each category of aspirin use ($p<0.05$ used as the cut-off for statistical significance). *Results:* A total of 385 men were diagnosed with a prostate cancer on or after December 1, 2001. The average age at diagnosis was 67.4 years and patients were followed for an average of 4.6 years. Aspirin use was reported by 45.1% on the first questionnaire after their PCa diagnosis. There was no statistical difference between the average ages (68.5 and 69.7; p:0.125) and pPSA level (6.5 and 6.9; p:0.045) of the two groups respectively. The incidence of PSM was about 18.9% (33/174) in GA and 28.9%(61/211) in GB $p<0.002$. The percentage of positive lymph nodes in patients with PSM in GB (47.5%, 29/61) was statistically higher than that in GA (27.2%, 9/33). With an average of 4.6 years follow-up period 22.7% (48/211) in GB and 32.7% in GA (57/174) contracted Br; it was interesting that there was no significant difference in Br between patients with negative or positive surgical margins. In stratified analysis we observed significant differences in association with pre-diagnostic aspirin use and prognostic risk of PCa in terms of Gleason score and stage of disease. Both were higher in patients not treated with NSAIDs. *Discussion and Conclusion:* These results indicate that earlier diagnosis of PCa is the first precondition to reduce the prognostic risk of disease progression; however, our retrospective cohort study showed significant differences in prognostic risk between patients who reported prolonged use of aspirin and the control group patients. The majority of the studies including our own observed a lower risk of PCa in relation to daily low-dose aspirin use. Additional studies with more detailed exposure measurement are warranted to evaluate questions about dose, the best age to begin treatment and duration of therapy. Randomised clinical trials will be essential to establish the efficacy and safety of the best treatment regimen.

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3

LIDOCAYNE SPRAY ADMINISTRATION TRANSRECTAL ULTRASOUND GUIDED PROSTATE BIOPSY: FIVE YEARS OF EXPERIENCE

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Introduction: In literature there are numerous studies that compare various local and general anesthetic techniques for transrectal ultrasound guided prostate biopsy (TPB), analyzing different variables of discomfort highlighted by patients undergoing this procedure: patient's structure, glandular volume, pathologies of the anal canal (1). However, no study has specifically evaluated an important component of the discomfort state during the procedure: the tone of the anal sphincter and the obstruction intrarectal ultrasound probe that causes pressure and stretching of muscle fibers and sensory nerve fibers (2). The aim of our study was to evaluate patient tolerance to TPB using anesthesia with Lidocaine Spray (LS). *Patients and Methods:* Between August 2008 and July 2013: 1022 consecutive male patients with elevated PSA and (or) abnormal digital rectal and (or) suspect TRUS scheduled for TBP 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 exam was performed to empty the bladder, due to the fact that in our opinion bladder repletion is an important element of discomfort during PB execution. All patients were treated with LS (10 gr/100 ml) applied 2 minutes before the TPB. The first intention was to obtain 14 cores in all patients who underwent the procedure. A verbal numerical pain score (VNS) from=0 no discomfort to 10=severe pain was given to the biopsied patients and they were separately asked to evaluate the degree of pain associated with the procedure. The evaluation was differentiated in two scales VNS, one for the insertion of the probe and the manoeuvres associated, while the other only for the biopsy. Chi square test was used to assess differences in the response between the two questionnaires and Fisher's test if necessary. *p*-Value less than 0.05 was considered statistically significant. *Results:* In only 8 patients we were not able to insert TRUS probe: in 6 of them because of the presence of fibrous anal and in the other 2 cases the reason was a 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 one. The 8.2% of cases (83/1014) referred severe or unbearable pain (score ≥7), 749 patients (74%) referred no pain at all. Only 21 patients would never repeat the same biopsy or would request a different type of anesthesia, while 831(82%) of them would repeat it in the

same way. Analyzing the two questionnaires a difference may be noticed in the tolerability of the procedure in the first questionnaire ($p<0.001$), but not in the second one ($p<0.125$). The patients were homogeneous in terms of pain with regard to the values of PSA and prostate gland volume. It is also shown that subjects aged >65 years tolerate the procedure better in the two questionnaires (average pain VNS was respectively 2.4 and 1.7) (3). *Discussion and Conclusion:* In our experience, TPB is generally well tolerated with LS as the only anesthesia. Our pain score data suggests that LS provides efficient patient comfort during TPB by reducing pain both during insertion probe and needle. This new technique represents 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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4

THE IMPACT OF TRANSRECTAL PROSTATE SATURATION BIOPSY IN ERECTILE FUNCTION

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Introduction: Prostate biopsy (PB) is considered a safe procedure and the gold standard in the diagnosis of prostate cancer (PCa). However saturation biopsies are also considered relatively safe, with similar risks but a slightly higher percentage of hematuria, lower urinary tract symptoms and erectile dysfunction (ED) (1, 2). We evaluated sexual function in men who had undergone transrectal prostate saturation biopsy (TPSB) at different stages of PCa and benign pathology. *Patients and Methods:* Between May 2009 and April 2013 our department studied 320 patients who had undergone TPSB because of clinical suspicious PCa, but negative prior PB. Saturation biopsy was the initial biopsy for 8 patients. All patients were treated under anesthesia with sedation. First we evaluated men's ED before PB, and then one and six months after the biopsy with the 5-item version of the International Index of Erectile Function (IIEF-5). Concomitant systemic diseases and medications that would interfere with ED were recorded. Histological results led to a division in two groups (GA:113 patients with neoplastic pathology; GB:207 patients with benign pathology). Measurements data were expressed as mean±standard deviation and analyzed using the Student's *t*-test. *p*-Value less than 0,05 was considered statistically significant. *Results:* Twenty-one of the 320 consecutive patients suitable for the study were excluded due to failure in completing the questionnaire in one of the three study phases. Patients' age (GA:71.2±6.5; GB:69.4±6.8), serum PSA levels (GA:8.7±5,4 ng/ml; GB:7.2±4.7 ng/ml), prostate volumes (GA:40.30±11,19 ml; GB:41±10,70ml) and number of cores (GA:28.2±4.3; GB:27.5±4.9) showed no significant correlation with changes in ED scores after TPSB in both groups (p:0.125). The mean IIEF-5 scores were in GA: 20.1±5.7, 16.1±5.7 and 18.6±5.6 before the PB, and 1 and 6 months after biopsy; while in GB: 19.8±5.2, 16.4±4.8 and 16.5±6.9, respectively. We have not found significant differences among pre-biopsy and post-biopsy first month IIEF-5 scores of the two groups (p:0.255). On the contrary, there was significant difference with the post-biopsy sixth month IIEF-5 scores (p:<0.003). Distribution of concomitant diseases: diabetes mellitus in 31 (10.3%), coronary artery diseases in 15 (5%), hypertension in 58 (19.4%) and other diseases in 17 (5.7%). *Discussion and Conclusion:* The resulting data may explain that ED during the first month post-biopsy in two groups may be caused by direct anatomical damage to the neurovascular bundle compression attributable to hematoma or edema, possible cause of acute prostatitis which causes pelvic pain. While six months after PB, the impact of ED present in the GA is explained by the fact that PCa effects include not only ED caused by the disease itself, but also caused by psychiatric disorders in turn caused by the awareness of having the disease or its possible treatments (3). Therefore, our study does not support as possible causes of ED the type of anesthesia used and/or the number of cores performed (p:0.125), because the only diagnosis of PCa has been proved to be an independent variable and predictive of ED (p:<0.003).

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5

SPONTANEOUS RUPTURE OF THE KIDNEY AFFECTED BY MULTIFOCAL PAPILLARY RENAL CELL CARCINOMA

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Introduction: Papillary renal cell carcinoma (PRCC) represents the 10% of the kidney's carcinomas (1). This disease affects more frequently the female gender(M/F:1/8) during the fifth-sixth decade, it usually shows like a sporadic disease, even though it could arise even as a hereditary form; in the first case the kidney presents a single tumor, while in the second case one or both kidneys are involved by bilateral neoplasms. Signs and symptoms are very similar to those of the more frequent clear cell carcinoma: haematuria, pain, palpable mass are the three classic manifestations. Nevertheless in the 40% of the cases the lesion is asymptomatic (2). We report here the only clinical case of spontaneous rupture of the kidney affected by multifocal PRRC in a man 53 years old. *Case Report:* A Caucasian 53 years old man arrived at our emergency room in October 2013 reporting intense pain to the left side arised about a couple of hours before, after some gardening. His past medical history showed obesity (BMI >30 kgm-2), diabetes, hypertension, chronic renal insufficiency with right atrophy since his birth. His past surgical history: heart transplant at the age of 40 years due to a dilated cardiomyopathy. Soon after his arrival the patient showed drowsiness and unconsciousness. On physical examination, oral temperature was 36.0˚C, blood pressure 80/50 mmHg, heart rate 110 beats/min and pulse oximetry 96% in room air. Laboratory tests shown haemoglobin: 6.9g/dL, white blood cells: 13.04×10^3 μL, haematocrit: 30% and creatinine 4.7 mg/dL. At the CT with contrast enhanced emergency carried out after a fast ultrasound, it was possible to appreciate the presence of a great amount of blood in the peri- and para-renal kidney zone, generated by a lesion of the kidney's parenchyma. The patient underwent a surgical exploration and a left nephrectomy. The histology exam of the surgical frame came out on the side of multifocal papillary renal cell carcinoma type 1 (with 42 outbreaks, which largest diameter measured circa 7mm). After 3 days of intensive care unit hospitalization the patient died because of cardio-circulatory complication. *Discussion and Conclusion:* This is the first case of spontaneous rupture of the kidney affected by multifocal PRCC in literature. Two are the histology types of multifocal papillary renal cell carcinoma, and it is fundamental to distinguish them since they have a different prognosis: Type 1 is more frequently multifocal, it is made of papillae covered by small cells with modest cytoplasm, with a low nuclear grade, and dislocated in one single layer upon the papillae basement membrane; Type 2: is made of papillae covered by cells with eosinophilic cytoplasm. Prognosis is better for type 1 than type 2, but it is anyway related to the tumor grade, to the tumor stage and to the diagnostic precocity. Papillary renal cell carcinoma of the first type has a prognosis much more better than the one that involves clear cell carcinoma, but worse than the one of the chromophobe carcinoma type. In literature, different cases, also bilateral, of multifocal PRCC have been described in patients with autosomal dominant polycystic kidney disease (3), but they were not so multiple (42 foci) in order to cause the spontaneous rupture of the renal parenchyma.

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CARDIOVASCULAR RISK AND PROSTATE CANCER: A POSSIBLE LINK TO PROSTATE CANCER AGGRESSIVENESS

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Introduction and Objectives: A possible relationship between prostate cancer and metabolic abnormalities (including central obesity, dyslipidemia, hypertension, insulin resistance and glucose intolerance) has been recently proposed. Furthermore, when concomitantly present, blood pressure and metabolic risk factors potentiate each other, leading to a total cardiovascular risk which is greater than the sum of its individual components. Aim of our study was to evaluate the association between cardiovascular risk and prostate cancer diagnosis and grade among a consecutive series of men undergoing prostate biopsy. *Patients and Methods:* From 2010 onwards, a consecutive series of men undergoing 12-core prostate biopsy at one center in Italy were enrolled into a prospective database. Indications for a prostatic biopsy were a PSA value ≥4 ng/ml and/or a positive digital rectal examination (DRE). Body mass index (BMI), as well as waist circumferences were measured before the biopsy. Blood samples were collected before biopsy and tested for: total and free PSA levels, fasting glucose, triglycerides and HDLs. Blood pressure was also recorded. Metabolic syndrome was also defined according to the Adult Treatment Panel III (ATPIII). We evaluated the association between cardiovascular risk (CVR) defined according to European Association of

Cardiology Guidelines 2007 and prostate cancer risk and biopsy Gleason score using logistic regression analyses. *Results:* 580 patients were enrolled with a median (IQR) age and PSA of 68 (61/74) years and 5.7 (4/8) ng/ml respectively. Median BMI was 27.3 (25.2/29.7) k/m^2 with 138 patients (23.7%) being classified as obese (BMI ≥30 k/m^2). 219 pts (37.7%) had MS. 406 pts (70%) presented a moderate/severe CVR. 236 patients (40.6%) had cancer on biopsy; 157 (66%) with moderate/severe CVR and 79 (34%) with low/no CVR (p=0.20). PSA was independently associated with higher risk of cancer (OR 1.071 per 1 unit PSA; CI: 1.033-1.111, p=0.01). Out of 236 patients with prostate cancer, 113 (49%) had Gleason score 6 [65 (57%) presented a low/no CVR] and 123 (52%) a Gleason score ≥7 [92 (75%) presented a moderate/severe CVR]. The presence of moderate/severe CVR was not associated with an increased risk of prostate cancer (OR: 1.380, CI: 0.886-2.149; p=0.154) but with an increased risk of Gleason ≥7 (OR: 2.082; CI: 1.036-4.181; p=0.031). *Conclusion:* In our single center study, patients with a moderate/severe cardiovascular risk are associated with an increased risk of high grade Gleason score when prostate cancer is diagnosed on biopsy. Although these results should be confirmed in a larger multicenter study, patients with moderate/severe CVR should be carefully evaluated for prostate cancer diagnosis. Even though the molecular pathways are yet to be understood, hypertension and metabolic factors should be considered as possible parameters involved in prostate cancer differentiation.

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SERUM LEVELS OF CHROMOGRANIN ARE NOT PREDICTIVE OF POORLY DIFFERENTIATED PROSTATE CANCER: RESULTS FROM A RADICAL PROSTATECTOMY COHORT

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Introduction and Objectives: To explore the association of Chromogranin A (CgA) levels and the risk of poorly differentiated prostate cancer (PCa) in men undergoing radical retropubic prostatectomy. *Patients and Methods:* Between 2008 and 2013 we prospectively enrolled a consecutive series of men with localized or locally advanced prostate cancer treated with radical retropubic prostatectomy. The risk of detecting poorly differentiated PCa as a function of CgA concentration was evaluated using crude and adjusted logistic regressions. *Results:* Overall 198 patients were enrolled. Median age was 66 (IQR: 61/69) years, median BMI was 26 (IQR: 24/29) kg/m^2; median PSA: 6.9 (IQR: 5/10.8) ng/ml; median chromogranin level was 54 (IQR: 43/71) ng/ml. Overall 73 pts (36.8%) presented an advanced disease (pathological stage ≥pT3) and 39 (19.6%) patients a Gleason score ≥8. We found no significant differences for the level of CgA in men with poorly differentiated PCa *vs*. low grade cancers (55 ng/ml IQR: 43/70 *vs*. 54 ng/ml IQR 43/71; p=0.922) or with advanced diseases *versus* localized disease (56 ng/ml IQR: 43/80 *vs*. 50 ng/ml IQR: 42/71; p=0.262) On multivariate analysis, PSA was the only independent parameter, associated with high grade Gleason score (OR: 1.038 95%CI: 1.004-1.073; p=0.029) or advanced prostate cancer (OR: 1.044 per unit 95%CI: 1.019-1.1146; p: 0.03). Serum CgA levels were not significantly associated with the overall risk of advanced PCa (OR: 1; 95%CI: 0.998-1.002; p=0.915) and of poorly differentiated PCa (OR 0.999 95%CI 0.995-1.002, p=0.4). *Conclusion:* In our cohort of patients, the serum level of CgA is not a significant predictor of poorly differentiated PCa on radical prostatectomy. According to our experience, CgA should not be considered a reliable marker to predict poorly differentiate or advanced prostate cancer.

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THE INFLUENCE OF PHYSICAL ACTIVITY ON PROSTATE CANCER DIAGNOSIS: A BIOPSY COHORT ANALYSIS

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Introduction and Objectives: A possible relationship between prostate cancer and physical activity has been proposed. The Physical Activity Scale for Elderly (PASE) questionnaire has been recently proposed to evaluate the association between physical activity and benign prostatic hyperplasia. Aim of our study was to evaluate the association between physical activity and prostate cancer (PCa) risk and grade in a consecutive series of men undergoing prostate biopsy. *Patients and Methods:* From 2011 onwards, a consecutive series of men undergoing 12-core prostate biopsy were enrolled into a prospective database. Indications for a prostatic biopsy were a PSA value ≥4 ng/ml and/or a positive digital rectal examination (DRE). Body mass index (BMI) and waist circumferences were measured before the biopsy. Blood samples were collected before biopsy and tested for: total PSA, glycemia, HDL, trygliceridemia levels. Blood pressure was recorded. Metabolic syndrome (MetS) was defined

according to the Adult Treatment panel III. PASE questionnaire was colelcted before the biopsy. *Results:* 286 patients were enrolled with a median age and PSA of 68 (IQR 62/74) years and 6.1 ng/ml (IQR 5/8.8) respectively. Median BMI was 26.4 kg/m^2 (IQR: 24.6/29); median waist circumference was 102 cm (IQR: 97/108) and 75 pts (26%) presented a metabolic syndrome. One-hundred and six patients (37%) had prostate cancer on biopsy. Patients with PCa presented a higher PSA (6.7 ng/ml, IQR: 5/10 *vs*. 5.6 ng/ml, IQR: 4.8/8; p=0.007) and a lower PASE score (108, IQR: 66/150 *vs*. 126, IQR 84/198; p=0.005). PASE score inversely correlate with waist circumference (σ: -0.196; p=0.004) and Age (σ-0.223; p=0.0041). On multivariate analysis PASE (OR: 0.996 per unit, 95%CI: 0.993-1.000; p=0.003) and PSA (1.054 per unit 95%CI: 1.013-1.116, p=0.04) were the only independent risk factors for prostate cancer diagnosis. *Conclusion:* In our single center study, a reduced physical activity evaluated by the PASE questionnaire is associated with an increased risk of prostate cancer on biopsy, although these results should be confirmed in a larger multicenter study. Eventhough the molecular pathways are yet to be understood, it is assumable that a reduced physical activity and the associated metabolic abnormalities may be considered as possible factors involved in prostate cancer pathogenesis.

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RECTAL ENEMA *VERSUS* POLYETHYLENE GLYCOL SOLUTION FOR PREVENTING TRANSRECTAL ULTRASOUND (TRUS) PROSTATIC BIOPSY COMPLICATIONS: A RANDOMISED CLINICAL TRIAL

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Introduction and Objectives: Transrectal ultrasound prostate biopsy (TRUS) is considered the standard procedure for the diagnosis of prostate cancer, however it is associated to a significant morbidity. Aim of our study was to evaluate and compare two different bowel preparations to prevent TRUS biopsy complications. *Patients and Methods:* From May 2012 onwards, a consecutives men undergoing TRUS 12-core prostate biopsy were enrolled into a prospective database. Indications for a prostatic biopsy were a PSA value ≥ 4 ng/ml and/or a positive digital rectal examination (DRE). Prostate biopsy was carried out as an outpatient procedure. Patients were randomized 1:1 to receive a rectal enema (Group A) the night before the procedure or PEG 1 gram/4 litres of water (Group B). A VAS scale to evaluate patients discomfort according to the two preparations was collected. Antibiotic prophylaxis by means of ciprofloxacin 500 mg b.i.d. was started 48 hours before the procedure and continued for 72 hours thereafter. All complications occurring within the first 30-day post-biopsy period were prospectively recorded and graded according to the Clavien Classification System (CCS). Sample Size was calculated. One-way ANOVA and Chi-square were used as appropriate for statistical analysis. *Results:* A total of 198 patients were consecutively enrolled. The mean age was 67.5±7.9 years, mean body mass index (BMI) was 27.2±4.2 Kg/m^2, the mean PSA value was 8.3±6 ng/ml and the mean prostatic volume of 61±28 ml. 98 patients were enrolled in Group A and 100 in Group B. 118 complications were recorded in 102. Overall post-biopsy morbidity rate was 50%. No significant differences for age, BMI, PSA, prostate volume and prostate cancer detection and low grade and high grade complications Table I according to the CCS were observed between the two groups (Table I).

Table I.

	Group A (98 pts)	Group B (100 pts)	p
Age (years)	68.2±7.3	67.0±8.4	0.398
BMI (Kg/m^2)	26.8±3.3	27.2±4.7	0.551
PSA (ng/ml)	9±5	7.3±4.5	0.091
Prostate Volume (cc)	61.0±30	60.5±27.5	0.699
Prostate cancer rate	43/98 (44%)	43/100 (43%)	0.731
VAS score	2±1	7±2	0.001
Low grade Complications (CCS <III)	54/98 (55%)	54/100 (54%)	0.324
High grade Complications (CCS≥ III)	6/98 (6.1%)	4/100 (4%)	0.539

Conclusion: Our study confirmed that a rectal enema should be considered the standard preparation in patients undergoing TRUS biopsy; it is effective as PEG and causes less discomfort. Although a cost-analysis was not performed it is also less expensive (1 *vs*. 7 euro per patient).

12
SERUM LEVELS OF SEX HORMONE BINDING GLOBULIN ARE NOT PREDICTIVE OF POORLY DIFFERENTIATED PROSTATE CANCER OR ADVANCED PROSTATE CANCER: RESULTS FROM A RADICAL PROSTATECTOMY COHORT

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Table I.

	Pathological stage			Gleason grade		
	T2	≥T3	*p*	6	≥7	*p*
N° Patients	125 (63.2%)	73 (36.8%)		61 (31%)	137 (69%)	
Total PSA (ng/ml)	6.2 (IQR 4.7/9.6)	8.7 (IQR: 6/13)	0.00	6 (IQR: 4.2/8.2)	7.4 (IQR: 5/12)	0.00
Testosterone (ng/ml)	3.7 (IQR: 2.9/4.7)	3.8 (IQR: 3-4.6)	0.769	4 (IQR: 3.2/4.8)	3.7 (IQR: 2.8/4.7)	0.148
SHBG (nmol/L)	37.7 (IQR: 30/43)	34.6 (IQR: 24/48	0.269	37.5 (IQR: 29.5/42.3)	35.7 (IQR: 28/45)	0.790

Introduction and Objectives: No consensus has been reached yet as to the relation of androgens and prostate cancer (PCa). Recent reports have shown that sex hormone binding globulin (SHBG) can predict prostate cancer stage after radical prostatectomy. Aim of our study was to evaluate the relationship between hormonal status and prostate cancer in a group of patients treated with radical retropubic prostatectomy. *Patients and Methods:* Between 2008 and 2013 we prospectively enrolled a consecutive series of men with localized or locally-advanced prostate cancer treated with radical retropubic prostatectomy. The risk of detecting poorly differentiated PCa as a function of CgA concentration was evaluated using crude and adjusted logistic regressions. *Results:* Overall 198 patients were enrolled. Median age was 66 (IQR: 61/69) years, median BMI was 26 (IQR: 24/29) kg/m^2; median PSA: 6.9 (IQR: 5/10.8) ng/ml; median SHBG level was 36 (IQR: 28/44) nmol/l, median testosterone level was 3 (IQR: 3/4.7) ng/ml. Overall 73 pts (36.8%) presented an advanced disease (pathological stage ≥pT3) and 137 (19.6%) patients a Gleason score ≥7 (Table I). 31% had abnormal DRE. 47 (238%) patients presented positive surgical margins. On multivariate analysis PSA was the only independent parameter associated with high grade Gleason score (OR: 1.122 95%CI: 1.029-1.224; *p*=0.009) or advanced prostate cancer (OR: 1.043 per unit 95%CI: 1.002-1.086; p: 0.039). Serum SHBG levels were not significantly associated with the overall risk of advanced PCa (OR: 0.992; 95%CI: 0.971-1.014; *p*=0.479) and of poorly differentiated PCa (OR 1; 95%CI 0.975-1.025, *p*=0.972). *Conclusion:* In our cohort of patients, the serum level of SHBG is not a significant predictor of a locally advanced or poorly differentiated PCa on radical prostatectomy. According to our experience, SHBG should not be considered a reliable marker to predict poorly differentiate or advanced prostate cancer.

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SECRETOGRANINE VGF (SGVII) AS A NEW MARKER FOR HIGH GRADE PROSTATE CANCER

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Introduction and Objectives: The protein VGF (SgVII) is considered as a new marker in neuroendocrine tumors, such as pheochromocytoma, neuroblastoma and ganglioblastoma. In prostate tissue there are neuroendocrine derivation cells, and during tumor progression, prostate cancer cells acquire characteristics defined "neuroendocrine" like the ability to produce Chromogranin-A (CgA). Assuming that the expression of VGF can be part of the neuroendocrine features acquired during the transformation or tumor progression, we evaluated the expression of VGF segretogranine (SgVII) in normal and neoplastic prostate tissue. *Materials and Methods:* The expression of VGF was assessed by immunohistochemistry with anti-VGF3 antibody (AV3) in 30 samples of tissue from patients with prostate cancer treated with Radical Prostatectomy in the period between January 2011 and January 2012.The expression of CgA was also assessed in High Grade (HG) tumors. Normal prostate tissue from the same group of patients was used as a control. We also evaluated the expression of VGF in prostate cancer cell line LNCaP with immunofluorescence, PCR and Western Blot. *Results:* VGF expression in prostate cancer is directly related to Gleason Score (Pearson's chi-square <0.0001 Cancer *vs*. No Cancer/Expression of VGF) (Table I). An interesting aspect appears in Higher Grade tumors (Gleason 5), where VGF is produced independently of CgA (5 tumors with high intensity positivity for VGF expression were tested for CgA, 2 of them were found negative for CgA expression). The studies conducted *in vitro* shows that the transformation of the prostate cancer's line LNCaP in neuroendocrine carcinoma cells mediated by IGF-1, also induces the production of VGF. *Conclusion:* This is the first study that shows a relation between VGF protein expression and Gleason Score. Further

Table I.

VGF Expression*	No Cancer (n. cases)	Cancer (n. cases)	Gleason 3 (n. cases)	Gleason 4 (n. cases)	Gleason 5 (n. cases)
Negative	30	19	11	6	2
+		15	7	4	4
++		3		1	2
+++		3			3
Total	30	40	18	11	11

*Based on immunohistochemistry reaction intensity.

studies are needed to define the role of VGF protein expression for the diagnosis of HG Prostate Cancer.

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METABOLIC MECHANISM REGULATING PROSTATE CANCER CELL MALIGNANT PHENOTYPE

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Introduction: Increasing evidence suggests a positive association between body mass index and advanced, aggressive and/or fatal prostate cancer. There is a positive association between obesity and PCa aggressiveness (1). Because obesity and PCa affect substantial proportions of the male population, the association between the two is of great public health significance. Partly, this relationship may be explained by detection biases. In fact, PCa may be underdiagnosed in obese men, because of decreased PSA values, larger prostate gland size and more difficult Digital-Rectal Examination (DRE). Presently, three mechanisms are most commonly proposed as basis of the association between obesity and aggressive PCa: The insulin/insulin-like growth factor (IGF-1) axis. Insulin resistance and type II diabetes mellitus are commonly associated with obesity and may also be linked to PCa through alterations in insulin, IGF-1 and IGFBPs (IGF binding proteins). IGF1 is a potent mitogen which has been associated with prostate cancer progression; Sex hormones. Because of the conversion of androgens to oestrogens by the enzyme aromatase produced by adipose tissue, lower testosterone levels may provide a microenvironment which favours and selects for androgen-independent tumour cells which are the more aggressive; Adipokine signaling. Leptin promote angiogenesis, proliferation of endothelial cells and stimulates the growth of androgen-independent PCa cells *in vitro*. In contrast, adiponectin levels has been reported to be inversely related to PCa risk and desease stage (2). Moreover, obesity results from a long-term energy imbalance, leading to an accumulation of lipid stores and an elevation of the circulating levels of FFAs (Table I), predominantly oleate (unsatured) and palmitate (saturated) (3).

Table I. *FFAs levels of obese study population.*

FFA		
Palmitoleic acid		1.25±0.10 (0.24-3.83)
Palmitic acid	77-350 μM	5.46±0.19 (2.61-8.66)
Linoleic acid		2.41±0.16 (0.30-5.64)
Oleic acid	101-590 μM	8.96±0.43 (3.10-18.05)
Stearic acid		2.17±0.12 (0.29-4.10)

We focused our attention on the role played by FFAs in PCa with aggressive behavior, investigating their effect on PCa cell viability, migration and drug response. *Materials and Methods:* We incubated Du145 and PC3, two androgen-independent PCa cell lines, with increasing concentrations of oleate or palmitate (the most abundant circulating fatty acids) alone and in combination with Docetaxel (first-line therapy in androgen-independent PCa) for 48 h. We evaluated cell viability and drug response by MTT assay and cell motility by wound healing assay. *Results:* We found that both FFAs had no significant effect on cell viability. Conversely, oleate significantly increased PC3 and Du145 cell motility, reducing wounded area by 30%. Moreover, the response to Docetaxel was decreased in presence of 200 μM oleate by 2-fold and 1.2-fold in Du145 and in PC3 cell lines, respectively. No significant effect was observed in palmitate-

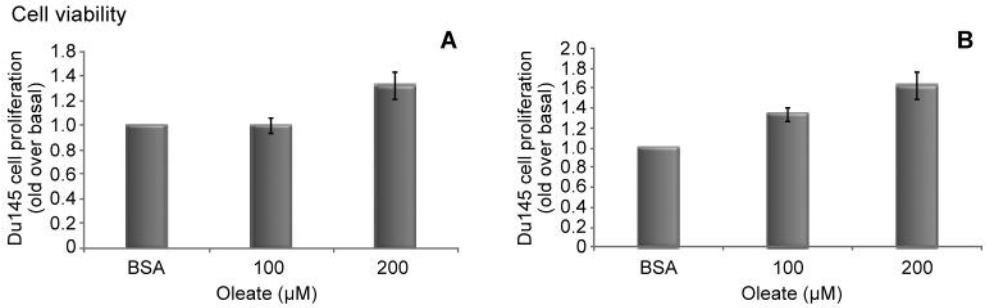

Figure 1. *Effect of Oleate on PCa cell viability PCa cells, Du145 (A) and PC3 (B).*

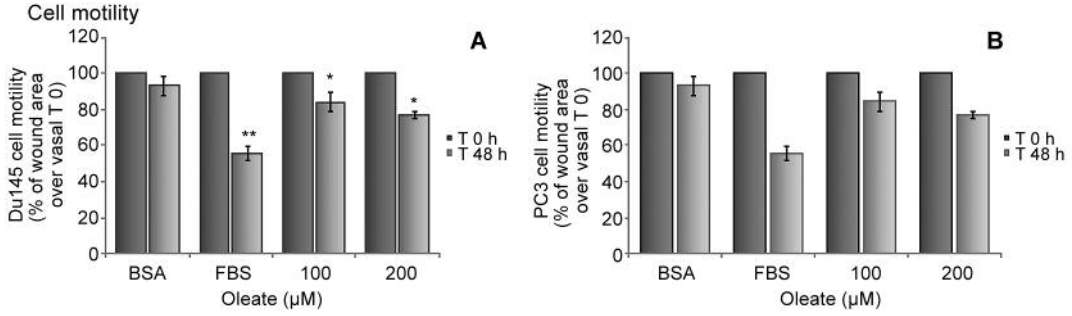

Figure 2. *Effect of Oleate on PCa cell motility Du145 (A) and PC3 (B).*

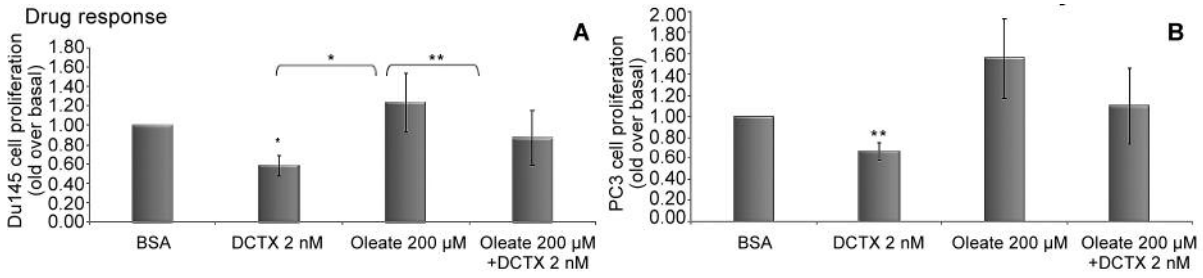

Figure 3. *Effect of Oleate on Docetaxel (DCTX) induced cell-death of PCa cells Du145 (A) and, PC3 (B).*

treated cell motility and drug response. *Discussion and Conclusion:* The effect of oleate, the most abundant circulating FFA in obese subjects, on viability, motility and drug response of PC3 and Du145, androgen-independent PCa cell lines suggests that oleate: had no significant effect on cell viability (Figure 1); significantly increased cell motility (Figure 2); significantly reduced the response to DCTX of Du145 cell line. Understanding the metabolic mechanisms involved in the association between obesity and PCa aggressiveness might lead to more effective use of existing therapies and new therapeutic targets (Figure 2) (Table I).

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PROSTATE MOTION ASSESSMENT USING A TEMPORARY-IMPLANTED WIRED ELECTROMAHNETIC TRACKING SYSTEM FOR HYPO-FRACTIONATED RADIOTHERAPY (HYPO-RT):A PRELIMINARY MONO INSTITUTIONAL EXPERIENCE

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Aim: The purpose of this work was to evaluate the safety and clinical utility, specially related to intrafraction displacements of the prostate gland, in Hypo-RT for definitive treatment for prostate cancer, using a temporary implanted wired electromagnetic tracking system and to assess the impact of these movements on treatment margins. *Patients and Methods:* We have studied 9 patients (pts), aged between 65-80 years, treated with radical Intensity Modulation Radiation Therapy (IMRT)- Image Guided RT (IGRT) for prostate cancer. No pt had diabetes mellitus or took anticoagulant therapy, 7 took drugs for hypertension, 4 received prior abdominal surgery and 1 underwent to a trans-urethral resection of the prostate (TURP). All patients had a low IPSS score (<8). All pts had low (6 pts) or intermediate risk (3 pts) according to NCCN categories. The planning CT scan was acquired in supine position, with a full bladder and empty rectum. The treatment was delivered with "Volumetric Intensity Modulated Radiation-therapy" (VMAT), with Varian Rapid Arc®. In low risk pts prescription dose was 70.0 Gy, to the prostate only, at 2.5 Gy/daily in 28 fractions; intermediate risk pts received on seminal vesicles 58.8 Gy and prostate 70 Gy, with simultaneous integrated boost (SIB) in 28 fractions, in combination with "short term" anti-androgen as neoadiuvant-concomitant- adjuvant hormone therapy. Each patient was implanted with an electromagnetic transmitter (Raypilot System®, Micropos Medical AB) and two gold seeds in the prostate gland. The implanted transmitter was surgically removed at the end of therapy. The tracking system, an add-on device to the linear accelerator composed by the implanted transmitter and a flat receiver placed on the patient bed, provides the 3-D real-time position of the transmitter itself, which is passively employed as a surrogate of prostate motion. Daily, the target localisation was initially evaluated using the tracking system and repositioned according to the gold seeds location, after kV portal images (On Board Imaging) have been acquired. The target motion was monitored during every treatment fraction without affecting radiation beam delivery. Real-time intrafraction motion displacement between actual and initial (prefraction) transmitter position was recorded at every fraction. Interfraction target displacements were evaluated comparing the positioning identified by the tracking system to the one based on the gold seeds location on the kV portal images. *Results:* Both transient excursions, typically within 20 seconds duration, and drifts of the prostate gland were observed during treatment. Spatial displacements >11 mm in the cranial-caudal direction were identified in 1 patient, >4 mm in the cranial-caudal and anterior-posterior directions in 3 patients, <4 mm in the remaining patients. Clinical Target volume (CTV) to Planning Target Volume (PTV) margins were retrospectively assessed with Van Herk's method, either considering or neglecting the contribution due to intrafraction motion. Acute toxicity was evaluated using CTCAE 4.0 schedule for genito-urinary (GU) or gastro-intestinal (GI toxicity); 6 pts referred frequency/urgency G1, 1 pt G2. In 4 pts we observed G1 and in only 1 pt G2 dysuria. We registered in 5 pts G1 and in 3 pts G2 nycturia. For GI toxicity we observed haemorrhoids G1 in 2 pts, rectal tenesmus G1 in 2 pts and diarrhoea G1 only in 1 pt. *Conclusion:* The implant was feasible and quite safe in all the pts and low acute rate toxicities were verified. Interfraction motion is more relevant in CC direction, likely because of daily variations in bladder and rectum filling. At the same time, the impact of intrafraction motion on the margins is larger in the AP direction, related to abdominal movements. The detected spikes during the registration are probably caused by sudden rectal air passage. This analysis provides warnings about hypofractionated treatments, specially in the case of an extremely hypoRT schedule: a) treatment target repositioning and tracking or beam-gating techniques should be implemented in the therapy execution protocol; b) intrafraction motion impact on treatment margins is not negligible. We need to extend this experience to other pts and longer follow up to evaluate the outcomes in terms of late toxicity.

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HYPO-FRACTIONATED INTENSITY MODULATED RADIOTHERAPY IN DEFINITIVE TREATMENT OF PROSTATE CANCER: A REPORT OF ACUTE TOXICITY

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Aim: Since the recognition that prostate cancer has a low α/β ratio, hypo-fractionated radiotherapy has become an attractive treatment option for localized prostate cancer. However, there

is not a long history in definitive treatment setting, with the use of hypo-fractionation. We report our preliminary experience with moderate hypofractionated radiotherapy (Hypo-RT). *Patients and Methods:* Between January 2011 and December 2013, a total of 56 patients (pts) affected by prostate cancer (high, intermediate and low risk according NCCN categories) were treated with definitive Hypo-RT. Pts median age was 69 (54-84); out of the 56 pts, 19 were "low"; 24 pts were "intermediate" and 13 pts were "high" risk; pts at high and intermediate risk also received hormonal therapy (anti-androgen or LHRH-A) before, during and after RT as short term or long term therapy. Related to comorbidities, 7 pts were affected by non insulin-dependent diabetes (DMNID), 18 pts had prior abdominal surgery and 9 pts underwent preview to a prostate disostruction surgery (TURP). All pts underwent a 3 mm slice CT simulation with empty rectum and full bladder; the treatment was delivered with "Volumetric Intensity Modulated RT (VMAT), with Varian Rapid Arc®. Pts with intermediate and high risk prostate cancer were treated with IMRT and simultaneous integrated boost (SIB). Pts at low risk were treated to the prostate with 67.5 Gy in 27 daily fractions (very low risk pts) or 70 Gy in 28 daily fractions (2.5 Gy/die); pts with intermediate /high or high risk pts were irradiated on prostate, seminal vesicles, pelvic nodes, respectively with a 73.5 Gy, 60 Gy and 54 Gy in 30 daily fractions (SIB); pts at intermediate risk received on prostate and seminal vesicles,respectively 70 Gy and 58.8 Gy in 28 daily fractions (SIB). Pts got IGRT as Kilovoltage CT (Cone Beam CT). *Results:* Acute toxicity was weekly evaluated using the CTCAE 4.0 score for genito-urinary (GU) and gastro-intestinal (GI) toxicity. All pts filled out IPSS question form before and at the end of the treatment. Only pts with a low-intermediate score (<12) were admitted to Hypo-RT. We observed increased frequency/urgency G1 in 24 pts, G2 in 12 pts and we had G3 toxicity in 1 pt only, while 9 pts needed prescription of α-blocker; 21 pts developed G1, 15 pts G2, 2 pts G3 nycturia while 16 pts referred G1 and 3 pts G2 dysuria. In 1 pt we scored haematuria G1 and 1 pt referred pollachiuria G3. One high- intermediate risk pt developed an urethral obstruction during the treatment, and needed bladder catheter. Most of pts got a deterioration of IPSS at the end of treatment with 18 points as maximum level scored. For GI acute toxicity we observed proctitis G1 in 4 pts and G2 in 1 pt, while we didn't register any G3 toxicity. Diarrhoea G1 was developed in 6 pts while 2 pts needed medical therapy with loperamide. We registered 1 pt with rectal pain G2 and 2 pts with transient rectal incontinence G1; 8 pts referred haemorrhoids G1, 3 pts received topical medication. Finally, in 49 pts we didn't register any medical therapy, while 36 pts didn't refer any GI symptom. *Conclusion:* Moderate hypo-fractionated IMRT(also with SIB and including pelvic RT) was feasible and safe. Low acute toxicity rates were reported, generally G1 and G2 graded. Based on our experience, patient's selection according to IPSS score, evaluation of comorbidities and attention to dose- constraints for organs at risk, are advisable in order to limit overall acute toxicity. Hypo-fractionation also results in shortened overall treatment times, thus reducing staffing and machine burden and, more importantly, pts stress. Our experience need longer follow-up to evaluate the outcomes in terms of late toxicity and oncologic end-points.

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THE PHYSICAL THERAPY FOR CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

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Introduction and Objectives: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) (NIH-CPSI IIIb) is characterized by chronic pelvic pain and LUTS. The aetiology of CP/CPPS is poorly understood and, eventhough many studies on pelvic floor muscle tone have been carried out, no clear cause-effect relationship between pelvic floor muscle tone and CP/CPPS has been found. In this study we evaluate the effect of biofeedback (BFB) therapy on CP/CPPS symptoms, and the correlation between symptom improvement and PFM tone. *Patients and Methods:* A retrospective analysis has been conducted on 88 patients with CP/CPPS NIH IIIb presenting in outpatient clinic between March 2009 and May 2012. Inclusion criteria: age greater than 18 years, pelvic pain and discomfort for at least 4 months, NIH-CPSI greater than 14. Exclusion criteria: UTI in the previous four months, malignancy, previous endoscopy, neurological diseases. All patients underwent a cycle of BFB. The NIH-CPSI questionnaire and pelvic floor muscle tone evaluation were used as treatment efficacy measure. Student's *t*-test and Pearson's correlation were employed for statistical analysis. *Results:* Differences between the NIH-CPSI mean of pain, quality of life, micturition and EMG scores before and after the biofeedback treatment were significant ($p<0.001$). Pearson's correlation showed a mild statistically significant correlation between EMG values and NIH-CPSI before treatment ($r=0.232$, $p<0.05$) but a mild inverse correlation between EMG values and NIH-CPSI after treatment ($r=-0.251$, $p<0.05$). *Conclusion:* Biofeedback therapy highly improved pain as well as voiding complaints and QoL in CP/CPPS type IIIB patients. On the contrary, no clear correlation between NIH-CPSI and PFM tone was found.

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FINGERPRINTING OF ULTRACONSERVED GENOMIC REGIONS(UCRS) IN BLADDER CANCER ANALYSIS REVEALS A UCR 8 AT THE TOP OF A NETWORK BETWEEN NON-CODING RNA AND MICRORNA

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Introduction: Urothelial carcinoma is the most common form of cancer in the bladder and can be divided into two groups defined by their distinct behaviors and different molecular profiles. These groups are characterized as low-grade tumors, which are always papillary and usually superficial, and high-grade tumors, which can be either papillary or nonpapillary and often invasive. Recently, thousands of long non-coding RNA (lncRNAs) have been identified and disease-associated lncRNA profiles, obtained with a variety of molecular approaches, have placed lncRNAs on the stage of integrated cancer biology (1). Functional studies have indicated that some lncRNAs are involved in human bladder cancer pathogenesis, acting as either oncogenes or tumor suppressors. In our previous study it has been demonstrated that a new class of lncRNAs, called transcribed ultraconserved regions (T-UCRs), is consistently deregulated in several human tumors (2). *Materials and Methods:* In order to assess whether T-UCRs can be detected and are differentially expressed in bladder cancer, cancer tissues (n=24) were compared to the control (n=4). Total RNA was extracted from each sample, and hybridized with version 4.0 of Dr. Croce's ncRNA microarray, that includes probes which are able to detect T-UCR transcripts both in sense, and antisense (A) orientation. We obtained specific signatures of de-regulated T-UCRs listed in Figure 1. *Discussion:* By using genome-wide profiling, we found that T-UCRs are de-regulated in bladder cancer, and some of them are able to enhance cell motility and growth *in vitro* by influencing the expression of motility-related genes. Based on the ability of RNA stems to form complexes with other nucleic acids and to be rapidly transcribed and degraded, we have demonstrate an extensive and dynamic regulatory network of the RNA signaling associated with cancer progression. In particular, we define a model that explains the effect of single TUCR perturbation on whole T-UCRs network of interactions and demonstrate the function of T-UCRs as natural miRNA decoys in the development of bladder cancer. In conclusion, the discovery of ultraconserved ncRNA as

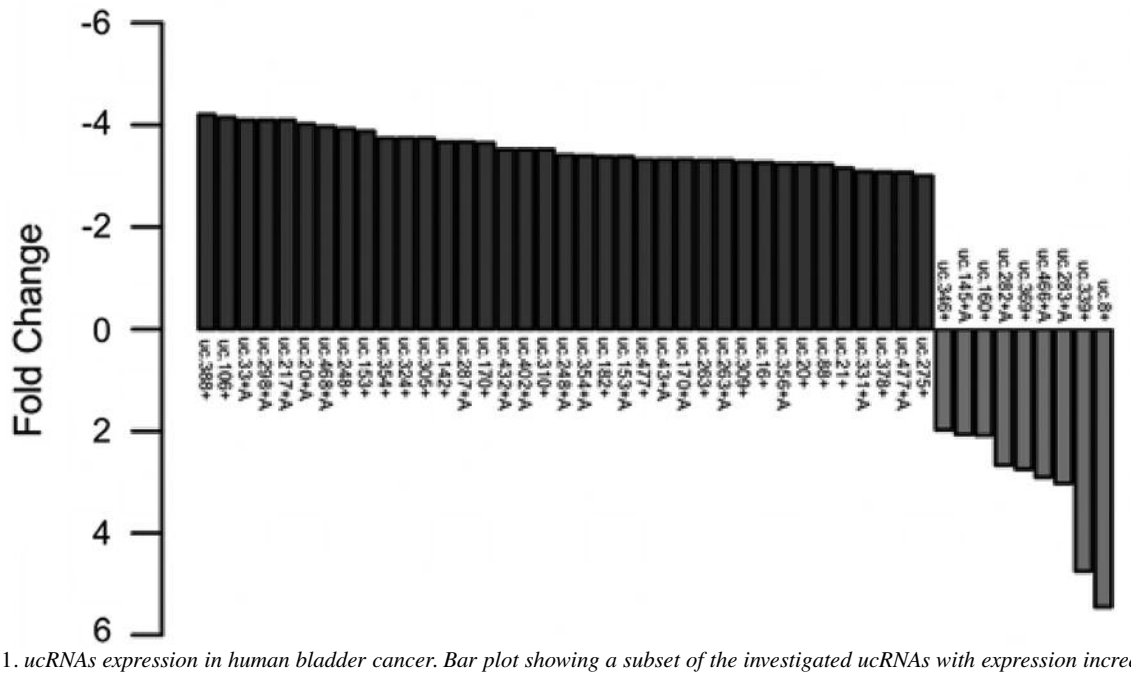

Figure 1. *ucRNAs expression in human bladder cancer. Bar plot showing a subset of the investigated ucRNAs with expression increase greater than 1 and expression decrease lower-3, in cancer with respect to controls.*

regulator of microRNA indicates also how conserved is this mechanism during evolution and opens up the possibility of a new biological mechanism that could be targeted by oligonucleotide gene therapy.

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AXITINIB, LASTING RESPONSE IN 4TH LINE OF TREATMENT: SEQUENCING OF AGENTS FOR METASTATIC RENAL CELL CARCINOMA

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Recently, the anti-vascular endothelial growth factor (VEGF) agents and mammalian target of rapamycin (mTOR) inhibitors have supplanted cytokines as the mainstay therapy and have led to prolongation of progression-free survival (PFS) and, in some patients, overall survival (OS). For these patients, sequential treatment with multiple lines of therapy may afford sustained clinical benefit. We present a case of a lasting response with axitinib in 4th line of therapy for mRCC. *Introduction:* Approximately 30% of patients with renal cell carcinoma (RCC) have advanced disease at their initial diagnosis, and 20-30% develop metastases after surgery for earlier-stage disease. The 5-year survival for patients who present metastatic renal cell carcinoma (mRCC) or locally advanced disease is 10-50%. The Memorial Sloan Kettering Center criteria, or Motzer criteria, stratify the patients into three risk categories: favourable, intermediate or poor risk, which corresponds to different survival (survival to three years 45%, 17% and 2% respectively) (1, 2). However, the survival of patients with metastatic clear-cell renal- cell carcinoma (mRCC) has improved with the availability of drugs targeting VEGF, or its receptors (VEGFRs), and mTOR (3). Currently approved and available mTOR inhibitors include temsirolimus and everolimus (4, 5); VEGF/VEGFR-targeted drugs are bevacizumab, sunitinib, sorafenib, pazopanib and axitinib (6-10). For these patients, sequential treatment with multiple lines of therapy may afford sustained clinical benefit. Vascular endothelial growth factor-tyrosine kinase inhibitors (VEGFr-TKIs) are recommended as first-line therapy for most patients with mRCC. Current clinical practice guidelines uniformly recommend treatment with the mammalian target of rapamycin (mTOR) inhibitor everolimus after initial VEGFr-TKI failure. Recent results of the AXIS phase 3 trial demonstrated improved efficacy with second-line axitinib *versus* sorafenib in patients who progressed on a variety of first-line therapies, including the VEGFr-TKI sunitinib (10). However several questions about the optimal sequencing of therapies in patients with mRCC remain to be answered. We report a case of lasting response with axitinib in 4th line of therapy for mRCC. *Case Presentation:* On March 2008, a 61 year old man consulted the Oncology Department of Reggio Emilia after a right radical nephrectomy and adrenalectomy; pathological examination confirmed Fuhrman grade 4 clear cell renal carcinoma with adrenal metastasis (pT3a N0/7). Further staging was negative for other metastatic sites. No haematological disorders were found. On February 2010, after two years of follow up, a control CT scan showed recurrent disease at left adrenal gland and mediastinal lymph nodes; a biopsy confirmed the presence of clear cell carcinoma cells on mediastinum. The patient's general condition was good and his performance status (PS) was 0, based on the Eastern Cooperative Oncology Group performance status criteria. According to the Memorial Sloan Kettering Cancer Centre prognosis criteria the patient was stratified as favourable risk and on March 2010, bevacizumab 10 mg/Kg and interferon 6MU 3 times per week was started. On February 2012, after almost two years of therapy, bevacizumab was suspended because of grade 3 persistent proteinuria. Therapy with interferon was continued until April 2012. On May 2012, disease progression in all metastatic sites (mediastinum and left adrenal gland) was observed on the CT scan control. On June 2012, sunitinib 50 mg daily 4 weeks on, 2 weeks of, was started and continued until September 2012, with a good tolerance and disease control. On October 2012, progression in mediastinal lymph nodes was observed again. After the second-line failed, important considerations were made on possible therapeutic choices. Better to continue with a sequence tyrosine kinase inhibitor (TKI) followed by another TKI? or TKI followed by mTOR? On November 2012, third line therapy with sorafenib 400 mg twice daily was started, but after 15 days, treatment had to be suspended due to G3 rash appearance (Figure 1). On December 2012, after skin toxicity complete resolution, therapy with axitinib was started at 5 mg twice daily for 1 month; then continued at 7 mg twice daily until August 2013. CT scan was repeated at 8, 20 and 28 weeks of Axitinib therapy with stable disease control (Figures 2 and 3). Treatment was in general well tolerated. Blood pressure was monitored at each clinic visit and once a day by the patient

without modifications on pressure values. No haematological disorders were found. Disease control with axitinib fourth line has lasted for 9 months, without significant toxicities.

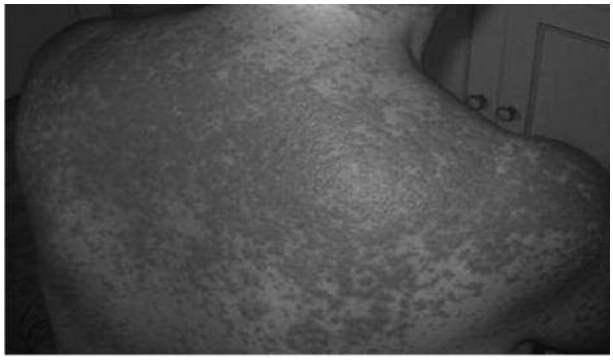

Figure 1. *Toxicity Sorafenib treatment.*

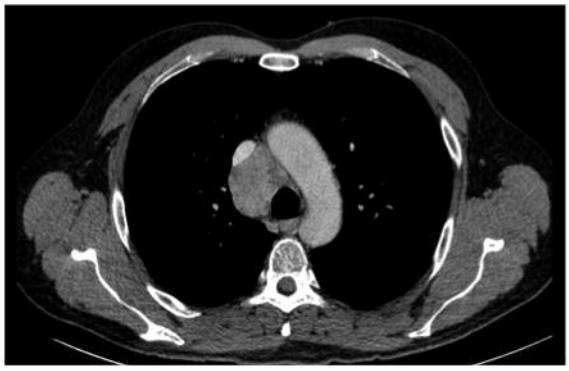

Figure 2. *Basal CT-SCAN therapy with axitinb (November 2012).*

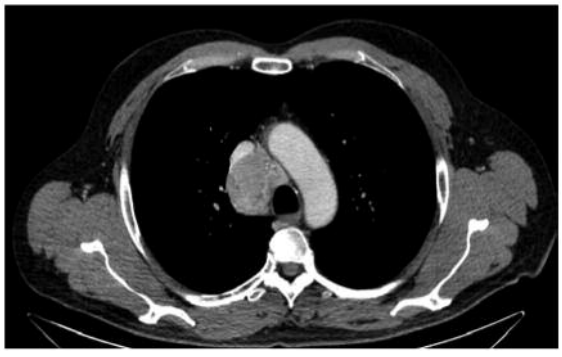

Figure 3. *CT-SCAN after 4 months of axitinb (February 2013).*

Discussion: The treatment of metastatic renal cell carcinoma (mRCC) has historically included immunotherapy, although targeted agents have revolutionized treatment strategies over the last several years. Currently approved and available mTOR inhibitors include temsirolimus and everolimus; VEGF/VEGFR-targeted drugs are bevacizumab, sunitinib, sorafenib, pazopanib and axitinib. Axitinib (INLYTA) was approved by the EMA for the treatment of patients with mRCC who relapsed after a previous therapy line consisting of sunitinib or cytokines. It's a potent and selective inhibitor of vascular endothelial growth factor receptors 1,2 and 3 and it is an important addition to currently available therapies for advanced RCC. Recent results of the AXIS phase 3 trial demonstrated improved efficacy with second-line axitinib *versus* sorafenib in patients who progressed on a variety of first-line therapies, including the VEGFr-TKI sunitinib (median PFS 6.8 months for axitinib *vs.* 4.7 months for sorafenib) (10). The peculiarity of the study was the absence of fixed dose of axitinib. Starting from an initial dose of 5 mg, if no particular toxicity was observed, an escalation to 7 mg was applied after 2 weeks, until final dose of 10 mg. The standard strategy in metastatic renal cell carcinoma (mRCC) is to use sequential treatment. Different pathways are known to be involved in the pathogenesis of mRCC and in the development of resistance to targeted drugs. Combinations of targeted drugs could theoretically achieve better inhibition of a given pathway, inhibition of different pathways, or inhibition of a pathway involved in the resistance to a given drug. However, there is as yet no clear evidence that combination therapy is of clinical benefit and excess toxicity has been observed. In many cases not all treatments at our disposition can be used: online pre-approvals; therapeutic sequense chosen; patients diseases that can absolutely contraindicated their use. To date, in clinical practice, the choice of possible treatment is based solely on clinical elements (haemoglobin, serum lactate dehydrogenase, corrected serum calcium level, nephrectomy status and Karnofsky Performance Status- PS) (2).These criteria are important to identify the clinical condition of the patient, but probably not to characterize the aggressiveness of metastatic disease. Using a combination of these factors, we stratify patients as being of favourable, intermediate or poor risk and based in these categories we decide treatment. The absence of response predictors remains an open chapter, as well as the identification of the more correct therapeutic sequence. Nowadays, the occurrence of side effects may be a good medium for the choice of therapy sequence. In fact, it is very important to remember that in metastatic disease, quality of life remains the main objective. *Conclusion:* Several questions about the optimal sequencing of therapies in patients with mRCC remain to be answered. The optimal sequence remains unclear. Unfortunately, there is a lack of biomarkers to drive decision making. Ours is certainly a selected, responsive and long-surviving case, but that highlights the possible efficacy of molecules used beyond the predetermined line.

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THE USE OF ENSEAL TECHNOLOGY CAN PREVENT THE FORMATION OF LYMPHOCELES IN THE COURSE OF RADICAL PROSTATECTOMY

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Introduction: Lymphoceles represent a common complication following pelvic lymphadenectomy and radical retropubic prostatectomy. *Objectives:* To evaluate the effectiveness of technology Enseal in the prevention of lymphocele after pelvic lymphadenectomy after open radical prostatectomy. *Methods:* From January 2011 to December 2013, 122 consecutive patients who underwent pelvic lymphonode excision during open radical prostatectomy with the use of Ethicon ENSEAL G2 Tissue Sealer, 25 cm, all performed by the same operator. 107 were followed up for at least 6 months. Patients were followed with ETG abdominal examination at 1 week, 3 week, 1,3 and 6 months after surgery in order to assess the presence of even asymptomatic lymphocele. *Results:* The medium number of lymph nodes removed was 12 (range 6-16). The median preoperative PSA was 6.5 ng/ml (range 4-29). The median Gleason score was 7 (range 6-9). In 3 patients lymphonode metastases were found on histologic examination. 6 patients (4.9%) develop lymphocele.1 patient develop lymphocele 1 week after surgery, 3 patients at 3 weeks, 2 cases at 1 month. In 3 of these the lymphocele was less than 80 cc and all the 3 patients were asymptomatic and it was not necessary to perform other procedure. 1 patient presented a bilateral llnphocele. 2 patients were subjected to percutaneous evacuative puncture and 1 was subjected to lymphocele marsupialization. *Discussion:* The results obtained in our patients treated with the use of technology En Seal were compared our data with the litterature performed with Bipolar forceps. We found a statistically significant correlation between the use of technology En Seal and the decrease in the number of lymphoceles occurred. *Conclusion:* The occurrence of postoperative lymphocele is one of the most frequent complications in the course of radical prostatectomy. The use of Enseal, on the basis of our data, decreases the incidence of lymphocele due to its action on the sealing lymphatics. An important role, in our opinion, seems to be played by PTC that decreases the lateral thermal damage and prevents the increase of the temperature inside the branches above 100˚C. That prevents the processes of carbonization of the tissues and the subsequent laceration of lymphatic endothelium that may be responsible for this lated complication.

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RECTAL SPARING *VIA* HYDROGEL SPACER FOR DOSE-ESCALATED HYPOFRACTIONATED RADIATION COURSE IN HIGH RISK LOCALIZED PROSTATE CANCER: ANALYSIS OF DOSIMETRIC AND TOXICITY OUTCOMES

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Aim: The aim of this study is to evaluate the contribution of an injection of an absorbable synthetic polyethylene glycol (PEG) hydrogel for temporarily separating the rectum and prostate during a dose-escalated hypofractionated course of radiotherapy for high risk prostate cancer (PCa) in order to decrease the rectal radiation-induced toxicity. *Patients and Methods:* Eight patients with high risk, localized PCa underwent a dose-escalated hypofractionated radiation

schedule of 16 fractions of 3.5 Gy for a total dose of 56 Gy to prostate and seminal vesicles, considered isoeffective to 80 Gy with conventional fractionation with regard to tumor control (a/b value of 1.5 Gy). Helical Tomotherapy (HT) was administered after the transperineal injection of spacing hydrogel in the Denonvillier space in order to increase the distance between the prostate and the rectal wall. All patients were simulated before and after spacer placement, using MRI scans for anatomical assessment of rectal separation. HT plans were generated on both scans for dosimetric comparisons. Procedure adverse events and acute GI toxicity according to RTOG were documented. *Results:* The hydrogel spacer was successfully injected in all patients without complications, with a median gel thickness at midgland of 11 mm (range, 6-16 mm). Dosimetric comparisons between preinjection and postinjection plans showed a statistically significant reduction ($p<0.005$) in rectal dose across high dose levels, resulting in a maximum reduction in rectal volume receiving 90% and 75% of the prescription dose of 19.6 Gy (35%) and 15.68 Gy (28%), respectively. No significant dose reductions were seen at low rectal dose levels. After a median follow up of 6 months (range 3 to 12 months), no patient experienced RTOG grade ≥ 2 rectal toxicity and two patients were classified as having RTOG grade 1 rectal toxicity in the last week of radiotherapy, completely resolved within 40 days. *Conclusion:* Early findings show that the decrease in high rectal dose levels obtained by the use of a hydrogel spacer is associated with negligible acute GI toxicity and allows dose-escalated hypofractionated radiotherapy. Longer follow-up is warranted to assess late toxicity and define which patients might benefit from this approach.

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EXPRESSION OF MATRIX ATTACHMENT REGION-BINDING PROTEINS IN HUMAN PROSTATIC CANCER: PARP-1 AND PARP-2 NEW PLAYERS IN TUMOR PROGRESSION

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Introduction: In eukaryotes, the genome is compartmentalized into chromatin loop domains by attachment to a supporting structure termed nuclear matrix (NM). The interactions of chromatin with the NM are a dynamic event cell type- and cell cycle-dependent and they occur *via* AT-rich DNA sequences called matrix attachment regions (MARs). MARs, in addition to regulate the higher-order organization of chromatin, affect the expression of their flanking genes (1). Previous studies have demonstrated that several MAR-binding proteins are dramatically dysregulated in tumours and often their expression is significantly correlated with a more aggressive phenotype (2). In human prostate cancer cells, we showed that there is a direct relationship between complexity of NM protein composition and cellular aggressiveness and that the interactions of NM with MAR sequences decrease in androgen-independent compared with androgen-dependent cells. These changes were synchronous with modifications in the nuclear distribution of the MAR sequences and with an increase in the chromatin loop size (3). Our findings prompted us to further investigate the MAR-NM proteins bond in an *in vivo* model, to evaluate its role in the development and progression of prostate cancer (PCa). *Materials and Methods:* Benign prostatic hyperplasia (BPH) and PCa were obtained from patients who had undergone radical prostatectomy for biopsy-proven PCa. Normal tissue (N) was collected from patients undergoing cystectomy for bladder cancer. NM proteins were extracted from different prostate tissues and MAR-NM proteins bond was characterized using a proteomic approach along with two-dimensional Southwestern analysis. For binding experiments, a highly repetitive bent DNA sequence of 370-bp (XmnI) containing a Base Unpairing Region was used as a probe. *Results:* On average 676 protein spots were detected in the NM isolated from normal (N), 804 from BPH and 1105 from PCa, showing that tumour tissue is characterized by a more complex NM protein pattern. Several spots corresponding to hnRNPs, Lamin A and B, MARPa, MARPb, Matrin3, SATB1, PARP-1 and PARP-2 strongly bound XmnI sequence. These proteins match those already identified in the prostate cancer cell lines (3). Moreover, a smaller number of spots bound the MAR sequence both in PCa with respect to N tissue and in aggressive (Gleason 8, 9) compared with more differentiated (Gleason score ≤7) PCa. These results demonstrate that, also *in vivo*, a loss of differentiation is accompanied by a remodelling of nuclear organization. PARP-1 and PARP-2 were the MAR-binding proteins that underwent more evident changes. Their expression levels progressively increased from N to BPH to PCa and the interactions with MAR sequence were strongly depended on tumour aggressiveness. Then, we examined PARP-1 and PARP-2 expression in 21 men with PCa, by immunohistochemical analysis. Positive nuclear staining was found in all samples and the proteins were significantly ($p<0.0001$) overexpressed in PCa with respect to BPH. No correlation was observed with Gleason score, but the expression of PARP-1 and PARP-2 was significantly ($p<0.05$) higher in the patients with seminal vesicles involved (n=4). To explore the role of PARP-1 and PARP-2 in PCa progression, human prostate cancer cells were treated with the PARP inhibitor ABT-888. A reduction in cellular viability was observed when androgen-independent PC3 cells were incubated with 10 μM ABT-888 for 72 h. In contrast, no effect

was seen on androgen-dependent LNCaP cells. Moreover, the treatment significantly inhibited PC3 cell migration and decreased the average loop size. These results suggest that PARP inhibition might lead to a less aggressive phenotype. *Conclusion:* Our study provides evidence that MAR-binding proteins are involved in the development and progression of PCa. PARP-1 and PARP-2 are the proteins that undergo major changes. They could play a key role in the compartmentalization of chromatin and in triggering a more aggressive phenotype. Thus, they could provide the basis for a new therapeutic approach to the treatment of PCa.

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TRIMODAL TREATMENT OF MUSCLE INVASIVE BLADDER CANCER IN ELDERLY PATIENTS

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Aim: To evaluate the effectiveness of trimodal treatment in elderly patients unfit to surgical therapy, pursuing organ preservation. *Patients and Methods:* Ten patients (six men and four women) with a histological diagnosis of muscle-invasive urothelial carcinoma of the bladder, were selected for trimodal approach and treated from June 2008 to December 2012. Cystectomy was evaluated for all patients, but considered not feasible for comorbidities. After TURB, patients were submitted to induction chemotherapy (two cycles with CDDP 60 mg/mq d.1 and gemcitabine 800 mg/mq d.1-8) before concurrent radio chemotherapy (CDDP 40 mg/mq weekly). In patients with elevated serum creatinine levels, carboplatin (AUC 5 for induction and AUC 2 for CCRT) replaced CDDP. Radiation therapy was performed with conventional fractionation (2 Gy per fraction) using 3D-CRT technique. The dose delivered to whole bladder was 66 Gy. Toxicities assessment was performed with clinical examination and weekly programmed blood samples, according to CTCAE scale (version 3.0). *Results:* Median age was 75 (range 68-82). There were no serious adverse events following TURB which limited the continuation of therapy. All patients completed both induction cycles and concurrent chemo-radiotherapy, with carboplatin administration for three of them. The genitourinary toxicity was G1 for seven patients, G2 for three. Rectal toxicity was G0 and G1, respectively for three and seven patients. At follow-up (median 24 months), seven patients showed no local recurrence, two presented lymph nodes metastases and one patient did not undergo planned visit. *Discussion:* Organ preservation therapies, in muscle invasive bladder tumors, have been developed for patients with severe comorbidities, such as elderly patients and all those who are not eligible for radical cystectomy (1). No uniform consensus has been reached about different options for preserving approach (partial cystectomy, TURB alone, TURB followed by chemo- or radiotherapy alone, *etc*.) (2). Considering the characteristics of our sample, consisting of elderly patients, we chose a maximal transurethral resection followed by cisplatin-based concurrent chemoradiotherapy. For this approach low-moderate toxicities are described (3) while being potentially curative. *Conclusion:* Our clinical data confirm the feasibility of the trimodal treatment in selected elderly patients unfit to surgical therapy. Organ preservation was obtained with a low incidence of side effects. The results encourage a multidisciplinary approach.

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FIBRONECTIN (FN) AND UROTHELIAL DAMAGE SECONDARY TO ADJUVANT INTRAVESICAL THERAPY

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Introduction and Objectives: Intravesical chemotherapy has been proven effective in preventing recurrence of low-risk non-muscle invasive bladder cancer (NMIBC). BCG is

recognised as the best conservative treatment for intermediate and high risk NMIBC. Maintenance for at least one year is required to ameliorate the efficacy of adjuvant therapy. Discomfort and toxicity often cause interruption of adjuvant therapy, BCG particularly. Almost 50% of the patients undergoing BCG does not complete one year. A biomarker of urothelium damage would be helpful for timely detection of toxicity in order to ameliorate patient's tolerance and compliance. The aim of the present study was to evaluate the gene expression of Fibronectin (FN) in bladder washing in relation with local toxicity due to adjuvant intravesical therapy. *Patients and Methods:* Out of 26 asymptomatic patients undergoing intravesical prophylaxis with mitomycin (40 mg/40 ml), epirubicin (80 mg/50 ml) or BCG Connaught (81 mg/50 ml) and 10 volunteers as control group, 62 samples of bladder washing were collected before, during and after therapy. The samples were analyzed by isolation of cellular RNA using a miRNeasy Mini Kit (Qiagen®). FN gene expression was analyzed by RT-PCR. The ΔΔCt method after normalization with endogenous reference 18s rRNA was adopted. An average Ct value for each RNA was obtained for triplicate reactions. Local toxicity was classified into 3 grades: 0-1. mild (no medical therapy); 2. moderate (medical therapy); 3. severe (instillation postponed for 1-2 weeks or intravesical solution of hyaluronic acid and chondroitin sulphate administered). *Results:* FN gene expression, compared to controls, was increased 1.1 fold after TUR and before intravesical therapy. During therapy it remained unchanged (1.0 fold). However it was increased 1.1 fold in absence of local toxicity, but to a median value of 3.6 fold in presence of severe toxicity. Particularly, the mean values, compared to controls, were 2.4 (range: 0.3-6.1), 1.1 (range: 0.1-2.3), 9.3 (range: 0.2-45.2), before therapy, in absence and in presence of local toxicity, respectively. Of interest, patients receiving intravesical hyaluronic acid and chondroitin sulphate solution showed a median FN gene expression of 0.2 fold (range 0.1-0.7), decreasing from 3 to 0.6 and from 4 to 0.2 fold in two patients contemporary with symptomatic relief. *Discussion:* Few studies have correlated the gene expression of FN to bladder urothelial damage, in interstitial cystitis (1). FN plays an important role on BCG activity (2). A marker of topical toxicity would be helpful to improve the tolerance and to reduce the drop-out rates of intravesical therapy. The measurement in bladder washing is a simple and direct evaluation of urothelial FN gene activity. This method avoids all the bias due to the evaluation of FN protein expression in urine. The overexpression of FN gene indicates the presence of urothelial damage and activation of repairing processes. Normal and downexpression indicate the absence or healing of urothelial damage. Preliminarily, our study shows a significant correlation between FN gene expression on bladder washing and local toxicity. Furthermore, FN seems to be reduced by the intravesical administration of intravesical hyaluronic acid and chondroitin sulphate solution. *Conclusion:* FN gene expression in bladder washing emerges as a simple and promising marker of urothelial damage. Further and larger studies should be justified.

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RADIOGRAPHIC RESPONSE ASSOCIATED TO SUNITINIB RECHALLENGE IN METASTATIC RENAL CELL CARCINOMA

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Background: Sunitinib is an oral multi-target inhibitor of the platelet-derived growth factor (PDGF) and the vascular endothelial growth factor (VEGF) receptors, as well as other tyrosine kinases. Although sunitinib yields a prolonged disease stabilization in the majority of patients, its use in renal cell carcinoma is inevitably associated to onset of resistance and requirement of salvage therapy. Mechanism of resistance to anti-VEGF targeted agents are distinct from those related to chemotherapy agents. As an example, in RCC xenograft models, the majority of the changes in gene expression associated to resistance to sorafenib, are reversed by reimplantation of the resistant xenografts into untreated mice. In humans, Grunwald *et al*. reported that 12 of 13 patients with prolonged PFS associated to first line sunitinib (median, 21 months), showed clinical benefit associated to third line re-exposure to sunitinib (median PFS, 6.9 months) after an mTOR inhibitor. We present a case showing a radiographic

response and a prolonged disease stabilization associated to re-exposure to sunitinib in the fifth line setting. *Case Report:* In November 2009, a 72-year old female patient with metastatic (lung, adrenal gland) renal cell carcinoma at good prognosis according to MSKCC criteria started sunitinib at standard doses, but stopped it after 7 cycles due to uncontrolled mucositis, hypertension and hypothyroidism. After receiving temsirolimus, sorafenib and everolimus, she was started on sunitinib in July 2013 at reduced doses (37.5 mg 4 weeks on, 2 off). She had osseous and lung metastatic disease at the time of sunitinib rechallenge. She obtained a confirmed radiographic response according to RECIST 1.1 criteria in the lung lesions as best response. As of February, 2014 the patient is still on sunitinib and has not experienced disease progression. *Conclusion:* Sunitinib rechallenge can be a powerful therapeutic option in selected cases and requires further assessment in a clinical trial.

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AKT ACTIVATION IS INVOLVED IN OLEATE-INDUCED DOCETAXEL RESISTANCE IN ANDROGEN-INDEPENDENT PROSTATE CANCER CELLS

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Objective: To define characteristics of the first cycle of intermittent androgen deprivation (IAD) that would predict outcomes in a long term follow-up. *Materials 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, chromogranina 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 an 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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OLEATE INCREASES SIRT-1 EXPRESSION IN PROSTATE CANCER CELLS

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Background: One increasingly interesting area in prostate cancer (PCa) research deals with the effects of dietary lipids on prostate cancer biology and clinical outcome in patients. Recently, some authors interestingly showed that prostate tumor cells have low glycolysis and glucose uptake rates, resulting in the dominant uptake of fatty acids over glucose. These studies suggest that catabolism of fatty acids, not glucose, may be the dominant bioenergetic source in prostate cancer and thus be an important fuel source for cell proliferation. Nevertheless, molecular mechanisms involved are still not clear. SIRT1, a highly conserved NAD+-dependent protein deacetylase may be a good candidate to investigate, since it was regulated by nutrient availability and plays an important role in PCa. SIRT-1 up-regulation promote cell growth and chemoresistance in DU145 and PC3 androgen-independent cells. Therefore, we aimed to investigate whether SIRT1 could mediate the effects of free fatty acids on prostate cancer cell. *Methods and Results:* We treated DU145 and

PC3 cells with oleate 200 μM for 24 h and we found an up-regulation of SIRT1 expression compared to control by immunoblotting analysis. This up-regulation is associated with increased proliferation and resistance to docetaxel treatment. *Conclusion:* These findings suggest that SIRT-1 may be a key player in the molecular link between metabolism, diet and prostate cancer.

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STONE FORMATION FROM INTRAVESICAL HEM-O-LOK CLIP MIGRATION AFTER ROBOT-ASSISTED LAPAROSCOPIC RADICAL PROSTATECTOMY

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Background: The spread of robotic and laparoscopic prostatectomy and the increased interest in hemostatic alternatives to suture ligation, technically time requiring, and to cautery to prevent any possible injury to the neurovascular bundles resulted in a wider use of HOLCs for ligation of the vasa deferentia, seminal vesicle arteries, and prostatic pedicles. Complications related to this commonly used device that has been shown to be safe and reliable for vascular control are rare and often represented by clip migration. *Methods and Results:* A 69-year-old man with a diagnosis of prostate cancer cT1cN0M0 with PSA 8 ng/ml was treated with a bilateral nerve sparing robotic radical prostatectomy; pathology showed a Gleason score 6 (3+3) disease, confined to the prostate (pT2c). PSA at 6 mth was 0.02 ng/ml. Hemostasis was achieved by using a combination of suture ligation, bipolar cautery, and different size of HOLC. In particular HOLC were used for control of pedicles of the prostate avoiding to use clip near the bladder neck. Six months after RARP, the patient presented to hospital with dysuria and decreased force of the urine stream. Imaging studies showed intravesical stone measuring 2 cm × 2 cm. He underwent a cystourethroscopy that demonstrated a normal-looking urinary sphincter and bladder and confirmed the presence of a HOLC which caused a stone formation. The stone was treated with Thulium laser cystolithotripsy procedure, after stone fragmentation, the HOLC was removed by stone forceps.The patient was discharged the following day, and the condition noted in his complaint disappeared 1 week later. *Conclusion:* Complications related to hem-o-lok clip migration are rare, anyway they can be serious and require surgery, we may prevent part of these adverse events removing all Hem-o-lok clips that are not adequately deployed at the time of surgery

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ABIRATERONE ACETATE IN CHEMO-NAÏVE ELDERLY PATIENTS: A SMALL ITALIAN EXPERIENCE

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Introduction: The androgen deprivation therapy (ADT), achieved by surgical or medical castration, is the standard of care in the initial management of advanced and metastatic prostate cancer. Medical castration is obtained combining LHRH analogs and anti-androgens but almost all treated patients with distant metastases develop a castrate-resistant prostate cancer (mCRPC) within 18-24 months. Currently, chemotherapy with taxanes is the standard of therapy in mCRPC patients. Two recent phase III trials have showed that abiraterone acetate (AA) and enzalutamide are able to prolong survival in patients failing to docetaxel. Recently in Europe, AA with prednisone has been approved for treatment of mCRPC in asymptomatic or mildly symptomatic chemo-naïve patients, while in Italy its use is still limited due to the current non-reimbursement of

the drug from the Italian Drug Agency. With these premises, we present two cases of elderly men with mCRPC observed in our institution. Although in both cases, the use of AA occurred only after docetaxel, they may represent two examples of treatment with AA in pre-docetaxel setting, due to the small cumulative dose of Docetaxel that they have received. *Patients and Methods:* Two Caucasian male patients of 86-years-old (patient A) and 90 years-old (patient B), respectively, underwent prostate biopsy due to an increasing PSA level (10-20 ng/ml) resulting in prostatic adenocarcinoma Gleason's score 7 (4+3) and 5 (3+2), respectively. Patient A received first an hormone therapy (HT) and he underwent RT only fifty-two months later when disease became symptomatic. Seventy-six months after diagnosis a bone scan revealed multiple bone metastases and the patient received palliative RT and started ADT. Eight months later a biochemical and radiological skeletal disease progression occurred. Patient B had an intermediate-risk prostate cancer and he received loco-regional RT in association with ADT. Two months after radiotherapy, a bone scan performed due to onset of pain revealed multiple bone metastases. The patient underwent palliative RT on pelvis and continued ADT. Twelve months after the diagnosis, a bone progression occurred. Both patients started a first-line chemotherapy with weekly docetaxel (30 mg/m^2). Chemotherapy was discontinued after only one dose due to intolerable haematological toxicity and severe gastro-intestinal toxicity (according to the Common Terminology Criteria for Adverse Events), respectively. Therefore, the patients received AA 1000 mg daily plus prednisone 5 mg twice daily. At the starting time they had an Eastern Cooperative Oncology Group performance status grade of 1. Biochemical response (with a >50% PSA decline) and a radiological stable disease as best response after 16 and 24 weeks of treatment was observed, respectively. Neither dose reductions nor treatment delay due to toxicities were required. The patients are currently alive and asymptomatic after 7 and 8 months of therapy, respectively. They are still on treatment. *Conclusion:* The trend toward the PSA response and to delay the pain onset observed in our two patients is consistent with the outcome reported in the earlier phase III study. It is early to venture a conclusion about the radiological PFS data, being our two patients still in treatment. However, AA was confirmed to be a well-tolerated drug even in our two elderly patients.

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NEOADJUVANT TEMSIROLIMUS IN ADVANCED RENAL CELL CARCINOMA: A CASE REPORT

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Background: Cytoreductive nephrectomy improves survival of patients with locally advanced or metastatic renal cell carcinoma (RCC). The combination of neoadjuvant therapy and surgery can optimize the outcome of patients with potentially unresectable primary renal tumors. *Case Report:* We report the case of a 62 years-old man, with a medical history of type 2 diabetes mellitus in therapy with oral glucose-lowering drugs. In September 2011, complained of haematuria, he performed a CT scan which showed a right renal lesion (13×10×9.5 cm) extended into ileopsoas muscle and vascular structures with venous tumor thrombi from the renal vein into inferior vena cava but not beyond Gerota's fascia. Further more, CT scan showed lymph nodes in the left obturatory and in the lomboaortic sites of about 10 mm and 15 mm, respectively. The patient was considered inoperable at surgical evaluation and he underwent to a CT guided renal biopsy resulting of renal cell carcinoma. He was classified in poor-risk group according to the MSKCC and Heng's score criteria: low Karnofsky performance status (70%); serum haemoglobin less than the lower normal limit (11.4 g/dL); time to diagnosis to treatment of less than 1 year (2 months) and high lactate dehydrogenase (632 U/L). Considering of the inoperability and the analysis of prognostic factors, he started Temsirolimus at the standard dose of 25 mg in a weekly intravenous infusion until January 2012. A total of 10 courses was administrated and the main toxicity experienced was hyperglycemia of grade 2 (according to the Common Terminology Criteria for Adverse Events) that no required dose adjustment or dose interruption but only the modification of oral antidiabetics. No haematuria was recorded. In February 2012 a spiral CT showed a large area of necrosis in the right renal lesion, a size reduction of lomboaortic lymph nodes (10 mm); no evidence of left obturatory lymph nodes and no change in caval thrombus was observed. Thus, the patient underwent to a radical right nephrectomy and tumor thrombectomy. No post-surgery complications was reported. Histological examination documented clear-cell renal carcinoma (ypT3b pN0 - stage III according to AJCC). After surgery, the patient began a follow-up program. Currently, no evidence of disease is documented and it has been achieved an overall survival of 27 months. *Conclusion:* Treatment with temsirolimus is safe and well tolerated and able to facilitate nephrectomy without increase surgical complications. The role of neoadjuvant therapy in

patients with locally advanced or metastatic RCC is not well-defined; largest studies to identified the duration of therapy, the timing of surgery and the selection of patients who may benefit from neoadjuvant therapy are needed.

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PATIENT'S COMPLIANCE TO BCG. DO WE ADEQUATELY CONSIDER IT?

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Introduction: Several studies and meta-analysis demonstrated that BCG is the best treatment for conservative management of high-risk NMI-BC with a net benefit in terms of both recurrence-free and progression-free survival (1, 2). Maintenance lasting minimum one year is recommended. In spite of the effectiveness, the amount of patients who complete the manteinance schedule does not exceed 50% (3). The reasons of BCG maintenance interruption remain still unclear. The aim of our study was to investigate the causes of low adherence to 1-year full dose maintenance BCG in a large series. *Patients and Methods:* The clinical files of consecutive patients affected by T1 HG NMI-BC and undergoing adjuvant BCG for one year, between 2000 and 2012, were reviewed. Main exclusion criteria were presence of Tis, previous T1 HG, number of tumors more than 3 and diameter greater than 3 cm, genitourinary tract infections or other disease potentially impacting tolerability and compliance to BCG. One-year BCG maintenance was scheduled according to the South West Oncology Group (SWOG) including 3 weekly instillations at 3, 6 and 12 months starting 21-40 days after TUR. No dose reduction was considered. Both local and systemic side effects and any reason of treatment suspension were recorded. BCG tollerability was classified in four grades: 0. no need of postponement, 1. one-week postponement, 2. two-week postponement, 3. one single instillation omitted, 4. definitive stop. *Results:* The files of 545 consecutive patients with HG NMI-BC, selected for conservative management at two tertiary referral centers were reviewed. Out of them, 411 patients (75.4%) satisfied the inclusion criteria. The induction cycle was completed and suspended by 380 (92.5%) and 31 (7.5%) patients respectively. Suspension was due to toxicity in 20 (4.8%) and to no toxicity-related reasons in 11 (2.6%) patients. Maintenance was initiated by 308 (74.9%) patients while 72 (17.5%) never started. Particularly, 32 (8.4%) patients refused it due to personal choice and/or practical limitation, 22 (5.8%) were withdrawn by the urologist before the first planned 3-week cycle due to persistent haematuria or early recurrence and 18 more patients (4.7%) never started and were lost at follow-up. Out of the 308 patients starting the 1-year maintenance, 215 (52.3%) patients completed it, while 93 (30.2%) did not. The manteinance regimen was interrupted by 9 patients (9.7%) due to recurrence, while 14 (15.1%) experienced grade 3 toxicity and 55 (59.1%) refused it in absence of grade 2-3 toxicity or other evident causes. Grade-I toxicity and/or mild side effects, not responsible for maintenance treatment modification, were recorded in 193 (62.7%) patients. *Discussion and Conclusion:* The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) recommend one year BCG maintenance as the elective intravesical adjuvant regimen in intermediate- and high-risk NMI-BC, conservatively treated. The scientific urologic community does not consider BCG-related toxicity as the major limiting factor. In the present study patient's compliance during the induction cycle reached 92%. However during the interval between the induction course and the first maintenance instillation, 50 patients (13%) became reluctant to treatment while 22 (6%) were excluded after cystoscopy for suspicious bladder lesion. Toxicity (moderate to severe) was responsible for the interruption of BCG maintenance only in a low number of patients. The high rate of patients who abandoned the treatment could be attributable to the persistency of mild symptoms causing consistent discomfort that justified the reluctance to carry on the therapy. Moreover the inadequate counseling in everyday clinical practice when compared to multi-institutional trials should be taken into account. A structured periodical counseling and a timely recognition and treatment of symptoms, might significantly ameliorate the acceptance of BCG maintenance.

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IMPACT OF PRE-OPERATIVE HEMOGLOBIN VALUES AND PERI-OPERATIVE BLOOD TRANSFUSION ON CANCER SPECIFIC AND OVERALL MORTALITY AFTER RADICAL CYSTECTOMY FOR BLADDER CANCER: RESULTS FROM A SINGLE INSTITUTION COHORT

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Introduction: Few studies investigated the impact of peri-operative blood transfusions (PBT) on cancer-specific (CSS) and overall survival (OS) in the context of bladder cancer (Bca). However, none of those have taken into account the role of pre-operative hemoglobin levels (Hb), which has been suggested to be related to systemic disease dissemination. Accordingly, the aim of the study was to evaluate the impact of both Hb and PBT on CSS and OS in patients treated with radical cystectomy (RC) for BCa. *Methods:* The study cohort included 1575 patients treated with RC for BCa between 1990 and 2012 at a single tertiary referral center. Complete clinical, pathological and follow up-data were available for all the patients. First, Kaplan-Meier curves were employed to assess the CSS and OS rates in the overall cohort. Subsequently, univariable (UVA) and multivariable (MVA) Cox regression analyses were used for prediction of CSS and OS. First the effect of PBT and Hb on CSS and OS were analyzed separately. Finally, both the variables were included in the same model. Covariates consisted of patient age at surgery, Hb, PBT, pathological T stage, pathological N stage. *Results:* Mean age at RC was 67 years. Overall, 580 (36.8%) patients received PBT (mean number of blood units received: 3). Mean and median Hb values were 12.4 and 12.6 mg/dL (range 8.0-17.5 mg/dL), respectively. With a mean follow-up time of 41 months, the 2 and 5 years CSS and OS were 83.1 *vs*. 75.2 and 68.3 *vs*. 59.8%, respectively. At UVA, patients who received PBT had a 2-fold higher risk of succumbing to CSM (HR: 2.11; $p<0.001$) and OM (HR 1.98; $p<0.001$) compared to patients who did not receive any PBT. Similarly, patients with higher Hb levels were more likely to succumb to CSM and OM than patients with lower Hb values (HR 0.84 and 0.85; all $p<0.001$). At MVA, both PBT and Hb were significantly associated with CSM and OM when included in different models (all $p\leq0.02$). Conversely, when both variables were included in the same model, only Hb remained significantly associated with CSM and OM (HR 0.89 and 0.91 respectively; all $p\leq0.03$). *Conclusion:* Despite the influence of PBT on CSM and OM which appears to be relevant even in bladder cancer, its effect on oncological outcomes disappears when Hb is taken into account. Further studies are needed to further investigate the possible immunosuppressive effect of PBT as well as the role of Hb and systemic dissemination of BCa.

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THE IMPACT OF NUMBER OF LYMPH NODE REMOVED IN THE DETECTION OF LYMPH NODE METASTASIS: A SENSITIVITY CURVE ANALYSIS

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Introduction and Objectives: To assess the correct number of lymph nodes (LNs) to be removed at Radical Cystectomy (RC) to ensure an accurate lymph nodes metastasis (LNM) staging. *Patients and Methods:* Between 1995 and 2012, 1016 RC for bladder cancer (BCa) were performed at a single tertiary care institution. Demographical, clinical and pathological variables were recorded for each patient. The relationship between the number of removed LNs and the probability to have LNI at final pathology examination was assessed in receiver operating characteristic (ROC) analyses. The ROC curve coordinates were used to graph the probability of finding LNI according to the number of removed and examined LNs. *Results:* Among the patients who underwent cystectomy, the prevalence of LNM was 35.7% (363 of 1016). T stage, grade, LVI, LND removed, type of BCa at last TUR and N Radiological Stage is strongly associated with LNM (all $p<0.001$). Gender, age at surgery and Carcinoma in Situ (CIS) at RC were not statistically significantly different between patients with or without pathologically confirmed nodal metastasis. ROC curve analyses were used to explore graphically the relationship between the numbers of removed and examined LNs and the probability of finding one or more metastatic LN in the overall population and in specific

subpopulations. The curve indicated that 38 and 45 LNs need to be removed to achieve a 90% and 95% probability respectively of detecting one or more metastatic LNs considering the whole population. If we consider N radiological status, less than 13 LNS need to be removed to achieve 95% of sensitivity in detecting LNM if N radiological status is positive. *Conclusion:* Our results show that it is necessary to extend lymphadenectomy in order to improve the sensibility in staging LNM. Considering overall population, it could be appropriate to remove not less than 25 LNs. Additionally, more extended staging lymphadenectomy could be appropriate in selected cases in which, based on clinical information (such as pre operative CT scan) there is a low probability to have LNM.

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IMPACT OF PREOPERATIVE THROMBOCYTOSIS ON PATHOLOGICAL OUTCOMES AND SURVIVAL IN PATIENTS TREATED WITH RADICAL CYSTECTOMY FOR BLADDER CARCINOMA

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Purpose: The aim of this study was to investigate the impact of pre-operative platelet count on pathologic findings at the time of RC for BCa and post-operative CSS and OS. *Patients and Methods:* A total of 906 consecutive patients treated with RC for Bca between 1995 and 2012 at a tertiary referral center were included in the study. Thrombocytosis was defined as >400.000 platelets/μL, in agreement with the standard assumed by the central laboratory of our institution. UVA and MVA logistic regression analyses were used to investigate the impact of pre-operative platelets count on pathologic stage. UVA and MVA Cox regression analyses were also adopted to predict both CSS and OS. *Results:* Mean age at cystectomy was 67.25. The mean and median platelet counts were 242.100 and 227.500. At mean follow-up time of 41 months, the 2 and 5-year cancer-specific and overall survival were found to be 83.1% and. 75.2% and 68.3 and 59.8%, respectively. At UVA analysis, thrombocytosis count was significantly associated with adverse pathologic disease stage ($p \leq 0.007$) and lymph node invasion ($p=0.05$). Platelet count was significantly associated to patient survival at UVA analysis (HR 1.76 and 1.39 for OS and CSS, respectively; all $p<0.05$). At multivariate Cox regression analysis, platelet count was documented to be significantly related only to the OS (HR 1.64,1.03-2.81; $p=0.05$). *Conclusion:* Pre-operative platelet count should be taken into account as a predictive factor of post-operative oncologic outcomes after radical cystectomy for bladder cancer and patients should be counseled accordingly.

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IS [11C]CHOLINE PET/CT ABLE TO MODIFY TREATMENT VOLUMES, DOSES AND PLANNING STRATEGY IN PROSTATE CANCER PATIENTS ELIGIBLE FOR RADICAL RADIOTHERAPY?

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Introduction: [11C]choline PET/CT has been emerging as a valid diagnostic tool for prostate cancer patients. Purpose of the present study is to assess the impact of [11C]choline PET/CT in decision making strategy for prostate cancer patients treated with radical radiotherapy (RT). *Patients and Methods:* Patients older than 18, with histologically proven prostate cancer who were eligible to receive radical RT were evaluated for this analysis. All patients underwent [11C]choline PET/CT for pre-treatment staging and simulation procedures to define treatment volume and prescription dose for RT. The clinical target volume (CTV) 1 and 2 were the prostate and, when indicated, seminal vescicles treated with doses of 73.5Gy and 60Gy respectively; CTV3 involved pelvic lymph node region, included in treated volumes in case of adverse risk factors with a total dose of 54 Gy. In case of positive lymph nodes at [11C]choline PET/CT, the volume that encompasses choline avid nodes (biological target volume: BTV) was contoured and treated with a total dose of 66Gy. The treatment was delivered to CTV1-CTV2-CTV3 and BTV in the same number of fractions (30) with simultaneous integrated boost technique by means of Volumetric Modulation Arc Therapy (VMAT-RapidArc©). *Results:* From May 2012 to December 2013, 50 consecutive prostate cancer patients were treated with radical RT and evaluated for this analysis in our department. The median Gleason Score was 6 (range 6-9), while the median value of prostate specific antigen (PSA) was 6 ng/mL (range 2.6-45.5). The median age at the moment of radiation oncologist evaluation was 74 years (range 60-81). In 8/50 patients (16%) the RT strategy was modified in terms of volumes and doses according to the [11C]choline PET/CT results. In fact, a BTV was integrated in the treatment planning and dose prescription schedule of all the 8/50 patients. With a median follow-up of 16 months

(range 3-22), no biochemical progression was found. *Conclusion:* Our experience confirmed how the implement of [11C]choline PET/CT can affect treatment strategy in terms of target definition, dose prescription and subsequently treatment planning. In particular, in the 16% of the evaluated patients, a high dose volume encompassing avid lymph nodes was added in the treatment. Further studies are necessary to assess if the introduction of [11C]choline PET/CT can have an impact also on clinical outcome.

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NERVE SPARING BUNDLE DISSECTION TO STATE THE TRAINING LEVEL OF THE ROBOTIC TRAINEE SURGEON

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Introduction: Over the past decade, there has been a widespread adoption of Robot Assisted Laparoscopic Prostatectomies (RALP) which determined a centralization of prostate cancer (Pca) surgery in high volume centers. Potential limitations contrasting this diffusion include cost, increased operative time, and a necessary "learning curve" (LC). As a result high-volume-robotic-surgery centers are supposed to solve the challenging task of incorporating this costly new technology into residency/fellowship training programs. The aim of this study is to guarantee acceptable perioperative outcomes meanwhile respecting the safety of the patient. Robotic training program paradigms have already been described and consist in achieving mastery in bedside assistance as the first goal and only afterwards the training at the console, according to the "step by step" method. In this way, the learning process is gradual, requiring an effort in developing skills and strategies, being thus safe for the patients and suitable to be standardized. It seems that trainees should not negatively interfere with the immediate perioperative outcomes (1) unless the nerve sparing (NS) step is considered (2). In fact, it was shown that, during the training, the operative time for each step decreases except for NS bundle dissection reflecting thus a higher accuracy and longer time spent to improve the quality of the dissection and guarantee the expected outcome (3). *Materials and Methods:* We retrospectively reviewed the first 20 RALP, 10 NS and 10 non NS (NNS) of six robotic surgery trainees. Immediate perioperative outcomes such as operative time, blood loss (BL), positive surgical margins rate (PSM) (as oncologic outcome surrogate) and the length of hospital stay (LOS) (as complication rate surrogate) were analyzed, together with data about erectile function (EF) maintenance or recovery. *Results:* Results are reported in Table I. Their descriptive analysis discloses a difference according to the rate of NS procedures

Table I.

Trainee	NS PSM (n°/5)		EBL (mL)		LOS (days)		Op. time curve (min gained(-) lost (+)/each procedure)	Potency	
	1-5	6-10	1-10	11-20	1-10	11-20		1-5	6-10
Ve	4	1	256	355	2.5	2.8	+1'	1 1 ? 1 1	0 0 0 0 1
Br	1	1	155	125	2.7	2.2	-2'	1 0 1 1 1	1 0 1 1 1
Bo	2	3	195	216	2.6	2.4	-0.7'	1 0 1 1 1	1 1 0 1 1

NNS / NS ≤ 1

Trainee	NS PSM (n°/5)		EBL (mL)		Hospital Stay (days)		Op. time curve (min gained(-) lost (+)/each procedure)	Potency	
	1-5	6-10	1-10	11-20	1-10	11-20		1-5	6-10
Ma	1	2	305	188	3.7	2.7	-5.9'	0 0 0 1 1	1 0 1 0 1
Ro	1	0	225	230	3.5	2.4	-4.2'	0 1 1 0 0	1 1 0 1 0
Co	3	1	195	175	2.5	2.3	-3'		

NNS / NS > 1

performed during the very first five and the second five procedures. BL, LOS, PSM-rate, and especially the overall operation time show improvement with time only in trainees performing more NNS procedures in their first 5 procedures. In this group, recovery of the EF improved after the first five NS procedures. *Discussion and Conclusion:* NS dissection of the bundles during RALP strongly impacts on the maintenance and/or recovery not only of EF, but also of continence. From our data, during the first part of the LC the NNS procedures should be preferred as a different approach to the NS bundle dissection, improving both the immediate outcomes of the procedure and the specific NS outcome, *i.e.* the EF preservation. In fact, operative time decrement ($p<0.05$), BL ($p<<0.05$), PSM rate and LOS evidently improved if during the first 10 RALP, the NNS procedures prevailed over the NS procedures. Even if EF maintenance rate is comfortable in both groups, the improvement occurred only in the latter LC setting (NNS/NS>1). A correct NS procedure intended as having a predictable outcome (EF preservation and no PSM) should be the final aim of the LC.

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EARLY AND COMPLETE CLINICAL RESPONSE TO SUNITINIB IN A PATIENT WITH METASTATIC RENAL CANCER

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Background: In recent years, targeted agents have replaced cytokine therapy as the standard of care for patients with mRCC. Targeted agents have substantially improved patient outcomes, but despite great improvements in the management of metastatic clear cell renal carcinoma, complete responses with antiangiogenic therapies are infrequent. Sunitinib is a multitarget tyrosine kinase inhibitor whose activity has been demonstrated in phase III and 2 expanded-access studies. In the present paper, we report the early and complete clinical response of multiple 3 metastases from a clear cell renal carcinoma after treatment with sunitinib. *Case Report:* On May 2001, a 45-year-old male patient with no significant comorbidities, was referred to the surgical department because of a 2 months history of abdominal pain that was refractory to symptomatic treatment; CT scan showed a right kidney neoplasm of 67x64 mm. He underwent a right radical nefrectomy and lymphadenectomy. Final pathology documented a clear cell renal cancer, Fuhrman grade 2, pT1bN0. After 6 years, during the follow up, the patient presented left rib pain. He performed a CT-scan which showed multiple metastases localized in left adrenal gland and bone (tenth left rib). On August 2007 he underwent left adrenalectomy and surgical removal of the posterior arch of the tenth left rib. Pathological examination showed metastasis of clear cell carcinoma. Th patient was referred to our oncology department. We decided to start treatment with IL-2 that the patient has performed from October 2007 to April 2008. On June 2008, a CT-scan showed multiple metastases localized in pancreas, renal lodge and left paracolic recess. The patient had a Karnofsky performance status of 100; both clinical examination and blood chemistry including Hb, LDH and calcium were normal. Considering the good performance status of patient, the absence of serious comorbidity, the good Motzer risk group, after cardiological assessment with ECG and echocardiography, on June 2008 he was placed on 50 mg sunitinib daily in a six weeks cycle according to a 4/6 schedule (4 weeks on treatment: 2 weeks off treatment). After 2 cycle, a CT-scan showed complete response of pancreatic, renal lodge and left paracolic recess. The patient was in ECOG PS 0 and asymptomatic, referring mild diarrhea. Patient continued treatment with sunitinib. On April 2011, the patient referred grade 2 mucositis, grade 2 Hand-Foot Syndrome, mild asthenia, and he was placed on 50 mg sunitinib daily in a three weeks cycle according to a 2/3 schedule (2 weeks on treatment: 1 weeks off treatment). On July 2011, hematological exam showed hypothyroidism and the patient started treatment with levotiroxine. A CT-scan performed on November 2011, showed complete clinical response. Patient continued treatment with sunitinib and periodic CT-scan that confirmed complete response disease. On November 2013, the patient referred grade 2 diarrhea, grade 2 mucositis, mild asthenia, grade 2 Hand-Foot Syndrome, and he was placed on 37.5 mg sunitinib daily in a three weeks cycle according to a 2/3 schedule (2 weeks on treatment: 1 weeks off treatment). A CT-scan performed on November 2013, showed complete clinical response. Up to now (February 2014) the patient is continuing sunitinib treatment according to a 2/3 schedule. There is a good control of arterial blood pressure, no electrocardiographic or echocardiographic alterations and

blood chemistry is normal. The patient is in good performance status (Karnofsky 100), with good tolerability. Last CT-scan demonstrated no disease recurrence. *Conclusion:* This case is an example of how the treatment with sunitinib can lead to a prolonged and complete clinical response with a good quality of life.

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PREDICTORS OF UPGRADING/UPSIZING IN LOW-RISK PROSTATE CANCER PATIENTS ON ACTIVE SURVEILLANCE: VALIDATION OF A MODEL

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Introduction: Prostate biopsy findings at diagnosis and during follow-up are essential criteria in Active Surveillance (AS). In a previous work (Nicolai *et al*. Eur Urol Suppl 2013) upgrading (UPG) and upsizing (UPS) at 1-year rebiopsy resulted to be independent outcomes with different, and sometimes opposite, risk factors. In that frame a combined model was also proposed to predict the probability of dropping out of AS starting from the separate probabilities of UPG and UPS. The aim of the present work is to validate the combined model in an independent population. *Materials and Methods:* The PRIAS-Siuro-ITA population was considered for external validation. Model for UPG considered: age (continuous variable, risk factor, OR=1.06), PSA density (continuous variable, OR=1.02) and prostate volume (>60cc, OR=0.2). The model for UPS included: age (continuous variable, protective factor OR=0.97), >5% core length containing cancer (5%core, OR=2.8), >1 positive cores at diagnosis (OR=1.6). Using the two separate models for UPG and UPS, the new combined model (OUT) for PCa reclassification after 1 year AS is given by P(OUT)=1–{[1–P(UPG)]×(1–P(UPS)]} (AUC=0.63). Performance on the independent population was evaluated through AUC and calibration. *Results:* 183 patients were included in the validation, 29/183 UPG and 15/183 UPS were registered. Distribution of clinical variables in this population is given in Table I. In the validation population, risk factors for UPG and UPS were confirmed, with Odds Ratios very similar to those of the original model (Figure 1a and 1b), with the only exception of prostate volume >60 cc and maximum core involvement which here have OR=0.6 and OR=1.04, respectively. AUC

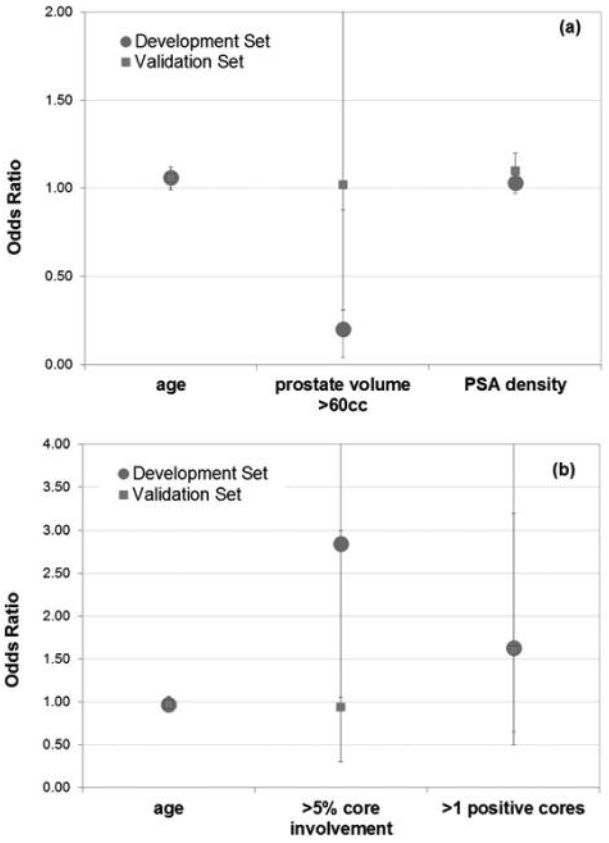

Figure 1. *(a) ORs for UPG model; (b) ORs for UPS model.*

was 0.62 (combined model) fairly the same as in the development population. Calibration was satisfactory (Figure 2). *Conclusion:* One-year biopsy is the main reason of withdrawal from active surveillance protocols due to increase of cancer volume (upsizing) and/or increase of grade (upgrading). External independent validation confirmed that factors predicting UPG *vs*. UPS are different, leading to consider these events as clinically separate.

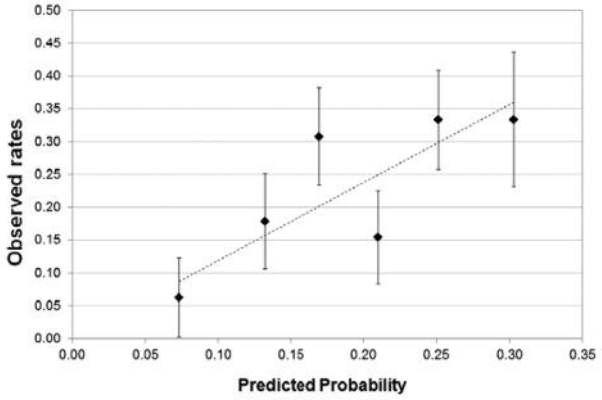

Figure 2. *Calibration plot for the PRIAS-Siuro ITA validation population.*

Table I. *Distribution of clinical variables in the validation population.*

	Minimum	Maximum	25th perc	Median	75th perc
Age (years)	42	80	60	65	70
Density (ng/ml/cc)	0.01	0.3	0.08	0.11	0.15
PSA (ng/ml)	0.5	10.0	4.3	5.6	6.7
Prostate volume (cc)	10	140	37	47	61
Stage			T1c=94%	T2a=6%	
Number of positive cores at diagnosis			1=67.2%	2=32.8%	

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LATE RECTAL TOXICITY AFTER RT FOR PROSTATE CANCER: CASES OF PATIENTS WITH MODERATE/SEVERE BASAL SYMPTOMS

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Aim: To evaluate long term late rectal bleeding and late fecal incontinence after high-dose RT for prostate cancer in a population of patients with moderate/severe gastrointestinal (GI) symptoms before RT. *Materials and Methods:*A prospective multicentre observational study was previously conducted with the aim of finding clinical/dosimetry predictors of late rectal toxicity. Late toxicity was evaluated with a self-reported questionnaire filled in by the patients before RT and at different times up to 7 years after RT. The delivered doses ranged between 70 and 80 Gy (1.8-2.0 Gy/fr). Individual information on co-morbidity, previous abdominal surgery, use of drugs and rectal DVHs was available. Predictive models for toxicity were previously developed for the population with no/mild basal GI symptoms. We here consider the subpopulation of patients with moderate/severe basal GI symptoms and the evolution of rectal morbidity in this group. *Results:* 1132 patients were enrolled in the trial, 81/1132 (7%) had moderate/severe basal GI symptoms (including high stool frequency, diarrhoea, tenesmus, rectal pain, rectal bleeding and fecal incontinence). 48/81 patients have data at 3 year follow-up, while 29/81 have 7 year follow-up information. In particular 10/81 patients exhibited severe basal fecal incontinence (use of pads) and 5/81 reported daily rectal bleeding before RT. 8/10 patients with severe fecal incontinence at RT beginning still had this complain one month after RT end, while at 3 year follow-up nobody in this group had moderate/severe incontinence, with only one patient exhibiting chronic grade 1 incontinence at 7 year follow-up. 2/5 patients complaining with severe rectal bleeding at RT beginning still had daily bleeding one month after RT end. At 3 year follow-up no grade 2-3 bleeding was registered in this subgroup and at 7 year follow-up no rectal bleeding at all was scored. The rates of grade 2-3 bleeding and incontinence in this population (48 patients having 3 year follow-up) were 6.3% and 2%, respectively. These rates were very similar to those that were registered for the population having no/mild symptoms at the basal level (7% and 3% for bleeding and incontinence, respectively). Due to the very low number of events, it was not possible to look for clinical/dosimetric predictors of late toxicity in this particular cohort. *Conclusion:* The availability of a large prospectively followed cohort of patients gave us the almost unique possibility to focus on the evolution of rectal toxicity after RT for prostate cancer for patients

exhibiting moderate/severe GI symptoms before RT. The results suggested that severe fecal incontinence and bleeding registered at RT beginning had a transient nature which was not exacerbated by RT dose. The 3 year incidence of late rectal bleeding and fecal incontinence in this particular cohort was very similar to that reported for the cohort of patients with no/mild basal GI symptoms (*i.e.* 6% and 2%, respectively).

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POST OPERATIVE CLINICAL OUTCOME IN PATIENTS 75 YEARS OLD AND OLDER TREATED WITH RADICAL CYSTECTOMY

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Objective: We have reviewed post operative complications, morbidity and clinical outcome in 34 patients 75 years old and older who were treated with radical cystectomy and urinary diversion in our Hospital from 2009 to 2013. *Methods:* Between January 2009 and December 2013, of 93 patients who underwent radical cystectomy, 30 men and 5 women were aged from 75 to 84 (median 79.59 years). Urinary diversion (25 UCS and 8 Bricker) was performed in 33 cases and bladder substitution in 2. All patients had significant comorbidity: 6 patients were ASA II, 22 were ASA III and 7 ASA IV. The median value of pre-operatory hemoglobin was 11.65, and of albumin 3.26 (5 patients had Hb <10 g/dl and 3 patients had albumin value <3.0 g/dl. *Results:* Median operating time was 225 minutes. Peri-operative mortality rate was 0%. Early post-operative complications occurred in 17 patients (50%). The most common early complications were problems of surgical wound (41%), disorientations (15%), dyspnea (14%), prolonged ileus (11%), heart cardiology and I.R.A. (8%). No secondary procedures were necessary. 9 patients (26%) had hypoalbuminemia marked (<2.6 g/dl). *Conclusion:* Radical cystectomy can be performed in elderly patients with acceptable peri-operative mortality and morbidity. However, because of the high incidence of minor medical complications, hospital stay is often prolonged, and significantly higher in patients with complications.

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CLINICAL AND DOSIMETRIC PREDICTORS OF ACUTE URINARY SYMPTOMS AFTER RADICAL RADIATION THERAPY FOR PROSTATE CANCER

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Introduction: A cohort multi-centric study started in 2010 with the goal of developing predictive models of genito-urinary (GU) toxicity and of erectile dysfunction after high dose radiotherapy (RT) for prostate cancer. The aim of this ad-interim analysis was to assess correlations between acute urinary symptoms as measured by the International Prostate Symptom Score (IPSS) at RT end and clinical/dosimetric risk factors. *Materials and Methods:* IPSS was prospectively filled in at start and end of RT; absolute (cm^2) bladder dose-surface parameters referred to the weekly delivered dose (DSHw) were chosen as dosimetric descriptors. Relevant clinical factors were prospectively collected: T stage, concomitant morbidities and drugs, use of hormonal therapy (AD), previous surgery, smoking, alcohol, age and BMI. Backward feature selection based on prediction optimization (minimization of residual) was used to select variables to be included in logistic models predictive of symptoms corresponding to the questions of IPSS questionnaire: moderate-severe symptoms (scores 3-4) were considered as end-points. KNIME software was used (KNIME GmbH, Germany). *Results:* By November 2013, 339 patients were enrolled in eight Institutes. Clinical/endpoint data were available for 264 patients: 140 treated at 2Gy/fr (70-80Gy) and 124 at 2.5-2.7Gy/fr (65-74Gy). Observed rates of moderate/severe symptoms were: frequency 19%, intermittency 13%, urgency 17%, weak stream 23%, straining 8%, nocturia 21%. Focusing on the stronger predictors, smoke emerged for frequency (OR=2.6), intermittency (OR=2.3) and urgency (OR=2.4); AD for intermittency (OR=4.5); T stage for urgency (OR=2.6) straining (OR=4.4) and nocturia (OR=2.1). DSHw parameters were correlated to an increased risk of all symptoms, while basal conditions were highly

important for weak stream and nocturia. All results were confirmed when excluding patients with severe symptoms before RT. Full models are presented in the Table I. *Conclusion:* Specific acute urinary symptoms are related to several clinical factors and DSHw parameters; nocturia and weak stream are significantly influenced by the basal condition.

Table I. *full multivariable models for acute urinary symptoms after radiotherapy for prostate cancer.*

S11.5w (continuous variable)	1.02	1.04-0.99
Intermittency (AUC=0.72)		
Smoke	2.3	8.7-0.63
Lymph node RT	1.4	4.8-0.43
Androgen Deprivation	4.5	20.4-1.00
S11.5w (continuous variable)	1.02	1.06-0.99
Urgency (AUC=0.70)		
Smoke	2.4	7.4-0.80
T stage (2-3 *vs*. 1)	2.6	7.2-0.92
S6w (continuous variable)	1.01	1.01-1.00
Weak stream (AUC=0.70)		
Basal weak stream	1.5	2.0-1.15
Use of antihypertensive drugs	1.5	3.6-0.59
S6w (continuous variable)	1.01	1.01-1.00
Straining (AUC=0.78)		
Alcohol	2.1	9.5-0.45
T stage (2-3 *vs*. 1)	4.4	24.5-0.80
S12.5w (continuous variable)	1.04	1.09-0.99
Nocturia (AUC=0.80)		
Basal nocturia	2.4	4.5-1.5
T stage (2-3 *vs*. 1)	2.1	6.5-0.9
S11.5w (continuous variable)	1.02	1.05-1.00

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SUNITINIB (SU) RECHALLENGE IN METASTATIC RENAL CELL CARCINOMA (MRCC): A SINGLE INSTITUTION EXPERIENCE

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Background: Introduction of target agents has radically changed mRCC treatment and many agents are available today. Inhibition of Vascular Endothelial Growth Factor (VEGF) and mammalian Target of Rapamycin (mToR) pathways represent the best strategies to treat these patients (pts) (1). SU, an oral inhibitor of the tyrosine kinase portion of VEGF receptors family, represents a standard of care in first-line mRCC therapy for good/intermediate prognosis pts (2). Unfortunately, despite of initial benefits, disease progression occurs in all pts due to onset of resistance mechanisms. In absence of a clear therapeutic sequential algorithm, mRCC treatment strategy is represented by an empiric, alternate, sequence of all available drugs. The precise mechanism by which a tumor who has progressed to a previous anti-VEGF agent then responds to the administration of a second one, still remains unclear. Basing on these concepts, it has been proposed that rechallenge with SU in pts who have progressed to a previous anti-VEGF molecule could be a reasonable therapeutic stategy (3). *Patients and Methods:* From January 2011 to January 2013 pts receiving SU rechallenge (50 mg/daily, 4 weeks on - 2 weeks off schedule) as their third line treatment for mRCC have been included in our evaluation of activity (in terms of objective responses), efficacy (both in terms of Progression Free Survival and Overall Survival - PFS and OS respectively) and safety [grade (G) 3-4 toxicities were evaluated]. *Results:* Number of pts was 9 (M/F: 6/3), median age 67 (range 43-75), Eastern Cooperative Group (ECOG) Performance Status (PS) 0-1 (7 pts) or 2 (2 pts). 4 pts had received prior surgery (nephrectomy) with radical intent, 3 pts had received palliative nephrectomy. Metastatic sites were represented by liver (5 pts), lung (6 pts), lymphnodes (6 pts), bone (2 pts) and 5 pts had multiple metastatic sites. Memorial Sloan Kettering Cancer Center risk's category was favorable/intermediate in 2/7 pts respectively. All pts received SU as first line treatment, while second line treatment was represented by Sorafenib/Pazopanib/Everolimus in 3/1/5 pts respectively. 3 partial responses (including 1 patient with stable disease during first-line SU), 4 stable disease and 2 progression disease were obtained and radical lombo-aortic lymphnodes surgery was performed in 1 patient due to major response. Median PFS was 7 months (range 2-10), 6 pts received further lines of treatment after SU discontinuation and median OS was 12 months (range 5-16). Treatment was mildly tolerated and no G4 toxicities were observed. G3 toxicities were represented by fatigue, hypertension, hand-foot syndrome, diarrhea, neutropenia and mucositis in 3/2/4/3/1/1 pts respectively. One patient needed treatment discontinuation due to concomitant G3 hand-foot syndrome, diarrhea and neutropenia, while schedule modification (50 mg/daily, 2 weeks on - 1 week off) was necessary in 2 pts due to toxicities. Moreover 2 pts needed Sunitinib dose reduction at 37.5 mg/daily. *Conclusion:* Overcoming resistance to previously administered agents, represents a hot topic in mRCC treatment. Our single institutional experience shows how rechallenge with SU may represent a valid therapeutic option in the course of global mRCC therapeutic strategy. Pts who have previously progressed to SU may have further benefit in terms of response and survival to re-exposure to the same agent, without worsening of toxicity profile. Further and larger investigations are needed to recognize which group of pts could benefit most from SU rechallenge.

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PROGNOSTIC IMPACT OF RETURB ON HIGH GRADE T1 BLADDER CANCER

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Objective: To evaluate whether pathological outcomes of ReTURB have a prognostic impact on recurrence and progression of primitive T1G3 bladder cancer. *Patients and Methods:* Patients affected by primitive T1G3 TCC of bladder underwent ReTURB. Patients with muscle invasive disease at ReTURB underwent radical cystectomy; those with non-muscle invasive residual (NMI-RT) and those with no residual tumour (NRT) received an intravesical BCG therapy. We compared recurrence and progression in NMIRT patients and NRT patients at restaging TURB. Patients were followed every 3-6 months with cystoscopy and urine cytology. *Results:* 212 patients were enrolled in the study. At Restaging TURB residual cancer was detected in 92 of 196 (46.9%) valuable patients: 14.3% of these were upstaged to T2. Histological results of Returb are shown in Table I. At follow up of 31.8 months, there were differences in recurrence and progression rates between NRT and NMIRT patients: 26.9% and 45.3% ($p<0.001$), 10.6% and 23.4% (p 0.03), respectively. Recurrence-free and progression-free survivals were significantly higher in NRT compared to NMIRT patients: 73.1% and 54.7% ($p<0.001$), 89.4% and 76.6 (p 0.03), respectively (Table II). *Conclusion:* ReTURB allows to identify a considerable number of residual and understaged cancer. Patients with NMIRT on ReTURB have worse prognosis than those with NRT in terms of recurrence and progression free survival. These outcomes seem to suggest a prognostic impact of findings on ReTURB that could be a valid tool in management of high grade T1 TCC.

Table I. *Histological outcomes of ReTURB.*

Stage and grade	pts (n)
T0	104
TaG1 (+CIS)	6 (1)
T1G1	4
T1G2 (+CIS)	1 (2)
TaG3	1
T1G3 (+CIS)	39 (2)
CIS	8
T2	28

Table II. *Outcomes of NRT and NMIRT patients.*

	NRT	NMIRT	*p*-Value
Pts (n)	104	64	
Age (years)	69.3±9.9	70.6±9.0	0.38
Mean follow up (months)	34.8±24.0	22.8±15.6	0.005
Multifocality at first TURB (%)	23.1	31.2	0.28
Recurrence rate % (n)	26.9 (28/104)	45.3% (29/64)	<0.001
Progression rate % (n)	10.6 (11/104)	23.4 (15/64)	0.03

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ZERO ISCHEMIA LAPAROSCOPIC PARTIAL NEPHRECTOMY: PRELIMINARY EXPERIENCE

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Introduction: Nephron sparing surgery is now reference standard for many T1 renal tumors. Although hilar clamping creates bloodless operative field, it necessarily imposes kidney ischemic injury. “Zero ischemia” partial nephrectomy allows to eliminate ischemia during nephron sparing surgery. We report our preliminary experience of “zero ischemia” laparoscopic partial nephrectomy realized by controlled hypotension. *Patients and Methods:* Patients with a single, clinical T1 tumor were candidates for “zero ischemia” laparoscopic partial nephrectomy. High-risk patients with severe, preexisting, cardiopulmonary, cerebrovascular, or hepatorenal dysfunction were not eligible. The preoperative work-up comprised medical history, physical examination, routine laboratory tests and CT scan or MRI. A transperitoneal approach was performed in all patients; four or five laparoscopic ports were inserted. The hilar vessels were

prepared in the event that bulldog clamping might subsequently be needed. Intraoperative monitoring included electrocardiogram, central venous pressure (CVP), electroencephalographic bispectral (BIS) index (BIS monitor™), NICOM (non invasive cardiac output monitoring), urinary Foley catheter. A controlled hypotension, to carefully lower the mean arterial pressure (MAP) while maintaining excellent systemic perfusion, was maintened at approximately 60 mmHg. To induce hypotension, the doses of inhalational isoflurane were increased. The renal lesion was excised using cold endoshears. Upon completion of tumor excision, blood pressure was restored to preoperative levels. Parenchyma was repaired with Vicryl™ sutures arrested with absorbable clips and Hem-O-lok™ . Biologic hemostatic agents were applied to the resection bed. *Results:* 27 patients affected by renal tumor (8 right, 19 left) underwent zero ischemia LPN. Mean age and mean BMI were 57.6 (±9.8) years and 27.7 (±7.2). ASA score was 1, 2 and 3 in 1, 13 and 13 patients, respectively. Renal score was 6 (4 pts), 7 (4 pts), 8 (3 pts), 9 (12 pts), 10 (2pts), 11 (2 pts) Mean tumor size was 41.6 mm (±18.6). Operative time, blood loss, ΔHb were 117 min (±45.9), 217 ml (±254.6), 2.0 gr/dl (±0.9), respectively. Blood transfusion was necessary in 2 patients. In all cases the procedure was performed without clamping. Hospital stay was 6.8 (±2.8) days. Three patients (11%) developed postoperative complications: 2 fever and 1 urine leakage managed conservatively (Clavien grade 1). Histological evaluation revealed 4 Oncocytomas, 1 AML, 22 RCC (15 pT1a, 7 pT1b). *Conclusion:* Zero ischemia LPN seems to be a safe and reproducible technique that allows sparing renal parenchyma and preserve renal function.

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STEREOTACTIC BODY RADIATION THERAPY IN THE TREATMENT OF OLIGOMETASTATIC PROSTATE CANCER: DEFFERING ANDROGEN DEPRIVATION THERAPY

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Objectives: In patients with metastasized prostate cancer Androgen Deprivation is considered the first line treatment. We investigated the role of Salvage Stereotactic Radiotherapy for patients with limited prostate cancer metastases to defer the initiation of palliative Androgen Deprivation Therapy (ADT). *Patients and Methods:* Between March 2009 and January 2013 a cohort of 25 patients with up to 3 synchronous Lymph node prostate metastases diagnosed on positron emission tomography (37 lesions with a median volume of 12.03 cc, range 0.66-111.67), following biochemical recurrence after local curative treatment were treated with Cyberknife Stereotactic Body Radiotherapy in our Center. The mean age of patient population at the time of the Cyberknife treatment was 68 years (range 55-84). Cyberknife prescription doses were 3000-3600 cGy delivered in 3 consecutive fractions of 1000-1200 cGy. The dose was prescribed to the mean 80% isodose by use on a non isocentric Cyberknife treatment technique. In 14 lesions (37%) Cyberknife Stereotactic Radiotherapy Treatment (SBRT) was performed as reirradiation (the recurrent lesion was situated in the previously irradiated volume). Clinical progression was defined as the detection of local progression or distant disease at reassessment. In case of an oligometastatic recurrence outside the previous Stereotactic Body Irradiated field, a re-treatment was performed. Androgen Deprivation (ADT) was initiated if more than 3 metastases were detected during follow up even if patients were still asymptomatic. Toxicity was scored using the Common Terminology Criteria for Adverse Events. *Results:* The Cyberknife treatment was well tolerated without any acute or late toxicity at all. There were no in field recurrences, resulting in a local control of 100%. Eleven and 3 patients, respectively required a second and third salvage treatment for metachronous metastatic disease. The median time to clinical progression was 13 months (range 4-30). After a median follow up of 30 months (range 12-50) the median time Androgen deprivation therapy (ADT) was deferred by 24 months *Conclusion:* The recent evidence of the potential toxic nature af Androgen Deprivation Therapy (ADT) suggests that effective local therapy might reduce the burden of systemic therapies usually given to patients with metastatic prostate cancer. Cyberknife salvage Hypofractionation Stereotactic Body Radiotherapy is a safe and effective treatment option in patients with lymph node prostate metastases and could defer initiation of palliative Androgen Deprivation Therapy.

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TREATMENT OF PROSTATE CANCER NODAL RECURRENCES BY TOMOTHERAPY

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Introduction: The management of biochemical failure after primary treatment in prostate cancer is hormonal therapy. When patients become castration resistant the next step involves hormonal manipulation of second level and after then

chemotherapy. The possibility to retard the use of hormone therapy using a local treatment, particularly in oligometastatic patients with a low growth disease, could turn away the starting of systemic treatment, and could prolong the bDFS. *Patients and Methods:* In this retrospective study, we analyzed 21 of 29 patients treated from 2010 by radiotherapy (RT) for prostate cancer with nodal relapse on pelvis and/or lumbar-aortic chain, detected at choline –PET-CT, that received previous radiotherapy associated with neoadjuvant, concomitant and adjuvant hormonal therapy, or prostatectomy with or without adjuvant radiotherapy and adjuvant hormonal therapy. 12 patients had a biochemical recurrence after the primary treatment and they were treated by salvage hormonal therapy. They started RT when they became castration resistant. All patients were treated with intensity-modulated radiotherapy technique (IMRT) with simultaneous integrated boost (SIB) on the PET positive nodes using helical @TomoTherapy and daily image guidance (IGRT) technique by megavoltage CT. Treatment consisted of one session per day for five days a week. The prescribed doses were:66-70.4 Gy/30-32 fractions on the prostate bed, 51-54 Gy/30-32 fractions on the pelvis, 51-54 Gy/30-32 fractions on the lumbar-aortic chain and 60-66 Gy/30-32 fractions on PET-positive nodes. *Results of radiotherapy:* In the 12 patients who started RT when they were in hormonal escape after primary treatment, the average DFS was 12.4 months (SD: 3-32 months). Eleven patients continued OT after RT until last follow up. All patients had a local complete response to radiation treatment but 13 had a recurrence of disease, confirmed by choline PET-CT, always outside the treatment field. The time to biochemical relapse was 10.3 months (SD 3-18 months). The DFS in patients without evidence of disease was 21.9 months (SD 10-38 months). The gastro-intestinal, genito-urinary, haematological acute and late toxicity was low and no toxicity of grade >2 was observed. *Discussion and Conclusion:* Several studies have been published treating the only positive nodes by stereotactic technique. The results, initially exciting, have not been confirmed for long time, because patients recurred quite quickly. On the base of this observations we believe that the treatment of the whole nodal areas with prophylactic doses, in association with the boost on the PET positive nodes, could consolidate the local treatment, reducing the risk of relapse in sites near the positive nodes. The setting of our patients included overall poor cases: we observed a 62% of relapsed disease, with a 17% (2/12) of patients free also if they were in hormonal escape before radiotherapy. If we considered only castration non-resistant patients, we oberved a 67% (6/9) of response. This setting of patients was certainly the group that can better benefit from local RT. Our approach results in a good response and an excellent tolerance to treatment, pointing out that the poor results of previous studies were not only due to the stage of disease but also due to the inadequacy of target delineation and treatment technique. Local radiotherapy should be considered before hormonal therapy in oligometastatic patients as part of a multidisciplinary management, but a longer follow up is necessary to confirm these results.

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PROSTATE HYPOFRACTIONATED STEREOTACTIC ABLATIVE BODY RADIOTHERAPY: DISEASE CONTROL AND QUALITY OF LIFE AT 6 YEARS

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Objectives: Hypofractionated Stereotactic Radiotherapy treatment may yield disease control for prostate cancer without increasing treatment toxicity. We tested Cyberknife Stereotactic Body Radiotherapy Treatment (SBRT) in men with clinically localized prostate cancer. *Patients and Methods:* From July 2007 through September 2012 a retrospective analysis was carried out on 139 consecutive patients with a median age of 76 years (range 60-86) years, mean prostate volume of 64.7 cc (range 20.64-164.38), and clinically localized prostate cancer. Cyberknife was used to deliver fiducial based image guided Hypofractionated Stereotactic Radiotherapy. The majority of patients 73 (53%) were low risk, 40 pts (29%) were intermediate risk and 26 pts (19%) were high risk patients using the NCCN criteria. Pre-treatment PSAs ranged from 1.75 to 27.88 ng.ml (median 7.6 ng.ml). Among the entire study cohort 11 of 26 high risks patients received Androgen Deprivation Therapy (ADT), ADT was not administered to any low – intermediate risk patients. The course of radiotherapy consisted of 3800 cGy over four fractions given daily. Heterogenous dose planning was used, dose was normalized to the 80% isodose line in order for the prescription dose to cover at least 95% of Planning Target Volume (PTV). Real-time intrafractional motion tracking was used. *Results:* Acute urinary symptoms (frequency, dysuria, urgency, hesitancy and nocturia) were common with 51% of patients (71 pts) experiencing grade I-II RTOG toxicity. No patient experienced RTOG grade 3 acute urinary toxicity. In 22% of patients (31 pts) RTOG late grade I-II urinary toxicity was observed, in 5

patients (4%) RTOG late grade 3 urinary toxicity was recorded following repeated urological instrumentation, including cystoscopy and urethral dilatation. No RTOG grade 3 acute and late rectal toxicity was observed. Six patients (5%), one with prior Turp, experienced incontinence. PSA after Cyberknife stereotactic radiotherapy gradually fell to an overall median of 0.20 ng/ml, at 30 months The actuarial median follow up was 40 months (range 18-78 months). The six years actuarial psa relapse free survival rate was 96.1% (CI: 94.3%-97.9%) with 100% for low risk, 89.3% for intermediate –risk and 96.2% for high risk respectively. No added benefit of Androgen Deprivation Therapy (ADT) was observed for the high risk group. To date 5 patients failed biochemically. One intermediate risk patient revealed local relapse 30 months after Cyberknife treatment. Two patients developed bone metastases, one died; in 2 patients we observed lymph node dissemination. All patients are alive except for twelve that died of unrelated causes. *Conclusion:* Cyberknife Stereotactic Radiation Therapy produces excellent biochemical control rates at up to 6 years with mild toxicity and minimal impact on quality of life. PSA relapse free survival rates after Cyberkife radiotherapy compare very favourably with other radiation modalities and strongly suggest durability of results.

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LONG-TERM FOLLOW-UP AND HRQOL IN PATIENTS UNDERGOING RADICAL CYSTECTOMY: STATISTICAL AND CLINICAL ISSUES

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Introduction: Patients undergoing urinary radical cystectomy (RC) and urinary diversion for bladder cancer had some limitations in health-related quality of life (HRQOL). At present there are not sufficient studies to evaluate the levels of discomfort caused by different urinary diversion in survivors. The aim of this study was to evaluate differences in HRQOL between patients with bladder cancer undergoing orthotopic ileal neobladder (IONB) and ileal conduit (IC) after RC (1). *Patients and Methods:* A total of 319 consecutive patients with bladder cancer (271 males and 48 females) underwent RC from five urological academic centres with subsequent urinary diversion (171 with IONB and 148 with IC) from June 2007 to September 2012 with no evidence of tumor recurrences and with active follow-up were enrolled in this study. Clinical and pathological data as well as oncological outcome were retrospectively analyzed and compared. HRQOL was analyzed using Italian version of EORTC QLQ-30 and EORTC QLQ BLM30 questionnaires. Clinical data were analyzed in order to evaluate the HRQOL differences between the two groups of patients. As null hypothesis was assumed that there was no differences between two of the urinary diversion groups in terms of HRQOL. Means values with standard deviations (±SD) were assessed for all items. Wilcoxon rank test was used to verify differences between two diversion groups. Statistical significance was achieved if p-value was ≤0.05 (two-sides). *Results:* Patients who underwent IONB was youngest than IC patients: median age were 66 years (range: 31-83) and 71 (range: 49-95) respectively. No significant differences were found in the pTNM – UICC stage (stage 0-I were 36.8% for IONB and 33.8% for IC) and in the follow-up (38 months and 35 months for IONB and IC respectively). Patients with IC showed a significant worsening in physical functioning (80.8±22.2 *vs*. 74.7±24.8 - p=0.006), in emotional functioning (84.9±20.9 *vs*. 78.7±24.7 - p=0.02), in cognitive functioning (93.1±12.6 *vs*. 85.4±21.2 - p=0.0002) in comparison with IONB. Patients with IC had high level of troubles in fatigue (19.5±21.4 *vs*. 29.6±27.0 - p=0.0006), in dyspnea (12.9±22.1 *vs*. 20.5±27.1 - p=0.007), in appetite loss (6.7±17.2 *vs*. 14.2±27.5 - p=0.01), in constipation (16.0±21.4 *vs*. 31.5±34.7 - p<0.0001), and in abdominal bloating flatulence (11.8±19.9 *vs*. 25.5±26.5 - p<0.0001) in comparison with IONB. *Discussion and Conclusion:* The patients with IC showed a higher number of troubles in comparison with the IONB group. In particular the patients with IONB seem to be able to improve their activity during the life contrary to the IC group. Cystectomy with any type of diversion remains a complication-prone surgery, nevertheless our results showed that IC showed higher troubles than IONB.

1 Urology *74(5)*: 1138-1143, 2009.

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QUALITY OF LIFE IN 171 PATIENTS WITH BLADDER CANCER UNDERGOING ILEAL ORTHOTOPIC NEOBLADDER:

LONG-TERM RESULTS

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Introduction: Patients undergoing urinary radical cystectomy (RC) and urinary diversion for bladder cancer had some limitations in health-related quality of life (HRQOL). At present there are no sufficient studies to evaluate the levels of discomfort caused by different urinary diversion in survivors. In the present study we used the validated Italian version of QLQ-BLM30 to assess bladder cancer-specific HRQOL in patients with ileal orthotopic neobladder (IONB) after RC. *Patients and Methods:* From June 2007 to September 2012, a total of 171 consecutive patients with bladder cancer (156 males and 15 females), who underwent RC with IONB in five urological academic centres, were included in this study. All patients had no evidence of tumor recurrence and were actively followed-up. Clinical and pathological data as well as clinical outcomes were retrospectively analyzed. HRQOL was analyzed using Italian versions of the EORTC BLM30 questionnaires. Questionnaire results were analyzed in order to evaluate the HRQOL in patients with IONB at different times of follow-up (1-18, 19-36, 37-72 and ≥73 months). Mean values with standard deviations (±SD) were computed for all items. Wilcoxon rank test was used to verify differences by comparing the short follow-up (1-18 months, first quartile) with subsequent quartiles of follow-up. Statistical significance was achieved if p-value was ≤0.05. *Results:* The median age of the patients was 66 years. The pTNM–UICC stages were 36.8% (0-I), 46.2% (II), and 17.0% (III-IV stage). 17 (9.9%) patients underwent adjuvant chemotherapy. The median of follow-up was 38 months. The number of patients for each quartile of follow-up were: 43, 42, 35, and 51, respectively for 1-18, 19-36, 37-72, and ≥73 months. Our data showed that patients with a long-term follow-up (≥73 months) had an improvement in HRQOL in urinary symptoms in comparison with patients with short-term follow-up (1-18 months) (34.1±23.6 *vs*. 18.9±21.1 - p=0.0004) as well as in sexual life (96.9±8.5 *vs*. 83.7±25.2 - p=0.005). Conversely we found a worse HRQOL in patients with long-term follow-up regarding the abdominal bloating and flatulence (8.9±22.2 *vs*. 17.6±20.9 - p=0.003). In addition in patients with an intermediate follow-up (37-72 months) we found a poor HRQOL in body image (23.8±27.6 *vs*. 35.6±27.5 - p=0.02), and sexual functioning (13.8±23.8 *vs*. 21.9±24.5 - p=0.04). *Discussion and Conclusion:* The patients with IONB show a progressive decrease of limitations of HRQOL during the years demonstrating a high adaptability to the new body image. Our study based on long-term follow-up in patients undergoing RC with IONB showed improvement in HRQOL with regards to the role of urinary symptoms and sexual life.

1 Urology *74(5)*: 1138-1143, 2009

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SURFACE ACTIVATED CHEMICAL-IONIZATION ELECTROSPRAY-NIST PLATFORM IN THE STUDY OF PROSTATE CANCER CANDIDATE METABOLOMIC BIOMARKERS BY MASS SPECTOMETRY

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Introduction: Mass spectrometry is widely employed in the cancer biomarker discovery field, in particular for analysis of low molecular weight metabolic biomarkers (1). Serum and urine represent readily available and matrix containing metabolic products for metabolome biomarker discovery. However, two problems affect the metabolome analysis: 1) the sensitivity of the currently available mass spectrometers and 2) the need to normalize biomarker signals in biological fluids (2). *Materials and Methods:* We have used a Surface Activated Chemical Ionization-Electrospray mass spectrometry (SACI-ESI) coupled to NIST data elaboration system (the SANIST platform) to solve these tasks focusing on cancer biomarkers. The innovative Surface Activated Chemical Ionization - Electrospray technology increases instrumental sensitivity, picking up many more metabolites than traditional approaches (3). To validate the new approach, we performed MS profiles

on a panel of subjects including 15 patients with prostate cancer and 15 age matched controls. The Surface Activated Chemical Ionization-Electrospray mass spectra were elaborated with a bioinformatic SANIST platform. *Results:* The use of the NIST software automatically normalizes the analyte signal by performing the ratio with respect to different endogenous reference compounds. Here we demonstrate how the application of the SANIST platform to a search for markers of prostate cancer has yielded promising results. *Discussion and Conclusion:* SACI-ESI coupled to the SANIST platform can facilitate MS-based discovery of potential biomarkers in serum and urinary analysis. Combined with a bioinformatic approach based on NIST data elaboration for the analysis of the MS spectra obtained, the potential for developing biomarkers with diagnostic capabilities is demonstrated in a clinical cancer diagnosis setting.

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A MULTICENTRE RETROSPECTIVE STUDY ON IRRADIATE PROSTATE CANCER: PRELIMINARY REPORT

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Introduction: Large data collections are normally interrogated using statistical models or to build nomograms and/or practical indications about therapies. Much less often they are used to properly validate mathematical models founded on biological assumptions, and to estimate with great accuracy the values of biologically relevant parameters. In the framework of the European ICT Project CHIC (Computational Horizons in Cancer), focused on the building of a common repository for data and models in the field of human cancer, the activity of each research group is challenged by a number of requirements: - data should be representative; - data should be properly pseudo-anonymized to be shared among groups in different countries, with possibly different legal issues; - data should be collected in a database easily included into larger or more structured ones; - the database size and structure are selected in order to be able to host also diagnostic images and meta-data, provisionally available from further perspective studies or analyses; data should be easily queried, using different statistical tools and different data mining approaches; - data should be protected against (in)voluntary hackerage. *Patients and Methods:* EUREKA-2 is a retrospective study on irradiated patients; it was authorized last July 2013 by the Ethical Committee of the IRCCS Candiolo, lead institution of clinical studies. Data collection started August 1st, 2013 too and pertains to: anamnesis, diagnosis, biopsy, staging, radiotherapy technique and adjuvant therapies, clinical and serological follow-up, toxicity. The local researcher compiled the data based on local database or directly from the medical records. When the data is missing, the patient (or family) is contacted by phone providing the ability to send the PSA or

Table I.

Radiotherapy center	Town	Leader	Local researcher	No. of data in feb	Final expected n.
IRCCS-FPO	Candiolo	Gabriele P.	Garibaldi E./ Cattari G.	200	800
Ospedale Maggiore Or. Piedmont University	Novara	Krengli M.	Beldì	250	350
San Luigi Gonzaga Turin University	Orbassano	Ruo Redda MG.	Allis S.	40	150
Ospedale Civile	Ivrea	Girelli G.	----------	----	800
Ospedale degli Infermi	Biella	Moro G.	----------	180	180
Ospedale Cardinal Massaia	Asti	Tessa M.		90	180
Istituto Europeo di Oncologia -Univ. H.	Milano	Orecchia R. Prof.	Fossa J. B.	---	800
Osp. Santa Chiara Pisa -University H.	Pisa	Panichi		75	250
Osp. Castelli	Verbania	Ballarè A.	Bona MC.	---	120
Osp. S. Anna	Como	Cosentino D.	Balcet V.	50	500

The number of patients to be accrued by July 31th, 2014, is foreseen to range between 3700 and 4100.

other tests or to go to the radiotherapist. *Results:* At the end of February, only 885 cases were sent to central database. *Conclusion:* At the end of July all data will be sent to central database and they will be analyzed firstly in terms of biochemical free survival and overall survival; the second step will be the implementation of multivaried analysis and, lastly, data will be used to obtain predictive nomograms.

1 Gabriele P, Garibaldi E, Guiot C and Gabriele D: Studio osservazionale retrospettivo multicentrico per la definizione di modelli prognostici sul cancro prostatico in pazienti radiotrattati EUropean multicentric REtrospective study evaluating prognostic factors on prostate K (cAncer) in radiotreated patients - EUREKA-2.

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MULTIDISCIPLINARY MEETING IN UROLOGY: THE CANDIOLO CANCER CENTER 3 YEARS OF EXPERIENCE

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Introduction: There is evidence that multidisciplinary care has the potential to significantly increase quality of treatments and also survival. This approach has many advantages including decreasing the waiting time to treatment, improving diagnostic/therapeutic path and ensuring correct application of guidelines, reducing errors due to duplicate tests, fragmentation and variability between different specialists. Moreover it allows to facilitate timely the access to physical/psycho-emotional rehabilitation programs and palliative care, to improve the management of recurrent disease, to facilitate enrollment in innovative and experimental therapies, to improve the education of involved health personnel in patients care and finally to increase patients satisfaction. *Patients and Methods:* In our Institute we started with urological multidisciplinary meetings in 2002. Until 2009 the staff included the Urologist, the Radiation Oncologist and the Medical Oncologist. Then, from middle 2010 the meetings were opened to other specialists involved in management of urological cancers as the Nuclear Medicine Physician, Radiologist and Nurse. Additional members are pathologist and member of the palliative care team. At the meeting is generally participating the patient and his family. Now the meeting is planned weekly, in the afternoon of Wednesday, for a total number of 45 meetings for year. In order to obtain our data we reviewed retrospectively the list of all patients who were evaluated in the context of our multidisciplinary visits. *Results:* From January 2011 to December 2013 we have seen globally 795 patients affected by urological cancers (70% prostate cancer, 12% bladder cancer, 12.5% kidneys cancer, 5% testicular cancer and 0.5% penis cancer). The number of patient is regularly increased from 2010 to 245 in 2011, to 263 in 2012 and lastly to 287 in 2013. *Conclusion:* Advantages of multidisciplinary meetings in our Institute can be summarized as follow: 1. Optimization of staging protocols in prostate in particular for the implementation of PCA3 test, multiparametric MR and choline PET in diagnosis, IMRT-IGRT in therapy; 2. Reduction of waiting time to start therapy for chemotherapy and palliative care; 3. More easily participation to international and national protocols, at present: 10 for medical oncology, 6 for radiotherapy, 2 for surgical oncology and 4 for radiology; 4. Organization of a regional scientific event in October 2012 and a post ASCO GU in April 2014. 5. Publication of papers related to prostate disease in international journals (1-3).

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PIEDMONT MULTICENTRE RETROSPECTIVE STUDY ON OPERATED PROSTATE CANCER: FIRST REPORT

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Table I.

Participating Hospital	Town	Unit Director	Local researcher	No. of cases in Feb	Final expected n.
Ospedale Molinette University	Torino	Gontero P.	Fiorito/Berta	400	500
San Luigi Gonzaga University	Orbassano	Porpiglia A.	Manfredi	110	550
Ospedale Maggiore University	Novara T	errone C.	Zacchero	185	350
Ospedale San Giovanni Bosco TO	Torino	Muto G.	Collura	360	360
Ospedale Santa Croce Cuneo	Cuneo	Arena G.	---	75	350
Ospedale Regionale AO	Aosta	Benvenuti S.	Gillo	50	200
Ospedale Gradenigo	Torino	Randone D.	Carchedi	120	400
Ospedale Cardinal Massaia	Asti	Bardari F.		125	175
Ospedale Civile/ASL Torino 4	Ivrea/Cirié	Annoscia S.	Genesi/Bellei	240	350
Ospedale Santissima Trinità	Borgomanero	Monesi G.	Arancio	25	250
Ospedale Maria Vittoria	Torino	Moroni M.	Gabriele	125	145
Ospedale Mauriziano	Torino	Comi L.	Carchedi	110	110

The number of patients to be accrued by july 31, 2014 ranges between 3750 and 4000.

Introduction: A great extent of "hidden" knowledge is potentially available querying properly the clinical data from patients affected by the same disease. Large data collections are normally interrogated using more or less complicated statistical models or to build nomograms and/or practical indications about therapies. Much less often they are used to properly validate mathematical models founded on biological assumptions, and to estimate with great accuracy the values of biologically relevant parameters. In the framework of the European ICT Project CHIC (Computational Horizons in Cancer), focused on the building of a common repository for data and models in the field of human cancer, the activity of each research group is challenged by a number of requirements: - data should be representative (similar in pertinence, accuracy, provenience, without bias in selection and treatment); - data should be properly pseudo-anonymized to be shared among groups in different countries, with possibly different legal issues; - data should be collected in a database easily included into larger or more structured ones; - the database size and structure are selected in order to be able to host also diagnostic images and meta-data, provisionally available from further perspective studies or analyses; - data should be easily queried, using different statistical tools and different data mining approaches; - data should be protected against (in)voluntary hackerage. *Patients and Methods:* EUREKA-1 is a retrospective study on prostatectomised patients: data collection started August 1st, 2013 and pertains to: anamnesis, diagnosis, biopsy, staging, radical prostatectomy and adjuvant therapies, pathology, clinical and serological follow-up, toxicity. The local researcher compiled the data based on local database or directly from the medical records. When the data is missing, the patient (or family) is contacted by phone providing the ability to send the PSA or other tests or to go to the urologist. *Results:* At the end of February the number of cases sent to central database is 1965, about half of the expected as the goal. *Conclusion:* At the end of July all data will be sent to central database and they will be analyzed firstly in terms of biochemical free survival and overall survival; the second step will be the implementation of multivariate analysis and, lastly, data will be used to obtain predictive nomograms.

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LONG PROGRESSION FREE SURVIVAL WITH AXITINIB IN HEAVILY TREATED PATIENT WITH CHROMOPHOBE RENAL CELL CARCINOMA

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Introduction: Axitinib is an oral second-generation selective inhibitor of vascular endothelial growth factor receptors approved for the treatment of advanced renal cell carcinoma. Recently, the results of a head-to-head phase III trial comparing axitinib to sorafenib as upfront therapy in patients affected by mRCC have been reported. *Patients*

and Methods: We report the case of a 67-year-old man with chromophobe renal cell carcinoma with liver, scheletic and pulmonary metastases who received axitinib after failure of interferon, sunitinib, everolimus and capecitabine. His history included hypertension, cardiovascular disease and dyslipidemia. In 2001 the patient underwent resection of the lower pole of the right kidney for chromophobe renal cell carcinoma. In 2007, liver, bone and lung metastases occurred and the patient was treated with IFN and then with Sunitinib, Everolimus, and lastly with Capecitabine. In October 2012 following further progression, axitinib at a dose of 5 mg bid was started. *Results:* After three months of treatment with axitinib, computed tomography (CT) showed a decreased number and size of liver lesions and stability in other sites. Clinically, the patient reported significant improvement in pain symptoms resulting in reduction of the analgesic therapy. Overall, the patient continued treatment for 13 months. Treatment was well tolerated with manageable toxicities. In November 2013 the treatment was discontinued because of disease progression in the brain, liver, bone and deterioration of the clinical condition. *Conclusion:* Axitinib could be a therapeutic possibility also for the treatment of renal tumors of not clear cell histology. The activity of axitinib is retained even after more than one previous treatments. Further phase III studies are needed to confirm the activity of axitinib in this setting of patients.

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FIRST DESCRIPTION OF PRIMARY PERIVASCULAR EPITHELIOID CELL TUMOUR (PECOMA) OF THE PROSTATE: A CASE REPORT AND LITERATURE REVIEW

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Introduction: We report an interesting case of primary epithelioid cell tumor (PECOMA) of the prostate in a 79 year-old man with non neurogenic male lower urinary tract symptoms secondary to prostatic obstruction. This patient underwent surgical intervention of transurethral resection of the prostate (TURP) because of non-response to drug treatment. Histological and immunohistochemical findings were consistent with perivascular epithelioid cell tumour. Perivascular epithelioid cell tumors, better known as PECOMAs, are mesenchymal tumors containing variable components of smooth muscle, fat and vessels. PECOMAs consist a very uncommon pathological finding. Perivascular epithelioid cell tumors are defined by the WHO as unusual mesenchymal tumors which present histologically and immunohistochemically distinctive perivascular epithelioid cells. PEC-derived tumors have been documented in various anatomical locations, including the uterus, skin, liver/falciform ligament, upper aero-digestive, bone, pancreas, colon. The uterus is the predominant site. In the genitourinary system, mostly urinary bladder, PECOMAS of the prostate are rare. This is the second report of a case definitively diagnosed as PECOMA in the prostate. *Case Report:* A 79-year-old man had a 3-years history of non-neurogenic male lower urinary tract symptoms (LUTS) secondary to prostatic obstruction not responsive to drug treatment with α- blockers and 5α-reductase inhibitors as a conservative treatment. He underwent transurethral resection of the prostate (TURP) because of non- response to conservative treatment. A pelvic transrectal ultrasound showed a gland of about 40 cc with some calcifications, without local lesions. The serum level of prostate-specific antigen was within normal limits, 2.3 ng/ml. The patient did not have tuberous sclerosis. The pathological findings were consistent with perivascular epithelioid cell tumour. Histological features showed aggressive behaviour, and the patient after oncology consulting underwent radiation treatment. Follow-up until December 2013 with cystoscopy and CT of the chest/abdomen/pelvis with intravenous contrast showed a disease-free survival. *Discussion:* PECOMAS are a family of mesenchymal neoplasms that have in common the presence of a unique cell type, the perivascular epithelioid cell (PEC). They are mesenchymal neoplasms that show dual differentiation with both melanoma and smooth muscle characteristics. PECOMAS include angiomyolipoma (AML), lymphangioleiomyomatosis (LAM), clear cell 'sugar' tumour of the lung and extra-pulmonary sites, clear cell myomelanocytic tumour of the falciform ligament/ligamentum teres and rare clear cell tumours of other sites. Recent molecular studies have shown that PECOMAS are linked to tuberous sclerosis, an autosomal dominant disease characterized by mutations or losses of TSC1 or TSC2 genes. PEComas have been described in different organs and are considered ubiquitous tumors. PECOMAs of the prostate are very rare. With only 1 case reported in the English medical literature. *Conclusion:* PECOMAs, also in the prostate, are malignant tumours. Their clinical behaviour varies widely. Despite the few cases in the literature and the absence of an established method of treatment, an aggressive surgery treatment is recommended.

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INFLUENCE OF PREVIOUS PELVIC RADIATION THERAPY IN THE OUTCOME OF RADICAL CYSTECTOMY

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Aim: To describe perioperative morbidity of radical cystectomy comparing patients with past medical history (PMH) of extravesical pelvic radiation therapy with patients never undergone radiation therapy. We particularly wanted to find pre-operative factors determining worse prognosis in radiotreated patients. *Patients and Methods:* We retrospectively collected data of any patients undergone radical or salvage cystectomy between January 2010 and January 2013. We analyzed the same parameters in both groups, radiotreated and not: indication to surgery, peri-operative complications according to Clavien-Dindo Classification of Surgical Complications (CDCSC), hospitalization time, bleeding and transfusions. We compared these parameters using Student *t*-test. *Results:* Between January 2010 and January 2013, 104 patients underwent radical cystectomy; first group of patients (GR 1) was made of naïfs patients for radiation therapy (n=89, 85.5%), second group (GR 2) was made of previously irradiated patients (n=15, 14.4%). Reasons for cystectomy in irradiated patients were: radiation cystitis (n= 3/15, 20%), bladder cancer (n=6/15, 40%), anal cancer (n=2/15, 13.3%), uterus cancer (n=2/15, 13.3%), prostate cancer (n=1/15, 6.6%), rectal cancer (n=1/15, 6.6%). We analyzed data separately for both groups. GR 1 showed mean age 72.19 (Standard Deviation, SD, 8.16), 75 males (84.27%) and 14 females (15, 73). Preoperative comorbidity according to Charlson Classification Index showed a mean score of 6.29 (SD 2.91). Urinary diversion was cutaneous ureterostomy (UCS) for 17 patients (19.10%), ileal conduit for 62 patients (69.66%), ileal neobladder (Y neobladder, Camey or Hautmann according to surgeon's preference) for 10 patients (11.24%). Mean preoperative Hemoglobin was 11,99 mg/dL (SD 1.72), mean hospitalization was 17.87 days (SD 13.87), mean number of blood sack transfusion was 2,27 (SD 2.58), mean day of return of normal bowel function was 5,79 (SD 2.32). GR 2 showed mean age 71,87 (SD, 9.2), 12 males (80%) and 3 females (20%). Preoperative comorbidity according to Charlston Classification Index showed mean score of 7.13 (SD 2.88). Urinary diversion was UCS for 5 patients (33.3%), ileal conduit for 10 patients (66.6%). No patient received ileal neobladder. Mean preoperative Hemoglobin was 10.9 mg/dL (SD 1.49), mean hospitalization was 29.87 days (SD 22.4), mean number of blood sack transfusion was 5.27 (SD 3.39), mean day of return of normal bowel function was 6.47 (SD 0.99). Surgical complicances, according to CDCSC, are reported in Table I for both groups. Preoperative comorbidities were assessed using Charlston Comorbidity Index: *t*-Student test showed no significant differences between two groups (p=0.3); non significant was also the mean day of return to normal bowel function (p=0.28). We found statistically significant mean preoperative level of hemoglobin (p=0.02), mean hospitalization (p=0.01) and mean tranfusions (p=0). *Discussion and Conclusion:* Higher surgical complications arising from previous radiation therapy are well known by urologists; considering that Charlston Morbidity Index did not show statistical significancy between two groups, the only radiation therapy seems to represent an independent factor of worse prognosis. Lower initial hemoglobin level and higher transfusion needing suggests the necessity to check blood parameters every day after cystectomy; previous radiation therapy does not affect the time of return to normal bowel function. Among 15 radiotreated patients, 6 patients (40%) developed *de novo* transitional carcinoma: in these cases radiation therapy could have played a significant pathogenetic factor for bladder cancer.

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2 Eisenberg MS, Dorin RP, Bartsch G, Cai J, Miranda G and Skinner EC: Early Complications of Cystectomy After High Dose Pelvic Radiation. J Urol, 2010.

Table I.

CDCSC	GR 1	GR 2
0	43.82%	0.00%
I	8.99%	6.66%
II	20.22%	26.66%
III a	17.97%	20.00%
III b	2.25%	20.00%
IV a	1.12%	13.33%
IV b	1.12%	0.00%
V	4.49%	13.33%

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IS VISCERAL ADIPOSITY INDEX (VAI) RELATED TO PROSTATE CANCER DETECTED BY BIOPSY?

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Introduction/Aim: Numerous clinical trials investigated the association between obesity and prostate cancer, yielding inconsistent results. Metabolic syndrome has been suggested to promote aggressive prostate tumors. In a previous study we failed to detect a relation between Body Mass Index (BMI) and prostate cancer Gleason score (1). BMI, although routinely adopted to measure obesity, has low sensitivity and specificity. A novel sex-specific obesity index, based on waist circumference (WC), BMI, triglycerides (TGs) and high density lipoproteins (HDL), the Visceral Adiposity Index (VAI), has been proposed to estimate the visceral adiposity dysfunction (2). The aim of our preliminary research was to correlate VAI and BMI with the presence of prostate cancer and the Gleason score at biopsy. *Patients and Methods:* Patients, undergoing prostate biopsy for palpable prostate nodule and/or elevated PSA levels, entered the study. After informed consent a transrectal prostate biopsy, 12 cores at least, was performed. The number of cores increased in re-biopsies (18-24 cores). A database including clinical, biochemical and pathological data was created. Prostate cancer detection at biopsy, Gleason score (6 or less *versus* 7 or higher), VAI, BMI and PSA values were statistically analyzed with Wilcoxon rank sum test. *Results:* Fifty-one patients were evaluated. The median age was 66 years (range 47-80). Two patients (3.9%) had a previous negative biopsy. The median BMI was 27.7 kg/m^2 (range 18.7-40) and the median VAI was 4.4 (range: 1.6-15.6). Median PSA was 8.5 ng/ml (range 3.2-53). A prostate nodule was palpable in 9 (17.6%) patients. The median prostate volume was 48 cc (range: 14-106). A prostate cancer was detected in 24 (47%) patients, with a Gleason pattern 6 in 14 (58.3%) patients and 7 or higher in the remaining 10 (41.7%). Among patients with positive prostate biopsy, median PSA BMI and VAI were 10.2 ng/ml, 27.8 Kg/m^2 and 5.8, respectively. Among patients with negative prostate biopsy, median PSA BMI and VAI were 7.0 ng/ml, 26.8 Kg/m^2 and 5.5, respectively. Only PSA levels were slightly related to biopsy positivity (p-value=0.08), no difference was detected for VAI (p-value=0.89) and BMI (p-value=0.19). Median PSA, BMI and VAI resulted 9.2 ng/ml, 27.8 Kg/m^2 and 5.6, respectively in patients with Gleason score of 6 or less, and 10.9 ng/ml, 27.7 Kg/m^2 and 5.8, respectively, in patients with Gleason score >6. Even in this case PSA levels were slightly related to prostate cancer aggressiveness (p-value=0.12), while no difference was highlighted for VAI (p-value=0.6665) and BMI (p-value=0.6394). *Discussion and Conclusion:* The identification of patients harboring an aggressive prostate cancer remains an important goal. The contradictory results on the relation between obesity and prostate cancer could be due to the low accuracy of BMI as a marker of metabolic syndrome. VAI has been recommended as an accurate indicator of adipose tissue activity. Nevertheless, our preliminary results do not detect any significant correlation between VAI, BMI, positivity of prostate biopsy and Gleason score.

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2 Amato MC, Giordano C, Galia M *et al*: Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care *33*: 920, 2010.

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CHROMOPHOBE RENAL CELL CARCINOMA: A SINGULAR CLINICAL CASE WITH GOOD EFFICACY OF SUNITINIB

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Background: Chromophobe Renal Cell Carcinoma (ch-RCC) is the third most common histotype of renal carcinoma. In the clinical trials, this histologic variety (ncc-RCC) is valued in a heterogenes grouping, including the Papillary Carcinoma, Collecting Duct and Unclassified RCC subtype. Although targeted therapies are commonly used, the efficacy for ncc-RCC is limited to a few retrospective analyses on small patient population and in the absence of differentiation among histologic subtypes. *Case Presentation:* A 61 year old man, with ECOG Performance Status=0 and a long history of disease, underwent left radical laparotomic nephrectomy in July 1999. The tumor was pathologically classified as Grade 3, Chromophobe type, with focal involvement of the renal capsule pT3 N0 M0, according to American Joint Committee on Cancer, stage III. Two years after nephrectomy, a routine abdominal US showed apparent inflammatory lesion of the gallbladder which was not modified for about 4 years. In February 2005 CT SCAN showed a consistent increase of the dimension of the suspicious lesion with infiltration of the gallbladder. Hereafter, the patient has been submitted to 5 surgical procedures: a) Resection of IV liver segment (March 2005); b) Resection of VII liver segment (March 2007); c) Left liver lobectomy with laparotomic radiofrequence (June 2007); d)

Inferior polar lineal neoplasm resection (July 2010); e) Lienal and distal pancreatectomy resection (March 2011). Chomophobe Renal Cell Carcinoma, in each practiced operation, has been histologically confirmed. Progression of disease was observed in June 2012. Sites of disease comprised liver and abdominal lymph nodes. From July 2012, once daily, 50 mg of Sunitinib was administered orally for 4 consecutive weeks followed by a 2 week rest. *Discussion:* Currently, thirteen Sunitinib courses have been administered. CT re-evaluation SCAN has shown stable disease with regression trend. All thirteen cycles have been moderately tolerated without necessary dose reduction. In particular, liver lesions at CT SCAN seem as cystic with hyperdense cercine and with internal proliferation of tissue. These lesions after three Sunitinib courses have shown regression of hyperdense cercine and internal tissue. Even if according to Recist Criteria stable disease is reached, the CT modification is clinically relevant as surrogate of disease control. ncc-RCC include a heterogeneous and poorly characterized group of tumor types for which few treatments have been approved. Despite some studies mostly uphold the use of mTOR inhibitors, there is a scarce level of evidence. Approximately 5% of renal cell tumors are chromophobe. Chromophobe RCC is histologically and genetically unique. Data regarding effective therapies for patients with metastatic chromophobe RCC are limited. Several case report suggest efficacy for the use of both VEGFR targeted therapies and mTORi in patients with metastatic ch-RCC. In this analyzed clinical case, the effectiveness of Sunitinib is congruent with many other clinical published cases, but the difference is in the duration of the clinical response (patient already submitted to medical treatment). This case and the other published medical cases, show that ch-RCC, in comparison to the other subtypes of ncc-RCC (which currently does not seem to be sensitive to the TKis), can be sensitive to the TKIs.

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IMPACT OF PELVIC MAGNETIC RESONANCE FOR PROSTATE CANCER STAGING: DOES IT WORTH TO RADIATION ONCOLOGISTS?

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Aim: To assess the accuracy of endorectal/transabdominal magnetic resonance imaging (MRI) in localized/locally advanced prostate cancer (PCa) staging. To assess the MRI clinical impact on different therapeutic approaches. *Patients and Methods:* From July 2008 to November 2013 one hundred and eleven consecutive patients (pts) with biopsy-proven PCa underwent endorectal/trans-abdominal MRI prior to be submitted to radiation therapy treatment with radical intent. ECOG status was 0-1 in all patients and their mean age was 72 years (range 57-80). All patients underwent digital examination, transrectal ultrasound and abdominal CT scan before being referred to our Institution. About T stage, 69 pts (62.1%) were T1a-c, 32 pts (28.8%) were T2, 5 pts (4.5%) were T3a and 5 pts T3b (4.5%). No patient was staged as T4 and only one patient experienced nodal involvement (N1) at the moment of diagnosis. Thirty-two of 111 pts (28.8%) had low risk, 47 pts (42.4%) intermediate risk and 32 pts (28.8%) had high risk prostate cancer due to clinical stage, Gleason Score and initial PSA value (see D'Amico classification). In our Institution all candidates to radical treatment were submitted to endorectal or transabdominal magnetic resonance imaging (MRI) to have a more accurate locoregional staging; high risk pts were also submitted to complete bone scan to exclude distant metastasis. All pts underwent high dose Radiotherapy +/- hormonotherapy due to their class risk obtained by complete staging (TR-US, MRI, bone scan). The impact of endorectal/transabdominal MRI was analyzed to discover its role in routinary clinic in terms of "stage migration" and advantages for therapeutic choices. *Results:* Regarding locoregional stage we obtained an "upstaging" in 63 of 111 pts (56.7%), particularly: 26 pts moved from T1 to T2a-c and 20 from T1 to T3a-b, 13 pts from T2a-c to T3a-b, 1 pts from T3a to T3b; in 3 pts we found metastatic nodal involvement to MRI imaging. Furthermore "class risk" cathegory and consequently our therapeutic approach was changed in 35 pts (32%) due to MRI imaging: 11 pts moved from "low" to "intermediate risk", 9 pts from "low" directly to "high risk", 15 pts from "intermediate" to "high risk". Due to this "clinical stage migration" we changed our therapeutic approach in 48 pts (43.2%); indeed we just modified radiotherapy volumes in 26 pts (23.4%) while total dose was differently planned in 17 pts (15.3%), hormonotherapy was added to radiotherapy in 21 pts (19%) in a neoadjuvant/concomitant/adjuvant setting. All patients underwent radical radiotherapy, 34 of them (30.6%) with conventional fractionation (mean dose=76.3 Gy, range=74-78Gy) and the other 78 pts (69.4%) with a moderately hypofractionated schedule (mean dose=70.2Gy, range=67.5-76.6; 2.2-2.5Gy a day). With a mean and a median follow up of 22 and 19 months respectively (range 3-58), all patients except one (dead due to secondary neoplasm) are still alive at the moment of analysis. *Discussion and Conclusion:* Endorectal/transabdominal MRI may be a highly reliable non-invasive technique for local staging of PCa showing an optimal diagnostic accuracy. Clinicians should consider utilizing MRI in the decision-making process in order to improve

therapeutic strategies and consequently clinical outcomes of localized/ locally advanced PCa patients.

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PROSTATE CANCER AND MODERN RADIOTHERAPY: IMPROVING TREATMENT PLANNING BY MAGNETIC RESONANCE IMAGING AND INTRAPROSTATIC MARKERS

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Aim: Description of combined use of intraprostatic gold fiducial markers, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) in Image Guided Radiation Therapy (IGRT) for localized prostate cancer to improve treatment planning and daily set-up verifying. *Patients and Methods:* Between December 2012 and December 2013, IGRT (70 Gy - 2.5 Gy/fr) was prescribed to 8 patients affected by localized prostate cancer. After intraprostatic gold fiducial marker implantation, patients underwent a planning CT (BRIGHT SPEED, G.E.) and a pelvic MRI (Achieve 1,5 T, Philips MS) with T2w SPAIR AX, T2w TSE SAG AX COR, T1 w TSE AX, Dyn THRIVE, T1 w contrast enhanced THRIVE AX. CT and MRI images were exported and the two data sets were fused. ONCENTRA system (ELEKTA) provided a point (intraprostatic marker) based registration. Each registration was always checked by a physician. *Results:* Fiducial markers were identified in MRI series of all patients. THRIVE AX was the most clarifying series. CT and MRI data were correctly aligned and Average Square Error was between 0.2 and 1.7 mm (median 0.9 mm). *Discussion and Conclusion:* There was a high accuracy in co-registration of CT and MRI images, with a median Average Square Error of 0.9 mm. In contouring the clinical target volume (CTV) was the prostate gland outlined on CT and axial MRI series. This modality can better define prostate, seminal vesicles, rectum and contribute to spare normal tissue irradiation.

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COMPLETE RESPONSE TO VINFLUNINE IN A PATIENT WITH METASTATIC UROTHELIAL CARCINOMA OF THE BLADDER

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Introduction: The prognosis and long-term survival for patients with metastatic urothelial carcinoma is poor. For cisplatin-based regimens, the combination of methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) has been the mainstream treatment for both advanced and metastatic bladder cancers. For cisplatin-ineligible patients, namely patients with renal impairment, symptomatic cardiac disease and poor performance status, alternative therapies consisting of paclitaxel, gemcitabine and carboplatin were shown to be of benefit. Vinflunine, a new synthetic vinca alkaloid, has been approved in Europe for the treatment of second-line transitional cell carcinoma of the urothelium and is also being developed for other malignancies (1). *Patients and Methods:* we reported a case of 70 years old man, affected by metastatic bladder cancer who reported a complete response after treatment with vinflunine, in the second line. In 2007, the patient was subjected to partial cystectomy for high-grade urothelial carcinoma infiltrating the muscularis. In October 2010, du to pulmonary recurrence of urothelial carcinoma, the patient started first-line chemotherapy with cisplatin and gemcitabine. Six cycles of chemotherapy resulted in stable disease. In August 2011, after nine months of progression free survival, a CT scan showed pulmonary progression disease and second line treatment with vinflunine was started. The first cycle was administered at a dose of 270 mg/m^2 and subsequent at a dose of 320 mg/m^2, as in the classic schedule. *Results:* After 4 cycles, the CT recorded partial response with a reduction in the number and size of lung lesions. 3 cycles of therapy with vinflunine were performed, until Febrary 2012, when the CT scan showed complete response on all metastatic sites. Treatment was well tolerated with manageable toxicities. Therapy was descontinued and the patient was followed-up. After 18 months of follow-up, no evidence of recurrence was noticed, but in August 2013 the patient died due to acute heart attack. *Discussion:* Vinflunine has proven to be a safety and efficacy second line treatment in a patient with metastatic bladder cancer. Furthermore, it presents a good profile of toxicity. *Conclusion:* In patient with metastatic bladder cancer, after cisplatin-based regimens, with good performance status, vinflunine represents gold standard.

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PELVIC OLIGOMETASTATIC PROSTATE CANCER AND RADIOTHERAPY:AN UPDATE

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Introduction: In 2012, three patients affected by prostate cancer with bone pelvic recurrence were treated with 3D radiotherapy for primary tumor and recurrence. *Patients and Methods:* First patient (A) was a 72-year-old man, treated with urinary dysobstruction therapy. At diagnosis, Prostate-specific Antigen (PSA) was 83 ng/ml, Gleason score 3 plus 3, clinical stage T2c N0 M1b, with a right bone pubic lesion (asymptomatic) identified to 11C-Acetate PET/CT. He was treated with Androgenic Deprivation Therapy (bicalutamide and LHRH analogue), with a good biochemical response (PSA 0.18 ng/ml). After 8 months radiotherapy was started for primary tumor site (prostate and seminal vescicles, 66 Gy in 33 fractions (fr), 2 Gy/fr) and bone lesion (36 Gy in 18 fr, 2Gy/fr). Radiotherapy finished on August 2012. Now he is continuing hormonal therapy only with three-monthly LHRH analogue. Second patient (B) was a 75-year-old man, treated with a radical prostatectomy and pelvic bilateral lymph node dissection. Pathologic classification was adenocarcinoma, Gleason score 4 plus 4, pT3a pN0. After 5 years, he was presented to radiotherapist for a biochemical relapse (PSA 0.72 ng/ml). A 11C-Acetate PET/CT identified a relapse in prostatic bed and left pubic bone (asymptomatic). He was treated with radiotherapy for prostatic bed (66 Gy in 33 fr, 2 Gy/fr) and bone lesion (36 Gy in 18 fr, 2Gy/fr). Treatment finished on July 2012. Hormonal therapy (LHRH analogue) was given only for six months. Third patient (C) was a 78 year-old man. He had two previous partial excisions of prostate gland in 1998 and 1999 (with a diagnosis of adenocarcinoma). Urologists had chosen hormonal therapy with monthly LHRH analogue. He was presented to radiotherapist at a biochemical progression (PSA level before radiotherapy 79.6 ng/ml). A 11C-Acetate PET/CT identified a relapse in prostatic bed, right pubic bone and sacrum (asymptomatic recurrences). He was treated with radiotherapy for prostatic bed (66 Gy in 33 fr, 2 Gy/fr) and two bone lesions (36 Gy in 18 fr, 2Gy/fr). Treatment finished on May 2012. He had a significant biochemical decrease. In March 2013, at a new PSA increase (149 ng/ml), chemotherapy (docetaxel) was prescribed for nine cycles. Now he is continuing only therapy with three-monthly LHRH analogue and monthly bisphosphonate. *Results:* Patient A had a 16 months follow up: PSA 0.02 ng/ml; last IPSS 2; no pain referred. No gastrointestinal toxicity. Patient B had a 17 months follow up: PSA 0.07 ng/ml; last IPSS 3; mild urinary incontinence. No pain referred. No gastrointestinal toxicity. Patient C had a 19 months follow up: PSA 0.9 ng/ml. He had a good biochemical response to the systemic combined therapy started at the progression. No relevant pain referred; asymptomatic for urinary problems. *Discussion and Conclusion:* Clinical and biochemical results seem to give an important confirm for the role of 3D radiotherapy on primary site and bone pelvic recurrence in selected patients with oligometastatic prostate cancer. Long follow up, good quality of life, no heavy late effects strengthen the choice of a not only palliative treatment.

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ESTIMATES OF PROSTATE CANCER BURDEN IN ITALY

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Introduction/Background/Aim: In Italy, prostate cancer incidence rapidly raised from the beginning of 1980' to the beginning of 2000 (1). In contrast, prostate mortality did not increase in the same period. Such an increase in the incidence was principally due to the diffusion of the prostate-specific antigen (PSA) test. The main informative source about cancer incidence are population-based cancer registries that in Italy cover about 40% of the population. However, the coverage is not uniform at a national level, except for statistics on mortality. We aim to produce estimates of the basic epidemiological indicators: incidence, prevalence and mortality of prostate cancer in Italy overall and as a function of region, time period and patients age. *Materials and Methods:* Incidence and prevalence rates were estimated using the data of mortality and relative survival and applying the MIAMOD method (2). The cancer registry data derived from the AIRTum (Italian Cancer Registry Association) database were used to estimate relative survival by geographic region, gender and age, and for the validation of incidence. The overall mortality, prostate cancer-specific mortality and population data for the period 1970-2007 were available in the ISTAT web-site. *Results:* We estimated an increase in the standardized incidence rates for prostate cancer, in particular for the period 1984-2005: incidence rates rose from 31 per 100,000/year to 93 per 100,000/year. Afterwards, rates slightly

decreased reaching a value of 89 per 100,000 in 2015.Standardized mortality rates (per 100,000) increased from 14 in 1970 to 19 in 2000. After the year 2000, the rates decreased reaching 15 per 100,000 in 2015. The prevalence was in rapid growth and in the years 2012-2015 about 1 men every 100 was living with a cancer. The annual incidence rates (per 100,000) in 2015 for the age groups 0-54, 55-64, 65-74, 75-84, 85+ were 5, 147, 528, 834, 826, respectively. The corresponding mortality rates were <1, 7, 41, 182, 523 per 100,000, whereas prevalence rates were <1%, 1%, 3%, 8%, and 11%, respectively. The standardized incidence rate in 2015 was lower in the South of Italy (62 per 100,000) compared to the other areas (North-west 100, North-east 105 and central 102 per 100,000). We did not observe differences for standardized mortality rates which were similar in all the areas. *Discussion and Conclusion:* The most significant result of this study is that prostate cancer mortality in Italy is decreasing. A similar trend was reported also in Norway and Finland, while in the USA, Canada and Australia mortality rates started to reduce in the '90s (3). In all these countries, the decline was anticipated by a sharp increase of the incidence. It is worth stressing that the high incidence rates were mainly due to the diffusion of the PSA test which lead to the identification of many indolent tumours. In the USA 60% of PSA detected tumours were overdiagnosed. It is likely that the Italian data reflect a similar situation.

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MULTIDISCIPLINARY MANAGEMENT OF METASTATIC PAPILLARY RENAL CELL CANCER PATIENT

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Introduction: Type 2 papillary renal cell cancer (pRCC) has a poorer outcome than clear cell RCC (ccRCC), being often associated with Fuhrman grade 3-4, TNM stage III-IV, absence of fibrous pseudocapsule and presence of microvascular invasion (1). The tyrosine kinase inhibitors (TKIs), which represent a standard therapy for metastatic ccRCC, apparently showed a lower activity in non-ccRCC. Very recent data demonstrated that, after Sunitinib or Sorafenib treatment, the median progression free survival (PFS) for type 2 pRCC is 8.9 *versus* 11 months of ccRCC, and overall survival (OS) for type 2 pRCC is 15 *versus* 32 months of ccRCC (2). Furthermore, preliminary data from phase II RAPTOR study recently showed safety and clinical benefit of the m-TOR inhibitor Everolimus as 1st line therapy for metastatic pRCC (3). *Patients and Methods:* We present a case-report of a 44-year-old male with diagnosis, on November 2011, of left kidney type-2 pRCC, Fuhrman grade 3, infiltrating the kidney's fat and metastatic to lungs, thoracic and abdominal lymphnodes (pT3 cN2 Mx). *Results:* After multidisciplinary clinical discussion, the patient was first submitted to cytoreductive left nephrectomy with lomboaortic lymphnodes exeresis and concomitant removal of a large paraneoplastic thrombus, extending along the inferior and superior vena cava, up to the right atrium. Subsequently he started psychological support and 1st line therapy with Sunitinib 50 mg/die for 4 weeks every 6, for 7 cycles, with thoracic partial response, but moderate toxicity which influenced some interruptions (fatigue G3, nausea G2, dysgeusia G2, plantar skin toxicity G2, diarrhea G2; CTCAE v3.0). On December 2012, due to pulmonary progressive disease (PFS=11 months) the patient started 2nd line therapy with Everolimus 10 mg/die, for 12 months, with further thoracic partial response and no toxicity >G1 (CTCAE v3.0). On February 2014, a progression in bone, lung, thoracic and abdominal lymphnodes occurred (PFS=14 months), with an ECOG performance status=1 related to bone pain; therefore the patient started a 3rd line therapy with Sorafenib 800 mg/die, a radiotherapy on bone (D7, 20 Gy) and Zoledronic Acid treatment (4 mg every 28 days). Currently, Sorafenib and Zoledronic Acid are ongoing, without notable toxicities, as well as psychological sustain. *Discussion and Conclusion:* In this case report, our young patient with type 2 metastatic pRCC was submitted to cytoreductive nephrectomy, followed by 3 lines of targeted therapies, obtaining a PFS of 11 months and 14 months after 1st and 2nd line therapy, respectively, with an OS of 27 months, values which are higher than those described in literature (PFS 9 months, OS 15 months). Our results have the limitation of a retrospective, single case-report experience. Nevertheless, even considering the huge biological heterogeneity of RCC, an effective multidisciplinary management of patients with metastatic RCC seem to be and essential.

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HORMONAL THERAPY IN ASSOCIATION WITH RADIOTHERAPY: TIME TREND IN OUR EXPERIENCE

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Background: Hormonal therapy (HT) of prostate cancer remains a challenge for urologists, medical and radiation oncologists. LH-RH agonists and antiandrogens, which had mainly been indicated for treatment of patients (pts) with distant metastases, has been added to radiotherapy (RT) to improve the efficacy of treatment. Recently, also LH-RH antagonists have become available. However, type and duration of HT is still unclear in pts undergoing RT. Although the majority of guidelines and published studies do not suggest the use of HT in low-risk pts, several studies have shown better outcome following combined RT and HT in pts with low and intermediate risk. No randomized trial has been designed specifically for each risk class to compare HT plus RT with RT alone. Therefore there are still doubts about the use of HT in the daily practice. This analysis evaluates our experience in the clinical use of HT combined with RT in prostate cancer. *Patients and Methods:* We retrospectively analyzed 434 pts with prostate cancer treated with radical RT with or without HT from October 2006 to December 2013. Median age was 74 years (range: 54-83). All pts underwent biopsy with histologically proven prostate adenocarcinomas and they all were treated with a median dose of 76 Gy (2 Gy/die) or 70 Gy (2.5 Gy/die). When prescribed, HT started between one and three months before RT, continued during the entire RT course and it was interrupted at different times after the end of RT. Pts were stratified according to stage, Gleason score and presenting prostate-specific antigen level. We analysed pts treated before and after the beginning of 2010 all together and separately, in order to notice any time trend. *Results:* Median and minimum follow-up were 51 months and 12 months, respectively. Median pretreatment PSA was 16.7 ng/mL (range: 2.9-207) and median Gleason score was 7 (range: 3-10). HT was prescribed for 85% of pts of whom 230 pts (53%) received total androgen deprivation, 117 pts (27%) received bicalutamide alone (150 mg/die) and 22 pts (5%) received LH-RH analogue alone. Among pts irradiated till 2009, 50% underwent a total androgen suppression, 30% took an antiandrogen and 3% received only a LH-RH analogue. Starting from 2010, each type of treatment was given to 59%, 19% and 12%, respectively. Pts receiving no HT decreased from 17% to 9%, despite the increase of low-risk pts during the last years. No significant statistical association was found between risk class and HT (chi-square test). *Discussion and Conclusion:* Interest has been increasing in the use of HT combined with RT in the management of localized prostate cancer. Several studies have provided some rationale for the use of this combination. Nevertheless, there are still many inconsistencies in the daily clinical practice regarding use, type and duration of HT. In United States the number of pts with favourable low-risk disease receiving HT is growing. Our analysis confirms that many pts with low-risk prostate cancer receive HT also in Italian daily practice. Probably this represents an overtreatment and HT is unnecessary even in intermediate risk pts. Other timing changes we noticed are a wider diffusion of complete androgen deprivation, a longer duration of neoadjuvant HT and a shorter duration of adjuvant HT. Randomized trials are mandatory to clarify the role of HT in association with RT.

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RELIABILITY AND SAFETY OF DYNAMIC SENTINEL NODE BIOPSY (DSNB) IN CLINICALLY NEGATIVE INGUINAL NODES PENILE SQUAMOUS CELL CARCINOMA (SCC)

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Introduction and Aim: Early detection of inguinal node metastases from penile squamous cell carcinoma (SCC) is mandatory. Inguinal lymph-node dissection (ILND) represents the standard management of nodal disease, but it is conditioned by severe morbidity. According to EAU guidelines ILND is advised in patients with invasive and/or high grade cancer (≥pT1G2). In high volume centers dynamic sentinel node biopsy (SNB) is performed to select patients for ILND in order to limit morbidity. This study analyzed data about patients with penile SCC and clinically negative inguinal nodes (cN0), stated by physical and ultrasound examination. The aim of the study is to assess the false negative rate, negative predictive value (NPV) and sensitivity, as well as complications of SNB procedure. *Patients and Methods:* From 01-2000 to 12-2013, 110 patients (pts) underwent DSNB: 21 pts had clinical groin metastasis on one side and were not considered in this study. 89 patients (mean age 59 years, range 21-80) with penile squamous cell carcinoma pT1-3 clinically bilateral N0 (cN0) were retrieved from our prospectively kept database. Lymphoscintigraphy was performed the day of the surgery to identify the inguinal sentinel nodes which was intraoperatively detected by gamma probe and blue dye detection and then removed. In 76 out of 89 patients SNs were removed in both inguinal groin successfully. In 12 pts DSNB was performed in one groin only and in 1 patients SN was not bilaterally identified due to absent visualization during lymphoscintigraphy or low signal at the gamma probe during surgical procedure. Consequently SN was not identified (cNx) in 14 out of 178 inguinal groins (7.8%), while the procedure was completed in 164/178 (92.2%) groins. In 11/164 groins (6.7%) we had positive sentinel node, which was followed by ILND: 6 had pN1 (SN was the only one pathologic node), 5 pN2-N3 disease (TNM 2002). After a median follow-up of 11 months (range 2-26 months) 12 out of 153 (7.8%) groins with negative SNB developed inguinal metastases; these pts underwent radical nodal surgery: 2 pts had pN1, 6 pts pN2 and 2 pts pN3 (2 pts had bilateral positive groins). 3/14 groins (21.4%) without SN identification had positive nodes: 1 pN1 underwent ILND at the same time of DSNB, 2 pN2 at follow-up (2 and 13 months). Overall, we recorded 26/178 affected groin (15%). As a whole ILND could be spared in 85% of groins (152/178). On the other hand the false negative rate was 7.3% (12/164) leading to a relatively good NPV of 86% (141/164), but to a fair sensitivity of 48% (11/23). The efficiency rate of the whole procedure (considering all 178 groins we intended to explore) is even lower as we detected only 11/26 (42.3%) of the metastatic groins. We did not find major complications. One pt developed an unusual intradermic metastatic spread, theoretically due to lymphatic drainage alteration after DSNB. *Conclusion:* ILND represents the gold standard management for patients with nodal metastases or at risk of metastases from penile SCC. Nevertheless, DSNB is a safe procedure with limited major complications which was able to spare ILND to 85% of our patients: NVP was 86% and sensitivity 48%. The efficiency rate of the intention to diagnose was even lower, as only 42% of metastatic nodes could be early detected. Special attention is mandatory in case of lack of groin signal following the injection of the radiotracer and a follow-up is advised also in case of negative bilateral sentinel node biopsy. The DSNB is a multistep procedure which requires accurate selection of patients and precise execution of the procedure.

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THE COMPLETE SAVING OF STRIATED SPHINCTER DURING RADICAL PROSTATECTOMY IDENTIFYING VERUMONTANUM

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Aim: Verumontanum can be considered an anatomical landmark in saving the maximal length of urethra and, consequently, the maximum of striated sphincter. Either by a retrograde or a antegrade approach to the radical prostatectomy, an anatomical preparation of the urethral sphincter with an excellent visualization of the apex is fundamental. After that, urethra can be resected with the maximum respect of anatomical boundaries of urethral sphincter and minimizing the risk of leaving prostatic tissue *in situ*. The aim of our study is to investigate functionally and oncologically the role of verumontanum as a landmark for the complete saving of striated sphincter in patients undergone radical prostatectomy. *Patients and Methods:* From January 2008 to December 2012 we prospectively collected the data of 159 patients undergone radical retropubic prostatectomy (RRP) for clinically localized prostate cancer. We determined two cohorts: Group A (77 patients) undergone RRP without the saving of verumontanum, and Group B (82 patients) undergone RRP with the saving of verumontanum. Both, Group A and B, were homogeneous in terms of preoperative PSA, pathological staging and pathological Gleason Score. Continence was evaluated with ICIQ-SF questionnaire at month 1, 3, 6, 12. *Results:* Mean follow-up was (range) 23.7 (13-57) months for Group A and 22.4 (13-59) months for Group B. In 6/77 (7.8%) cases of Group A and in 8/82 (9.7%) of Group B a positive apical surgical margin was found (p=0.3219): of these patients, 3 in Group A and 4 in Group B developed biochemical recurrence (p=0.4877). Overall, 94.3% of Group A and 95.3% of Group B patients completely fulfilled our continence criteria (no pads and ICIQ-SF≤2) at a minimum follow-up of 24 months; continence was obtained within the first month in 55 (76%) patients of Group A *vs*. 60

(78%) of Group B, 58 (80.5%) *vs*. 68 (87.5%) within the third month, 65 (90.3%) *vs*. 72 (92%) within the sixth month and in 72 (94.3%) *vs*. 78 (95.3%) respectively. The saving of verumontanum was not significant in overall continence (p=0.09) but was influential in early recovery of continence (p<0.0001). *Discussion:* An anatomical intraoperative landmark in saving the maximum of striated sphincter may be represented by verumontanum. In our experience, radical retropubic prostatectomy with the saving of verumontanum determined an early continence recovery without increasing the risk of leaving prostatic tissue *in situ*. The limit of this study is represented by the small number of both groups and the exiguity of events; our pilot study underlines the need of large, randomized trials to define the role of verumontanum in overall and early continence recovery.

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CONTINENCE RECOVERY IN PATIENTS UNDERGONE RADICAL CYSTECTOMY AND ILEAL ORTHOTOPIC NEOBLADDER

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Aim: Radical cystectomy plus ileal orthotopic bladder substitution is a choice for primary invasive bladder cancer and for high grade, refractory to conservative therapy, multifocal and quickly recurrent superficial bladder cancer, in young patients determined to maintain an adequate self corporeal image. During radical cystoprostatectomy an anatomical preparation of urethral sphincter with an excellent visualization of prostatic apex is essential. After that, urethra can be resected with the maximum respect of anatomical boundaries of urethral sphincter and minimizing the risk of leaving prostatic tissue *in situ*. The aim of our study is to investigate functionally and oncologically the role of verumontanum as a landmark for the complete saving of striated sphincter in patients undergone radical cystectomy and ileal orthotopic bladder substitution. *Patients and Methods:* From January 2008 to December 2012 we prospectively collected the data of 63 patients undergone radical retropubic cystoprostatectomy plus ileal orthotopic bladder substitution for clinically localized bladder cancer. We compared the intraoperative identification and saving of verumontamum and follow-up data determined through urodynamic evaluation. Clinical, surgical and complete follow-up data were available in 55/63 patients. The urethral sphincteric mechanism was evaluated with urodynamic study in different positions at a minimum follow-up of 12 months. After that, to compare intraoperative findings every patient underwent urethrocystoscopy to confirm the presence or absence of verumontanum. Continence was evaluated with ICIQ-SF questionnaire at month 1, 3, 6 and 12. *Results:* Mean follow-up was (range) 28.5 (12-52) months. In 6/55 (10.8%) cases it was found transitional cancer in bladder trigone was found. In two cases a pT2b prostatic carcinoma Gleason 3+3 was found. None of the cases showed a positive apical surgical margin. Overall, 45/55 (81.8%) patients completely fulfilled our continence criteria (≤1 pad/die and ICIQ-SF≤2/2/2) in daytime and 36/55 (65.4%) on nighttime at a minimum follow-up of 12 months. In 22/55 (40%) patients with verumontanum (Group A) continence was obtained within the first month in 3/22 (13.6%) cases *vs*. 0/33 in patients without the saving of verumontanum (Group B), 7/22 (31.8%) *vs*. 7/33 (21.2%) within the third month, 14/22 (63.6%) *vs*. 19/33 (57.6%) within the sixth month and in 19/22 (86.3%) *vs*. 24/33 (72.7%) at a 12-months follow-up in Group A and B respectively. The saving of verumontanum was statistically significant in overall continence (p=0.0067) and influential in early recovery of continence (p<0.0001). Urodynamic evaluation demonstrated a significantly longer functional urethral length in Group A patients (mean, range: 32, 28-37 mm) *vs*. Group B patients (25, 16-31 mm) (p=0.0036). Overall 19/22 patients of Group A demonstrated a Valsalva leak point pressure ≥40cmH_2O *vs*. 24/33 of Group B. *Discussion:* The recovery of continence in patients with orthotopic neobladder is a crucial functional outcome. Verumontanum can be considered a visual intraoperative landmark in saving the maximum of striated sphincter and, consequently, the maximum of striated sphincter through an anatomical preparation of prostatic apex. In our experience, the saving of verumontanum during radical cystectomy and ileal orthotopic bladder substitution improved overall and early continence recovery. The limit of this study is represented by the small number of patients in both groups and the exiguity of events; our pilot study underlines the need of large, randomized trials to define the role of verumontanum in overall and early continence recovery.

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COST-EFFECTIVENESS ANALYSIS OF MONEY-SAVING PROCEDURES IN ROBOT-ASSISTED UROLOGIC SURGERY

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Aim: In literature the feasibility and safety of robotic surgery is widely demonstrated since it allows minimally invasive procedures and oncologic and functional results comparable to standard open procedures with fewer major

Table I. *Robotic tumoral enucleation*.

First 20 cases				Last 20 cases			
Item	no.	Unitary cost (€)	Total cost (€)	Item	no.	Unitary cost (€)	Total cost (€)
Sterile drape for arms	2	100	200	Sterile drape for arms	2	100	200
Sterile drape for camera	1	100	100	Sterile drape for camera	1	100	100
Cadiere Forceps	1	471	471	Cadiere Forceps	1	471	471
Hot Shears (Monopolar Curved Scissors)	1	753	753	Hot Shears (Monopolar Curved Scissors)	1	753	753
Meryland Bipolar Forceps	1	636	636	Large Needle Driver	1	516	516
Permanent Cautery Hook	1	470	470	Robotic trocar	3	0	0
ProGrasp Forceps	1	500	500	Sterile robotic trocar mount	3	37	111
Large Needle Driver	2	516	1032	12" laparoscopic trocar	2	92	194
Robotic trocar	2	0	0	Sterilizable suction irrigator	1	0	0
Sterile robotic trocar mount	3	37	74	Laparoscopic needle driver	1	0	0
5" laparoscopic trocar	1	92	92	Johan grasping forceps	1	0	0
12" laparoscopic trocar	2	92	194	Hem-o-lok Clips (5-pieces blister)	2	12	24
Single-use suction irrigator	1	105	105	Endo Catch	1	70	70
Tip for suction irrigator	1	21	21	Monocryl 0 MH1	3	6	18
Laparoscopic needle driver	1	0	0				2457
Laparoscopic scissors	1	70	70				
Johan grasping forceps	1	0	0				
Hem-o-lok Clips (5-pieces blister)	2	12	24	Mean saving: 49.2%			
Endo Catch	1	70	70				
Monocryl 0 MH1	3	6	18				
Monocryl 2/0 UR6/SH	1	6	6				
			4836				

complications and shorter length of hospital stay. On the other hand, the Da Vinci System determines higher costs of each single procedure than the relative open and laparoscopic surgery. The aim of this study is to evaluate the financial implications of minimally invasive surgery such as robotic radical prostatectomy (RRP) and renal robotic tumoral enucleation (RTE) performed as standard techniques or as a money-saving procedures and to compare functional and oncological results. *Patients and Methods:* From April 2011 to January 2014 149 patients underwent robotic surgery for prostate (84 patients) and renal cancer (65 patients). We identified the first set of patients treated after the initial learning curve (Group A) and the latest ones (Group B) of each procedure. The first 8 prostatectomies and the first 5 tumoral enucleations were performed following the standard procedures and adopting the prescribed instrumentation. During our experience we redefined the procedures excluding from operating kits some tools to minimize costs. In the present study we compared costs and surgical outcome between the first set of patients and the latest one. Technical features of prostatic and renal surgery are summarized in Table I and II respectively. *Results:* Instrumentation costs of both, radical prostatectomy and tumoral enucleation, were significantly lower in the last 20 procedures: 2577€ *vs*. 4961€ for RRP and 2457€ *vs*. 4836€ for robotic RTE, saving the 48% and the 49.2% respectively (Tables I and II). Mean (range) operating time for RRP in Group A was 208.4 (160-265) minutes *vs*. 168.3 (142-170) minutes of Group B (p=0.0041). Both groups of robotic radical prostatectomies were similar in intraoperative blood loss (p=0.482), histopathologically-confirmed positive surgical margins (p=0.089) and hospitalization (p=0.195). Regarding renal tumoral enucleation mean (range) operating time for RTE in Group A was 110.6 (70-165) minutes *vs*. 98 (80-140) minutes of Group B (p=0.5151); intraoperative blood loss and hospitalization resulted comparable (p=0.487 and p=0.379 respectively). In both groups there were no positive surgical margins, while in Group B a peritumoral pseudocapsule incision was discovered. *Discussion:* This study should be considered a step in driving down costs of Da Vinci - assisted surgery by reducing the number of laparoscopic and robotic surgical instruments and adjusting the relative passages of each procedure. Our instrumentation expedients, compared with conventional robotic radical prostatectomy and robotic nephron sparing

Table II. *Robotic radical prostatectomy.*

First 20 cases				Last 20 cases			
Item	no.	Unitary cost (€)	Total cost (€)	Item	no.	Unitary cost (€)	Total cost (€)
Sterile drape for arms	3	100	300	Sterile drape for arms	2	100	200
Sterile drape for camera	1	100	100	Sterile drape for camera	1	100	100
Cadiere Forceps	1	471	471	Cadiere Forceps	1	471	471
Hot Shears (Monopolar Curved Scissors)	1	753	753	Hot Shears (Monopolar Curved Scissors)	1	753	753
Meryland Bipolar Forceps	1	636	636	Large Needle Driver	1	516	516
Permanent Cautery Hook	1	470	470	Robotic trocar	3	0	0
ProGrasp Forceps	1	500	500	Sterile robotic trocar mount	3	37	111
Large Needle Driver	2	516	1032	12" laparoscopic trocar	2	92	194
Robotic trocar	3	0	0	Single-use suction irrigator	1	105	105
Sterile robotic trocar mount	3	37	111	Tip for suction irrigator	1	21	21
5" laparoscopic trocar	1	92	92	Laparoscopic needle driver	1	0	0
12" laparoscopic trocar	2	92	194	Johan grasping forceps	1	0	0
Single-use suction irrigator	1	105	105	Hem-o-lok Clips (5-pieces blister)	2	12	24
Tip for suction irrigator	1	21	21	Endo Catch	1	70	70
Laparoscopic needle driver	1	0	0	Monocryl 2/0 UR6/SH	2	6	12
Laparoscopic scissors	1	70	70				2577
Johan grasping forceps	1	0	0				
Hem-o-lok Clips (5-pieces blister)	2	12	24	Mean saving: 48%			
Endo Catch	1	70	70				
Monocryl 2/0 UR6/SH	2	6	12				
			4961				

surgery, determined a saving up to 49.1% for each single procedure. In our experience intraoperative blood loss, operative time, intra and postoperative complications, hospitalization and the finding of histopathologically positive surgical margins was comparable to the standard procedures.

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DETRUSOR HYPOCONTRACTILITY AFTER OPEN RETROGRADE, ANTEGRADE AND ROBOT-ASSISTED RADICAL PROSTATECTOMY: FUNCTIONAL AND URODYNAMIC PRELIMINARY DATA

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Objectives: The aim of the study is to evaluate functionally and urodynamicaly the newly-onset of detrusor hypocontractility in patients undergone radical prostatectomy through different approaches. *Patients and Methods:* We peospectively evaluated 59 consecutive patients undergone open retrograde (ORP), 64 open antegrade (OAP) and 52 robot-assisted radical prostatectomy (RRP) for clinically localized prostate cancer. Groups were homogeneous in terms of clinical and pathological staging, preoperative PSA and bioptic and pathological Gleason Score. Functional follow-up included the administration of ICIQ-SF questionnaire at months 1,3,6 and 12 and uroflowmetry at the 6th month postoperative. In case of non pathological flow and post micturition residual (PMR)≥30cc in patients without preoperative PMR we performed urodynamic evaluation according to International Continence Society (ICS) recommendations. *Results:* Data were complete for 53 patients undergone open retrograde (ORP), 61 to open antegrade (OAP) and 52 to robotic-assisted radical prostatectomy (RRP). Mean follow-up was (range) 23.7(13-49) months. Overall, 88.5% of ORP, 89.2 of OAP and 90.5% of RRP Group patients fulfilled our continence criteria (≤1pad and ICIQ-SF≤2) at a minimum follow-up of 12months. In ORP Group 11/24(45.8%) patients without preoperative PMR developed a postoperative PMR≥30cc, 12/27(44.4%) of OAP and 8/32(25%) of RRP. These patients

were further investigated through urodynamic study. In ORP Group we identified a true newly-onset PMR significantly linked to a detrusor hypocontractility in 8/11(72.7%) patients: mean Qmax, PDet and PMR of patients with true PMR were (range) 11.8(5.9-14.5)mL/s, 31.7(18.1-45.1)cmH_2O and 42(32-56)cc *vs*. 13.2(8.2-16.2)mL/s, 33.7(20.6-47.2)mmH_2O and PMR<30cc in the remaining 3 cases. In OAP Group mean Qmax, PDet and PMR of the 6/12(50%) patients with true PMR were (range) 13.6(6.8-19.4)mL/s, 32.4(19.6-45.3)cmH_2O and 36.4(32-48)cc *vs*. 14.5(8.1-15.3)mL/s, 37.8(21.2-48.9)mmH_2O and PMR<30cc in the remaining 6 cases. In RRP Group mean Qmax, PDet and PMR of the 2/8(25%) patients with true PMR were (range) 14.2(9.1-19.3)mL/s, 36.2(25.5-46.9)cmH_2O and 35.4(32-38.4)cc *vs*. 15.1(10.7-19.5)mL/s, 40.4(30.2-50.6)mmH_2O and PMR<30cc in the remaining 6 cases. A significant correlation of surgical procedure to the onset of detrusor hypocontractility which were greater in ORP Group *vs*. OAP one (p=0.0036), in OAP Group *vs*. RRP one (p=0.006) and in ORP Group *vs*. RRP Group (p<0.0001). The exiguity of RRP patients with true PMR did not allow the comparison of various nerve-sparing techniques. *Conclusion:* A newly-onset post micturition residual in patients undergone radical prostatectomy may be due to a detrusor hypocontractility; its various prevalence among the surgical techniques may be referred to different nervous fibers of hypogastric plexus stress during isolation of seminal vesicles: thus, bladder mobilization and traction are greater during open retrograde than open antegrade and robot-assisted prostatectomy in which bladder manipulation is usually limited to the neck region. The extension of pre- and post-operative urodynamic evaluation to patients with and without preoperative PMR and to nerve-sparing procedures could better define the efficacy of PMR as a signal of detrusor hypocontractility.

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CLAMPLESS ROBOT-ASSISTED RENAL TUMORAL ENUCLEATION: INTRA AND POSTOPERATIVE IMPLICATIONS OF CONTROLLED HYPOTENSION

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Aim: The most important limitation to nephron sparing surgery (NSS) is usually represented by renal ischemia. Since the introduction of NSS techniques, several approaches have been applied (cold ischemia, early declamping of renal hilum, selective arterial branches clamp, superselective clamping, preoperative embolization of tumoral arterial branches) to avoid or to reduce renal ischemia. In literature is emphasized in order the need of keeping down renal ischemia under 20-30 minutes to reduce the risk of irreversible damage to renal parenchyma. The aim of this study is to evaluate the feasibility and safety of robotic-assisted renal tumoral enucleation (RTE) with controlled hypotensive anesthesia to avoid hilar clamping and eliminate renal ischemia. *Patients and Methods:* From April 2011 to January 2014 65 consecutive patients underwent robotic surgery for clinically localized renal cancer. Overall 61/65 patients presented no major contraindications to hypotensive anesthesia; mean age (range) was 64 (42-79) years. RTE is usually performed through a transperitoneal approach without renal hylum isolation. Tumoral enucleation is performed by blunt dissection using the natural cleavage plan between the pseudocapsule and renal parenchyma. In postoperative period, patients were evaluated by daily physical examination and routine blood tests on day 1 and 3. Additional examinations were performed in selected cases. *Results:* Mean arterial pressure during controlled hypotension was 66 mmHg (ranging between 62 and 95 mmHg) and hypotension was prolonged meanly for 10.8 (range: 8.5-20.3) minutes. Mean (range) operative time was 98.7 (71-182) minutes with mean blood loss of 150 ml (55-480 ml). No patients required intraoperative blood transfusions. Mean (range) tumor size was 27 (10-68) mm and mean postoperative hospital stay was 3.1 (2-10) days. Overall 3 patients developed postoperative complications: 1 anemia treated by blood transfusions and 2 delayed canalization that required nasogastric tube insertion. No patients developed major medical complication (syncope, heart failure, stroke). In two cases we observed fatigue that regressed on postoperative day 3. Mean (range) pre- and post-operative serum creatinine was 1.0 (0.7-2.2) and 1.2 (0.7-2.7) mg/dl respectively (p=0.487); mean estimated pre and postoperative glomerular filtration rates were 85.9 and 75.2 ml/minute/1.73m^2. At histopathological evaluation no positive surgical margins were found; in only 2 cases a peritumoral pseudocapsule incision was discovered. *Discussion:* In literature it is widely demonstrated the need of minimizing ischemia during nephron sparing surgeryfor renal tumors. Controlled hypotension may be an alternative to warm ischemia with renal hilar clamping or to superselective clamping of arterial branches. Robotic assisted zero ischemia tumoral enucleation technique is a reasonable approach to renal tumours irrespective of dimensions. Moreover, in our series, avoiding hilar clamping did not increase the intra and postoperative complication rate and provided excellent functional outcomes. Limit of this study: available data are not adequately mature to determine long-term functional outcomes and further experience and follow-up is mandatory.

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CONTRAST-ENHANCED ULTRASOUND (CEUS) IN DIFFERENTIATING LOW/HIGH-GRADE BLADDER CARCINOMA THROUGH SIGNAL TIME/INTENSITY CURVES: PRELIMINARY DATA

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Aim: To evaluate the efficacy of time/intensity curves (T/IS) for quantitative analysis of contrast kinetics during contrast-enhanced ultrasound (CEUS) in differentiating low and high-grade bladder carcinomas. *Patients and Methods:* We prospectively evaluated with CEUS 82 patients with cystoscopically-detected bladder tumors. Lesions were first scanned with a gray-scale ultrasonography and color Doppler US to obtain their location and size and the best imaging plane to observe the lesions and the normal adjacent bladder wall. Thereafter, contrast enhanced agent (SonoVue, Bracco®, Milan, Italy) was injected intravenously as a bolus (average 2.5 ml/sec) 4.8 ml dose followed by 10 ml of normal saline flush. Each exam lasted about 3 min following bolus injection. One post-contrast cine clip was acquired lasting approximately 150 sec. If necessary, the injection was repeated 15 min later. 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). All patients underwent transurethral resection (TURBT) according to EAU Guidelines recommendations. In case of multifocal tumors, every lesion was sent separately for histopathological evaluation. Perfusion kinetics have 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:* Overall, conventional gray-scale ultrasonography and CEUS identified 110 of the 134 bladder lesions discovered during cystoscopy. At histopathological evaluation all tumors were transitional cell bladder carcinomas; of these, 74/110 (67.2%) were high-grade and 36 (32.8%) low-grade. A significant correlation was found between type I and II patterns and high-grade carcinomas, while low-grade lesions usually presented type III-IV curves (p=0.0032). Mean (range) peak of signal intensity (SI) enhancement of high-grade tumors was 41(35-55)%, while lower mean (range) peaks of SI enhancement such as 28(17-32)% were more representative of low-grade lesions (p=0.00681). The correlation between CEUS plus T/IS curves and pathological staging was statistically non-significant (p=0.18). With regards to the small series, the T/IS curves showed a sensibility of 86.5% and a specificity of 91.2%. None of the patients has suffered adverse reactions to CEUS contrast agent, and no renal function worsening was suspected. *Conclusion:* Contrast-enhanced ultrasound can be useful to better define bladder carcinomas: time/intensity shapes and the quantitative analysis of contrast kinetics may help in distinguishing between biologically aggressive urothelial tumors to low-grade lesions. Wider series may lead to a more accurate predictivity of T/IS curves and to develop a tailored preoperative planning and timing; moreover, CEUS may be useful in postoperative follow-up of patients with Ta-T1 tumors non-suitable for the recommended repeated cystoscopic schedule.

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CONTRAST-ENHANCED ULTRASOUND (CEUS) IN EVALUATION OF DETRUSOR MUSCLE INVASION IN BLADDER CARCINOMAS: PRELIMINARY DATA

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Aim: To evaluate the efficacy of time/intensity curves (T/IS) for quantitative analysis of contrast kinetics during contrast-enhanced ultrasound (CEUS) in determining the detrusor muscle invasion in bladder carcinomas. *Patients and Methods:* We prospectively evaluated with CEUS 82 patients with cystoscopically-detected bladder tumors. Lesions were first scanned with a gray-scale ultrasonography and color Doppler US to obtain their location and size and the best imaging plane to observe the lesions and the normal adjacent bladder wall. Thereafter, contrast enhanced agent (SonoVue, Bracco®, Milan, Italy) was injected intravenously as a bolus (average 2.5 ml/sec) 4.8 ml dose followed by 10 ml of normal saline flush. Each exam lasted about 3 min following bolus injection. One post-contrast cine clip was acquired lasting approximately 150 sec. If necessary, the injection was repeated 15 min later. 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). If detrusor muscle invasion was suspected the patient was addressed to a contrast-enhanced CT (CECT). All patients underwent transurethral resection (TURBT) according to EAU Guidelines recommendations. The bladder wall with the detrusor muscle underlying the lesion was sent separately for histopathologic evaluation. *Results:* Overall, conventional

gray-scale ultrasonography and CEUS identified 110 of the 134 bladder lesions discovered during cystoscopy. At histopathological evaluation all tumors were transitional cell bladder carcinomas; of these, 36 (32.8%) were Ta low-grade (LG), 8/110 (7.2%) Ta high-grade (HG), 60/110 (54.5%) were T1 HG and 6/110 (5.5%) T2. CEUS demonstrated a matching diagnosis with histopathological evaluation in identifying the depth of bladder wall invasion in 6/8 (75%) of Ta LG, 13/36 (36.1%) of Ta HG, 37/60 (61.7%) of Ta HG and in 5/6 T2 cases (83.4%). A significant correlation was found between CEUS and histopatology in the evaluation of the depth of bladder wall invasion in Ta LG *vs*. T2 cases (p=0.00297), but it was not significant in characterizing Ta HG from T1 HG tumors (p=0.216). With the obvious limitation of the small series and the variability of interpretation CEUS seemed to be more accurate than CECT in evaluating cT2a tumors. T/IS shapes of exophytic part of tumor was comparable to the underlying invaded bladder wall, while a slight increasing of signal intensity (SI) enhancement in endophytic *vs*. exophytic parts of the evaluated carcinoma (p=non-evaluable) was observed. With regards to the small series, the T/IS curves showed a sensibility of 100% and a specificity of 83.4% in identifying cT2 tumors. None of the patients has suffered adverse reactions to CEUS contrast agent, and no renal function worsening was suspected. *Conclusion:* Contrast-enhanced ultrasound adequately defines bladder carcinomas: time/intensity shapes and the quantitative analysis of contrast kinetics can distinguish biologically aggressive urothelial tumors from low-grade lesions. Moreover CEUS may represent a low-cost, highly-sensitive exam to evaluate detrusor muscle invasion in bladder carcinomas. Wider series are justified to develop a tailored preoperative planning and timing; moreover CEUS may be useful in postoperative follow-up of patients with Ta-T1 tumors non suitable for the recommended repeated cystoscopic schedule.

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CONTRAST-ENHANCED ULTRASOUND (CEUS) IN DETECTION OF SESSILE BLADDER CARCINOMAS: PRELIMINARY DATA

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Objective: According to scientific literature and EAU guidelines the most accurate diagnostic exam for detection and follow up of vescical lesion is cystoscopy. In daily practice, ultrasonography is often adopted as a non-invasive examination proposed to avoid iterate invasive procedures. The most important limitation of ultrasonography is the low detection rate of small and sessile tumors and the inability to identify the aggressiveness of bladder tumors. The aim of the study is to evaluate the efficacy of contrast – enhanced ultrasound (CEUS) in detecting sessile bladder carcinomas to tailor a preoperative planning and timing and high-sensitive, non invasive postoperative follow-up. *Methods:* We prospectively evaluated with CEUS 82 patients with cystoscopically-detected bladder tumors. Lesions were first scanned with a gray-scale ultrasonography and color Doppler US to obtain their location and size and the best imaging plane to observe the lesions and the normal adjacent bladder wall. Thereafter, contrast enhanced agent (SonoVue, Bracco®, Milan, Italy) was injected intravenously as a bolus (average 2.5 ml/sec) 4.8 ml dose followed by 10 ml of normal saline flush. Each exam lasted about 3 min following bolus injection. One post-contrast cine clip was acquired lasting approximately 150 sec. If necessary, the injection was repeated 15 min later. A quantitative analysis of enhancement was performed using a dedicated software (QONTRAST, manufactured by Esaote for Bracco Group) that elaborates colorimetric maps and processes Time/Intensity (T/IS) curves on region of interest (ROI). All patients underwent transurethral resection (TURBT) according to EAU Guidelines recommendations. In case of multifocal tumors, every lesion was sent separately to histopatologic evaluation. *Results:* During preliminary cystoscopic evaluation, 39 sessile and 95 papillary tumors were found. Overall, conventional gray-scale ultrasonography (US) and CEUS identified 110 of the 134 bladder lesions discovered during cystoscopy. Preliminary gray-scale US identified 17/39 (43.6%) sessile lesions and 61/95 (64.2%) papillary lesions; mean (range) dimensions were 9 (5-22)mm and 12 (4-36)mm respectively. Overall, after contrast injection 30/39 (76.9%) sessile and 80/95 (84.2%) papillary lesions were discovered. All lesions undiscovered during gray-scale US were found to be very slightly exophytic (mean 2mm, range 1-6mm). At histopathological evaluation all tumors resulted in transitional cell bladder carcinomas; of these, sessile lesions were identified as Ta low-grade (LG) in 3/39 cases (7.7%), Ta high-grade (HG) in 7/39 (17.9%), T1 HG in 28/39 (71.8%) 1 T2 (2.6%). Overall, 31/95 (32.7%) papillary lesions were found to be Ta low-grade (LG), 7/95 (7.3%) Ta high-grade (HG), 52/95 (54.8%) were T1 HG and 5/95 (5.2%) T2. CEUS resulted in a statistically significant (p<0.0001) detection of both, sessile and papillary tumors and had a better detection rate compared to standard greyscale US: 43.6 *vs*. 76.9 for sessile tumors and 64.2 *vs*. 84.2 for papillary tumors, respectively. None of the patients has suffered adverse reactions to CEUS contrast agent, and no renal function worsening was suspected. *Discussion:* In our experience

CEUS demonstrated to be a safe, fast and low cost-procedure. It doesn't require a long learning curve and the hard disk storage of every exam allows to perform time/intensity curves in post processing phase. CEUS can be useful to better define bladder carcinomas: in our experience CEUS demonstrated a high detection rate for both papillary and sessile tumors.

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MULTIMODAL TREATMENTS FOR CLEAR CELL RENAL CELL CARCINOMA: TWO CASE REPORTS OF NEPHRON-SPARING STRATEGIES

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Aim and Background: The scenario of kidney cancer has been drastically changing during the last 10 years, shifting from a treatment orphan panorama to a multimodal approach based on less invasive surgery, targeted therapies and non-surgical options for localized disease. We report results on two different cases of multimodal treatment tailored on patient and finalized to renal function preservation. *Patients and Methods:* Patients were diagnosed and treated at the University Hospital of Trieste, Italy. Both of them received TKIs first followed by a nephron sparing approach. *Results:* Case 1. A 67 years old man, PS 0 suffering only from mild hypertension and left congenital contracted kidney with normal kidney function. In 2013 a thorax and abdomen CT scan showed a 4 cm mesorenal mass in the right kidney, without distant metastases. The kidney biopsy evidenced clear cell RCC (ccRCC), Furhman G2. Disease local extension and mesorenal location did not allow partial nephrectomy at the diagnosis. Sunitinib was administered at the dose of 50 mg o.d. 4 weeks on/2 weeks off. The main toxicity experienced was G2 hypertension. After 2 cycles, a reduction in size (2.5 cm) and vascularisation of the lesion was observed and the patient underwent right nephron sparing surgery with final diagnosis of pT1 ccRCC, G2, R0. After 6 months of follow up, kidney function was preserved with no evidence of disease progression. Case 2. A 77 years old woman; PS 1 with clinical history of mild hypertension, right emicolectomy for stage III colon carcinoma in 2006, right quadrantectomy for stage II breast carcinoma in 2009. In 2005 the patient underwent right nephrectomy for ccRCC (pT2, G2) and in 2011 left kidney nephron sparing surgery for ccRCC (pT1a, G1). In 2013 bilateral metastases and left kidney mesorenal relapse (2×1.8 cm) appeared. Pazopanib at the dose of 600 mg o.d. was started. Main toxicity experienced from the patient was G2 hypertension. After 2 cycles of treatment, a CT scan showed size reduction of pulmonary metastases and of kidney relapse (1.1 cm). The treatment is still ongoing and we are considering the patient for cryoablation of the kidney lesion in order to avoid local progression and maintain renal function. *Discussion and Conclusion:* The incidence of RCC is increasing and observational studies have shown equivalent oncological outcomes with a lower rate of postoperative decline in kidney function for partial *versus* radical nephrectomy for early stage tumours (1). Renal failure can be the consequence of intrinsic abnormalities in non-neoplastic kidney and comorbid conditions (including diabetes, hypertension, congenital contracted kidney) or, in a small proportion (2-4%), to a methacronous controlateral RCC (2). Since 2007 several oncological treatments have been available for metastatic/ inoperable RCC, with a 30% response rate. Cryoablation and radiofrequency ablation are promising therapies in patients with small renal tumours (<4 cm), who are considered poor candidates for more involved surgery (3). We report about two different cases in which a multimodal approach has been preferred to radical nephrectomy alone to preserve long-term kidney function. Renal preservation must be taken into account when planning the treatment because of detrimental effects on patient quality of life and related costs (*e.g.* long-term dialysis). The role of targeted therapies in facilitating nephron sparing treatments has not been established yet, despite promising results in neoadjuvant setting for advanced disease. Multimodal treatments with a nephron sparing aim should be further evaluated in multicentre randomized clinical trials to define cost-effectiveness and long-term oncological results.

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PROSTATE VOLUME: A TOXICITY PREDICTOR IN RADIOTHERAPY AND AN INTERESTING TARGET FOR NEOADJUVANT HORMONAL THERAPY

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Introduction: Neoadjuvant androgen deprivation has several advantages in the treatment of prostatic cancer. These include

apoptosis of cancer cells, radiation sensitization and prostate volume reduction. Hormonal therapy has favorable effects not only on outcome but also on toxicity in men treated with radiation therapy. In fact prostate dimensions may influence the incidence of radiotherapy-associated toxicity since large target volumes increase the risk of irradiation of surrounding normal tissue, in particular rectum, which is the principal dose-limiting organ at risk. The aim of this study is to correlate prostate volume with irradiated rectal volume. *Patients and Methods:* From January to December 2013, 63 patients with prostate cancer (age: 64-86 years) received a conventional or hypofractionated radiation therapy with curative intent. Patients were stratified according to stage, Gleason score and PSA. All patients received neoadjuvant hormonal therapy that started at least two months before the radiotherapy onset. Treatments were delivered using four to six coplanar 10-18 MV photon beams at a dose of 80 Gy in 2 Gy fractions or 70 Gy in 2.5 Gy fractions. Target volumes included prostate with or without seminal vescicles. Final target volumes (CTV1) included whole prostate in 58 patients and prostate and seminal vescicles in 5 patients. We looked for rectal volumes receiving 50 Gy (V50) and 65 Gy (V65), or the corresponding doses in hypofractionation according to the linear-quadratic model with an alpha/beta ratio of 4 for rectal tissues. *Results:* Prostate volumes (in ccm) and rectal volumes (in %) were obtained from dose-volume histograms. Median target volume was 56.1 ccm (range: 24.7-171.5 ccm). Median V50 was 41.9% (range: 11.3-59.7). Median V65 was 23.1% (range: 3.1-33.5%). We studied the correlation between CTV1 and V50/V65 predicting for rectal toxicity. Both parametric and non-parametric tests were performed. We found a statistically significant correlation between target volume and V50 (p=0.02) or V65 (p=0.0001). The larger the target volume, the larger is the rectal volume receiving radiation, especially at higher dose levels. Our analysis shows that prostate volume represents a toxicity predictor in the radiation therapy of localized prostate cancer. *Discussion and Conclusion:* Many descriptive studies confirm the clinical experience of a significant size reduction of prostatic volume during androgen suppression. The most pronounced changes occur during the first 3 months after the start of hormone manipulation and continue till 9 months; thereafter, no further substantial reduction of volume occurs. If we consider an established fact that androgen deprivation causes prostate downsizing, neoadjuvant hormonal therapy can decrease rectal toxicity in men undergoing radiotherapy. Randomized studies on neaoadjuvant hormonal therapy and radiotherapy should assess also this interesting aspect along with the benefits on outcome.

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NEPHROGENIC ADENOMA-LIKE CLEAR CELL ADENOCARCINOMA OF THE BLADDER IN A PATIENT WITH ENDOMETRIOSIS

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Introduction: Clear cell adenocarcinoma (CCA) of the lower urinary tract is an uncommon malignant tumor with uncertain histogenesis, usually occurring in women and sometimes associated with endometriosis (1-2). A recent study identified a subset of urinary CCA where either the entire lesion or its major component strikingly resembles nephrogenic adenoma (NA) (2-3). Such peculiar variant, called nephrogenic adenoma-like clear cell adenocarcinoma (NA-like CCA), is extremely difficult to diagnose in small specimens, and was never been observed concurrently with bladder endometriosis (2, 3). We report a case of NA-like CCA of the urinary bladder observed in a 50-year-old female patient with a long history of endometriosis. *Patients and Methods:* A 50-year-old woman went to our observation with hematuria, after a prolonged history of endometriosis and hormonal treatment to get pregnant, followed by a triple birth. A routine control ultrasonography displayed a periuterine thickening involving the rectal wall, with a projection into the bladder lumen. Cystoscopy revealed a multicystic polypoid protrusion, measuring 1 cm in largest diameter, in the left lateral wall of the bladder that was resected, allowing the diagnosis of NA-like CCA, coexisting with endometriosis. A repeated bladder trans-urethral resection showed adenocarcinoma and endometriosis remnants. The patient moved to another hospital and underwent bladder resection, hysterectomy and

rectum resection with multiple peritoneal biopsies. *Results:* The specimen consisted of multiple fragments. Histological examination of the formalin-fixed material showed a neoplastic proliferation of tubular and cystic structures containing necrotic material with focal papillary and solid areas. Neoplastic cells showed multifocal hobnail features, and diffuse nuclear atypia with frequent mitotic figures. Neoplastic cells were diffusely immunoreactive for cytokeratin 7, estrogen receptors, racemase, and PAX-8; they were negative for cytokeratin 20, p63, and cytokeratin 34βE12. The proliferation index, evaluated by Ki-67 nuclear expression was 35%; p53 nuclear expression was 25%. These features allowed the diagnosis of NA-like CCA of the bladder, invading the lamina propria. Other fragments showed histologic findings consistent with bladder endometriosis. *Discussion and Conclusion:* CCA of the urinary tract is a rare, aggressive type of carcinoma arising predominantly in the urethra or bladder of postmenopausal women and associated with poor prognosis (2). The histogenesis of these tumors is still unclear. They were originally regarded as mesonephric (wolffian) lesions, but this theory has largely been abandoned (1-2). A paramesonephric (müllerian) origin has also been suggested because of the association with concurrent endometriosis in some cases and the expression of CA125 (1-2). The nephrogenic origin (tubular cell differentiation) has also been suggested because of the peculiar immunohistochemical profile, histologic features similar to NA and a documented evolution of nephrogenic metaplasia to CCA (2-3). Coexistence of NA-like CCA with endometriosis represents an exceptional finding and may confirm the possibility that such lesions may arise from more than one tissue of origin (3).

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SIURO-PRIAS-ITA PROJECT: FOUR YEAR EXPERIENCE ON ACTIVE SURVEILLANCE

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Introduction: We hereby report on the 4 year SIUrO-PRIAS-ITA experience on Active Surveillance (AS). Special focus is given on the correlations between Active Treatment Free Survival (ATFS) and patient's characteristics at diagnosis, with the aim of investigating the ability to predict disease reclassification. *Materials and Methods:* In December 2009 the SIUrO-PRIAS-ITA project started including patients in PRIAS (Prostate cancer Research International: Active Surveillance). Eligibility criteria are: iPSA≤10 ng/ml, Gleason Score≤6, T1c or T2a, PSA density≤0.2 ng/ml/cc, maximum 2 positive cores. Actuarial ATFS was assessed using Kaplan-Meier analysis. Correlation between ATFS and clinical risk factors were determined using the log rank test and Cox Proportional Hazards Model. *Results:* Between December 2009 and January 2014, 480 patients were enrolled in SIUrO-PRIAS-ITA. Median age at inclusion was 65 years (range 42-80 years), median iPSA was 5.46 ng/ml (range 0.5-9.91ng/ml). 355/480 patients (74%) are still on AS with a median follow-up of 21 months (range 2-59 months), median time

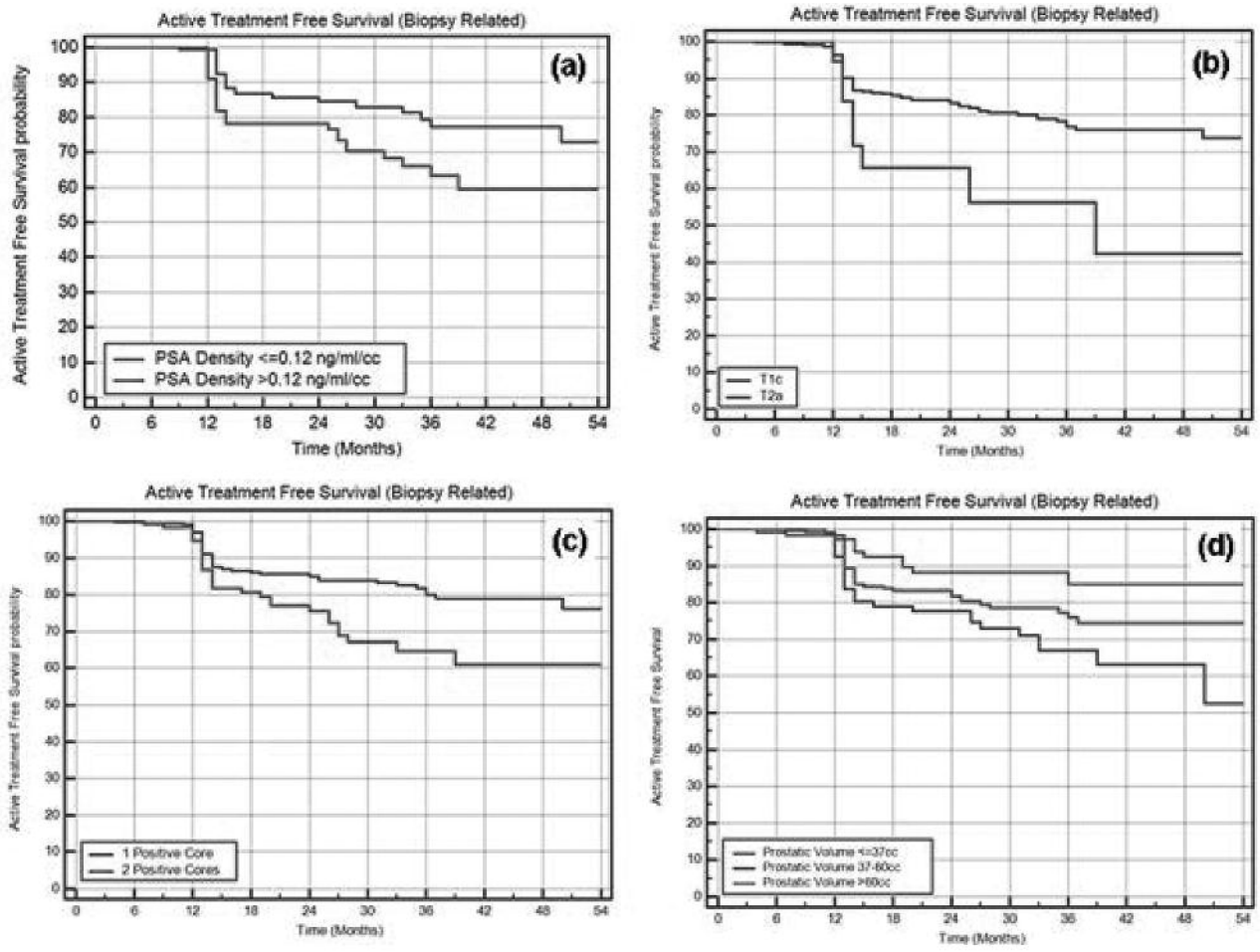

Figure 1. *Kaplan-Meier curves for Active Treatment Free Survival (biopsy related causes): (a) as a function of PSA density; (b) as a function of DRE; (c) as a function of number of positive cores; (d) as a function of prostatic volume.*

in AS is 14 months (range 0.13-58.8mos). 137/480 (28.5%) patients had two positive cores at diagnostic biopsy. 457/480 (92.5%) patients were classified as T1c at DRE. 80 patients (16.6%) dropped out from AS because of disease progression/reclassification: 6 due to PSA doubling time and 72 due to upgrading and/or upsizing at re-biopsy (54/72 at 1 year re-biopsy). 36 patients dropped out due to off-protocol reasons (mainly comorbidities or personal choice). Biopsy-driven ATFS resulted to be correlated to PSA density≤0.12 ng/ml/cc (p=0.022, ATFS at 30 months 83% *vs*. 78%, ATFS at 48 months 77% *vs*. 43%), prostate volume (p=0.01, volume stratified in three groups: ≤40 cc, 40-60 cc, ≥60cc, ATFS at 30 months 73% *vs*. 78% *vs*. 88% respectively, ATFS at 48 months 63% *vs*. 74% *vs*. 85%), DRE=T2a (p=0.009, ATFS at 30 months 80% *vs*. 56%, ATFS at 48 months 76% *vs*. 42%), number of positive cores at diagnostic biopsy=2 (p=0.006, ATFS at 30 months 84% *vs*. 67%, ATFS at 48 months 79% *vs*. 60%), and number of total cores at diagnostic biopsy≤12 (p=0.019, ATFS at 30 months 73% *vs*. 84%, ATFS at 48 months 69% *vs*. 77%). Kaplan Meier curves are shown in Figure 1. Best fit multivariable Cox model for biopsy-driven ATFS resulted in a 3-variable model (overall p=0.03, AUC=0.70) including DRE= T2a (risk factor, p=0.04, HR=2.2), prostate vol≤60cc (risk factor, p=0.18, HR=1.86) and PSA density (continuous variable, risk factor, p=0.33, HR=1.03). *Conclusion:* AS is feasible in selected men with early prostate cancer. Most drop outs occurred due to 1 year re-biopsy, which should probably be considered as a confirmatory biopsy. PSA density, DRE, number of positive cores at diagnostic biopsy and prostate volume correlate with biopsy-related ATFS as risk factors for reclassification. Cox multivariable model confirms the independent value of PSA density, DRE and prostate volume.

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EXTRAPERITONEAL RADICAL CYSTECTOMY: EXPERIENCE IN THE ELDERLY PATIENT (>78/80 YEARS)

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Introduction: The incidence of bladder cancer increases with age. Individuals over the age of 70 years develop the disease 2-3 times more frequently than those aged between 55 and 69 and 15-20 times more often than in subjects between 30 and 54 years old. The peak incidence is observed around 85 years of age. Due to demographic changes, we expect the tripling of the number of octogenarians in the next 25 years, and as a result an increase of elderly patients with bladder cancer, non-invasive, but also invasive. Therefore, the morbidity and mortality from invasive bladder cancer will become more relevant clinically, socially and financially. Radical cystectomy is the gold standard in the treatment of locally advanced bladder cancer, although sometimes surgery is a palliative option for improving the quality of life of the patient or to fix are the continuing complications affecting these patients, such as hematuria, anemia, pelvic pain, hydronephrosis and Ira. The role of cystectomy in the elderly is not clearly defined. There are few works published by centers of excellence, which document the feasibility of this approach in the elderly, and it is still unclear whether these findings can be extrapolated to a broader base (1, 2). We therefore carried out extraperitoneal radical cystectomy in elderly patients (>78 years). The aim of our study was to evaluate the feasibility and simultaneously the morbidity and mortality of this procedure in elderly patients. *Materials and Methods:* From April 2002 to December 2012, at the Department of Urology of Rummo of Benevento 235 patients, underwent radical cystectomy and urinary diversion; among them 70 had more than 78 pcs aa (range 75 - 89aa, age average 79.2 yr). Of the 70 pcs over 78 years of age, the last 35 treated (June 2008 to December 2012) were subjected to radical cystectomy extra-peritoneal. All patients underwent radical cystectomy with packaging ureterocutaneostomy unilateral or bilateral. In this work we have considered the effects pcs over 78 years of age where cystectomy, elective or "save" was performed by extraperitoneal approach by comparing them with a similar group of pieces in which the surgery was performed with standard technique trans-peritoneal. In the post-operative complications were evaluated in the short term (peri-operative) and long-term were also calculated blood loss and the number of units of packed red blood cells transfused, estimated the total number of inpatient hospital days from the date of cystectomy, calculated the incidences of complications on length of stay. *Results:* The operative time was 120 minutes (100-180 min), the mean blood loss of 400 cc (250-800 cc). The patients were evaluated in the immediate post-operative and then at 3 and 6 months. The mean hospital stay was 8 days (5-18 days). 23 patients are alive at fifteen months. Early medical complications were 1 pulmonary microembolism resolved with medical therapy, 2 cases of respiratory failure treated with medical therapy department, 3 cases of disorientation, 1 death in the immediate post -operative heart failure, and 1 death per ima. Were transfused an average of 2 units of packed red blood cells/pcs (taking into account that many were malignancies bleeding)Early surgical complications. 2 cases of hematoma/abscess pelvic cavity, 2 of diastasis of the wound, was 1 of occlusive intestinal subjected to exploratory laparotomy and found to be a spontaneous perforation of an ischemic ileal loop. Medical complications later. 1 case of stroke within 20 days after death. Late complications surgery. 1 case of hematoma/abscess pelvic cavity, 1 lymphocele, 1 incisional hernia of the median. *Discussion and Conclusion:* Radical cystectomy is the treatment of choice for invasive bladder cancer or non-muscle invasive unresponsive to other therapies, and such therapy can be applied in cases of election or need. Our study evaluated the feasibility of cystectomy in elderly patients, proving that age is not a priori an element that can be ruled out only by surgery, thanks to continuous improvements in surgical and anesthetic techniques. For this reason, extraperitoneal surgery was performed predominantly in elderly patients. Complications in patients undergoing cystectomy due to extraperitoneal were lower than trans-peritoneal approach (34 % *versus* 46%). In particular, the extraperitoneal approach, reduced operative time, blood loss and incidence of discanalizzazione, wound dehiscence, and, to a lesser extent, reduced respiratory and thromboembolic complications. It aslo increased mobilization and channeling power recovery. The hospitalization was shorter than 5 days, while the longest was 18 days (patient with hospitalization complicated by melena). The average hospital stay of patients in whom cystectomy was performed by extraperitoneal was 8 days, compared to 10 days in the other group of pcs. Radical cystectomy extraperitoneal is a technique based on a precise knowledge of the anatomy, requires a careful dissection, intrinsically superior to the conventional technique. In our series, it appears that the extraperitoneal approach allows a postoperative burdened with fewer complications, with an earlier mobilization and channeling, which allows the recovery power already in the 2nd - 3rd day to some, a lower incidence of thromboembolic events, dehiscence of the wound and, to a lesser extent, reduced incidence of respiratory complications.

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LONG-TERM SURVIVAL OF A PATIENT WITH CHROMOPHOBE RENAL CELL CARCINOMA TREATED WITH A SEQUENCE OF TARGETED THERAPIES

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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, the efficacy of these molecules on other subtypes of renal cell carcinoma still remains uncleared. We describe a case of a 58-year-old male patient (B.A.) who underwent nephrectomy on January 2000 for a histologically confirmed chromophobe renal cell carcinoma (ChRCC), infiltrating the parenchyma and renal capsule (T3N0Mx). In 2003 a CT scan detected abdominal, retoperitoneal and splenic hilar lymph node metastases, and the patient was enrolled in an experimental protocol using IL2-2 + IFNα 2. In April 2007 the size of all lymph node metastases increased, so the patient started treatment with Sunitinib (50 mg/die standard schedule), obtaining an initial tumour response (<30% reduction of the size of metastases) then a stable disease till December 2010, when a CT scan control showed disease progression with onset of liver metastases. Sorafenib (800 mg daily) was started and the treatment was continued till July 2011, obtaining stable disease. In August 2011, due to disease progression, we chose to begin treatment with Everolimus (10 mg daily), continued for almost two years, when a CT-scan showed disease progression with onset of lung metastases. In August 2013 the patient began a new treatment with Bevacizumab (10 mg/kg every two weeks + IFNα2 3.000.000 UI, three times a week). This treatment is currently ongoing and is very well tolerated. All the treatments were well tolerated and didn't require dose reduction. Maximal adverse effects of Sunitib were G2 hyperthension and subclinical hypothyroidism. Sorafenib determined G2 hyperthension, Everolimus caused G2 hand-foot syndrome, G2 anaemia and Herpes Simplex Virus reactivation. This case suggests that even in "not clear cell" 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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CXCR4 INHIBITION REDUCES BONE METASTASES BY AFFECTING TUMOUR GROWTH AND TUMORIGENIC POTENTIAL IN PROSTATE CANCER PRECLINICAL MODELS

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Background: The majority of prostate cancer (PCa) patient morbidity can be attributed to bone metastatic events, which poses a significant clinical obstacle. Therefore, a better understanding of this phenomenon is imperative and might help to develop novel therapeutic strategies. *Methods:* In this report, we analyzed the expression of CXCR4 in human tissues from prostate cancers, and tested *in vitro* and *in vivo* the capabilities of two CXCR4 receptor antagonists, Plerixafor and CTE9908, in order to interfere with bone metastasis of prostate cancer cells. We used two experimental *in vivo* models that resemble sub-clinically and clinically evident bone metastases. *Results:* We observed that bone-derived PCa cells express higher CXCR4 levels than other PCa cell lines; this was also the case in human PCa samples. SDF-1 induced tumor cell migration and invasion, as well as MMP-9, MMP-2 and uPA expression, which were reduced by Plerixafor. Plerixafor reduced PCa cell proliferation and was more effective when PCa were co-cultured with stromal cells, possibly due to high levels of SDF-1a expressed by stromal cells. Plerixafor and CTCE-9908 delayed tumor growth, reduced angiogenesis and bone lesions, increased survival rates, and changed the bone microenvironment. The incidence of X-ray detectable bone lesions was reduced from 80% (8/10), in controls, to 40% (4/10) and 50% (5/10) following Plerixafor and CTE9908 treatment, respectively. Bone-associated tumor growth and associated bone erosion were efficiently decreased in Plerixafor- and CTE9908-treated animals with respect to controls. Kaplan–Meier probability plots showed significantly improved overall survival following Plerixafor and CTE9908 treatment. The reduced intra-osseous growth of PC3 tumor cells after intratibial injection, as a result of Plerixafor and CTE9908 treatment, correlated with decreased osteolysis and serum levels of both mTRAP and type I collagen fragments (CTX), respectively. The anti-metastatic potential of Plerixafor correlated with decreased secretion of proteolytic enzymes (MMP-9, MMP-2 and uPA) and reduced migratory and invasive capacities *in vitro*. *Conclusion:* In summary, our report provides novel information on the potential activity of CXCR4 inhibitors on the formation and progression of prostate cancer bone metastases, and supports this treatment as a useful approach in men with advanced PCa with established metastatic disease or at high risk of bone lesions.

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ANTITUMOR EFFECTS OF SAFFRON-DERIVED CAROTENOIDS IN PROSTATE CANCER CELL MODELS

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Background: Saffron, a spice derived from the flower of *Crocus sativus* L., is rich in carotenoids, mainly crocin (CR, hydro soluble compound) and crocetin (CCT, liposoluble compound). Preclinical studies have shown that dietary intake of carotenoids has antitumor effects suggesting their potential preventive and/or therapeutic roles in cancer. We have recently reported that saffron extract (SE) and CR exhibit anticancer activity by promoting cell cycle arrest in prostate cancer cell models. It has also been demonstrated that CCT is produced after SE gastrointestinal digestion by CR hydrolysis. Aim and *Methods:* The aim of the present report was to investigate whether dietary support with SE, CCT, and CR affected *in vivo* tumor growth of two preclinical models of prostate cancer (Pca). Two aggressive Pca cell models, the PC3 and 22rv1 cell lines, were xenografted into nude mice and tumor-bearing animals were treated by oral gavage with SE, CR, and CCT. *Results:* CCT showed the highest antitumor effects when compared to CR and SE. All treatments reverted the epithelial-mesenchymal trans-differentiation (EMT) as shown by the significant reduction of N-cadherin and beta-catenin expression and the increased expression of E-cadherin. Additionally, SE, CR, and CCT inhibited PCa cell invasion and migration through the downmodulation of metalloproteinase and urokinase expression and activity, suggesting that these agents may affect some mechanisms of metastatic processes. *Conclusion:* Our findings suggest that CR and CCT may be dietary phytochemicals with potential antitumor effects in biologically aggressive Pca cells.

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LIPID METHABOLISM AS THERAPEUTIC TARGET FOR PROSTATE CANCER

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Background: One of the most conserved features of all cancers is a profound reprogramming of cellular metabolism, favoring biosynthetic processes and limiting catalytic processes. Cancer cells synthesize *de novo* large amounts of fatty acids and cholesterol, irrespective of the circulating lipid levels and benefit from this increased lipid synthesis, in terms of growth advantage, self-survival and drug resistance. Fatty acid synthase (FASN) and Alfa-methyl-acyl-CoA racemase (AMACR) are overexpressed in PCa. FASN is a key metabolic enzyme that catalyses the synthesis of palmitate from the condensation of malonyl-CoA and acetyl-CoA *de novo* and plays a central role in energy homeostasis, by converting excess carbon intake into fatty acids for storage. The biological role of AMACR in cancer is complex, linking lipid metabolism with nuclear receptor (*e.g.* FXR and PPAR) activity and expression of enzymes such as cyclooxygenase-2 (COX-2). Increased fatty acid synthesis and the use of branched fatty acids may play an important role in the development and progression of PCa. Inhibitors of FASN and AMACR show antitumor effects, making lipid metabolism a promising therapeutic target. *Materials and Methods: In vitro* effects of Orlistat (FASN inhibitor) and Trifluoroibuprofen (TFIP) were verified by using three non-tumor prostate epithelial cell lines and a series of 8 PCa cell lines and 6 cell derivatives whereas *in vivo* experiments were performed in PC3 and 22rv1 xenografts grown in male Cd1 nude mice and treated with 50 mg/Kg/day TFIP administered by oral gavage and 240 mg/kg/day orlistat administered by intraperitoneal (*i.p.*). *Results:* AMACR and FASN enzymes were expressed in PCa cells lines and their expression was much stronger in androgen-independent compared to androgen-dependent cells. FASN inhibition induced a G_2/M cell cycle arrest associated with early autophagy and followed by a late apoptosis. This agent also reduced growth factor-dependent Akt/mTOR pathways through down-modulation of Her2 and c-met signaling. AMACR inhibition induced: (1) down-modulation of AMACR expression; (2) suppression of the survival Akt/mTOR signaling pathway and (3) down-modulation of cyclin D1 and survivin with G_2/M arrest and apoptosis. TFIP and orlistat possessed high antitumor effects in PCa cell models. *Conclusion:* AMACR and FASM are good pharmacological targets for

treatment of PCa, and TFIP and orlistat are suitable anticancer compounds to be administered by orally.

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MULTIPLE RENAL ONCOCYTIC TUMORS: HISTOLOGICAL, IMMUNOHISTOCHEMICAL AND CYTO-GENETICAL COMPARATIVE ANALYSIS

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Background: Renal oncocytosis (RO) is a rare pathologic condition characterized by the presence of multiple oncocytic tumors with a spectrum of histological features ranging from renal oncocytoma, hybrid oncocytic tumor and rarely chromophobe renal cell carcinoma, sometimes overlapping. Hybrid oncocytic tumors in RO are identical to their sporadic counterpart, and are composed of sheets of cells with mild nuclear pleomorphism resembling renal oncocytoma and perinuclear cytoplasmic clearing typical of chromophobe carcinoma (1). Cases of RO are described in association with Birt-Hogg-Dubè syndrome (BHD), an autosomal dominant inherited disease characterized by skin lesions (fibrofolliculomas of the face, head and neck), pulmonary cysts and renal neoplasms (2). Here we analyze histological, immuno-histochemical (IHC) and cytogenetical features of 35 lesions in 9 patients with RO not associated with BHD syndrome. *Patients and Methods:* We retrospectively analyzed 35 lesions in 9 patients with RO diagnosed from 2009 to 2013 in pathology department of the S.Orsola-Malpighi Hospital (Bologna) and the San Luigi Gonzaga Hospital (Orbassano, Turin). The histology of all lesions was reviewed by three dedicated uro-pathologists. IHC for cytokeratin 7 (CK7) and fluorescence *in situ* hybridi-zation (FISH) for chromosome 1, 6, 7 and 17 copy number variation were performed in all 35 nodules. *Results:* The median age of the patients at nephrectomy was 60.1±15.2 years (range 41-85), 6 (66.6%) patients were male and 3 (33.3%) female. Four (44,4%) patients had bilateral lesions. Among the 35 lesions, 25 (71.4%) were renal oncocytomas, 2 (5.7%) oncocytomas with infiltrative features, 3 (8.6%) "hybrid oncocytic tumors", 2 (5.7%) mixed tumors with oncocytoma and papillary renal cell carcinoma, 1 (2.9%) chromophobe carcinoma (ChRCC), 1 (2.9%) clear cell carcinoma (CCRCC) and 1 (2.9%) was a papillary renal cell carcinoma (PRCC). Median tumor size was 2.82 cm (range 0.8-9 cm). The IHC profile showed a negative or focal immunoreactivity for CK7 in all the oncocytic lesions except for the ChRCC. CK7 was also positive in the papillary component of the two mixed PRCC/oncocytomas and the PRCC. The case of CCRCC was not immuno-reactive for CK7. FISH analysis confirmed the histological diagnosis of renal oncocytomas in 27 cases, with no losses or gains in chromosome 1 and 6. One of the three "hybrid oncocytic tumors" showed loss of chromosome 1. The two cases with mixed PRCC/oncocytoma were diploid in the oncocytoma part while showed gain of chromosome 17 in the papillary counterpart. Cytogenetic analyses confirmed the diagnosis of the other non oncocytic lesions: ChRCC (loss of chromosome 7/17), PRCC (gain of chromosome 7/17) and CCRCC (loss of chromosome 3p). After a median follow-up of 21.4±9.56 months, 9 patients were free of metastasis and 8 free from recurrent disease. *Discussion and Conclusion:* RO is characterized by multiple tumors with a spectrum of different histological features often overlapping between benign and malignant lesions. The number of the lesions, their bilateral location and the unclear histology of some tumors in RO alltogether make a nephron-sparing surgical approach difficult. Our data show that most patients harbor benign or low malignant potential tumors that can be treated conservatively. However, the occurrence within RO of renal cell tumors with non-oncocytic features, suggests the use of needle biopsies to investigate the histological type of any lesion before surgical decision.

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TOXICITY PROFILE OF ABIRATERONE ACETATE PLUS PREDNISONE IN CASTRATION RESISTANT PROSTATE CANCER (CRPC) AFTER DOCETAXEL THERAPY: A SINGLE INSTITUTION EXPERIENCE

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Background: Abiraterone acetate (AA) is approved by FDA as second line treatment for patients (pts) with CRPC that experience disease progression after first line docetaxel chemotherapy. AA is a potent inhibitor of both 17a-hydroxylase and 17,20-lyase (CYP17) activity. This inhibition may produce an increase in the concentrations of steroids synthesized upstream of the CPY17, with consequent adverse effects as hypokalemia, fluid retention and hypertension. *Patients and Methods:* Since November 2011, 28 pts with CRPC treated at IRCCS of Candiolo received AA plus prednisone (5 mg twice daily). Pts had undergone previous treatment with one or more lines of chemotherapy, in particular 89.3% of pts (25/28) had been treated with docetaxel (schedule 75 mg/m^2 1/21), 35,7% of pts (10/28) received two lines of chemotherapy (docetaxel followed by mitoxantrone), 10.7% of pts (3/28) underwent chemotherapy with docetaxel with weekly schedule, one patient was treated with two lines of docetaxel, and one patient with a rechallenge of docetaxel after previous docetaxel and mitoxantrone chemotherapies. Twelve patients are still undergoing treatment with AA. We recorded all grades toxicity (according to NCI-CTACE v 4.0), with special regard to those related to the mineralcorticoid excess that may be induced by AA. *Results:* All pts included in the study had a good performance status (ECOG 0-1). Median age was 72.5 years (range 54-79) and 10 pts (35.7%) were older than 75 years. Hypertension was the most frequent adverse event and occurred in the totality of pts, though it was not worsened by therapy with AA and only 7 cases (25%) presented grade 3 toxicity. Hypokalemia occurred in 7.1% of pts (2/28), all cases were grade 1, without any indication for prompt correction. The incidence of fluid retention was 14.3% (4/28) and grade 1 or 2 peripheral oedema accounted for most of these events. There was no onset of cardiac arrhythmias. Other common toxicities included back pain (32.1%), fatigue (39.3%), arthralgia (21.4%) diarrhea (18%), vomiting (7.1%) and nausea (7.1%). Anemia occurred in 21% of patients and was of grade 3 in one case. *Conclusion:* Abiraterone acetate has a very favorable toxicity profile, with low incidence of grade 3 toxicities and is a feasible treatment even for patients with hypertension.

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SYSTEMATIC REVIEW OF PENILE METASTASES: ANALYSIS OF THE RESULTS OF THE LAST 10 YEARS

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Background: Penile metastasis is a relatively uncommon event with about 500 cases reported in the literature from 1961 to the present. The aim of our study was to conduct a systematic literature review of the past 10 years on this particular subject. *Materials and Methods:* We conducted a systematic search in PubMed (http://www.ncbi.nlm.nih.gov), from January 2003 to April 2013, including the combination of the following terms: "penile/penis tumor", "penis/penile metastasis", "penile/penis cancer", "malignat priapism", limiting the search to articles in English. Embase and the Cochrane Library were also searched for the same keywords. *Results:* A systematic review identified 63 articles published between January 2003 and April 2013 for a total of 77 patients with an age range between 53 and 92 years and a mean follow-up of 1 year. 20 patients (26%) had metastasis of bladder origin, 19 (25.1%) prostatic, 15 (19.1%) colorectal, 7 (9.0%) pulmonary, 3 (3.9%) dermal, 3 (3.9%) esofagic, 2 (2.6%) renal, 2 (2.6%) secondary to lymphoma, 1 (1.3%) respectively from carcinoma of tongue, jaw, thyroid gland, seminal vesicles, glomangiosarcoma, leukemia myeloid lineage. In 4 cases (5.2%) penile metastasis was synchronous with the primary tumor. In the remaining 73, the average time between the onset of the primary tumor and the penile metastasis was 41 months (range: 4-60). In 35 patients (45.5%) metastasis was manifested as painful nodule in 31 (40.3%) with priapism, in 7 (9.1%) as a lump indolent, in 3 (3.8%) with hematuria, and 1 (1.3%) with ulceration. In agreement with Kendi *et al.* (Urol Nephrol, 2006), MRI proved to be the best diagnostic tool/stadiante. The primary therapeutic approach for the local control of the disease, has been surgical in 40 cases (51.9%), hormonal in 27 cases (35.1%), radiotherapy in 5 cases (6.5%) and chemotherapy in 5 (6.5%). The median survival after the diagnosis of penile secondariness was 10 months (range: 6-18 months). *Discussion:* Secondary lesions of the penis are relatively rare with a high prevalence of malignancy of bladder origin, prostate and colon/rectum. In agreement with Chaux *et al.* (Int J Surg Pathol 2011), penile metastasis is justified as genitourinary and colon/rectal cancers. No therapy was significantly higher from the prognostic point of view and the choice of approach should be considered by evaluating the performance status of the patient and the local extension of the lesion and systemic. *Conclusion:* The small number of

cases, the poor prognosis and lack of targeted therapeutic choices impose a registration of cases and a constant review of the literature in order to identify shared and effective therapeutic lines.

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INCIDENCE AND PROGNOSTIC IMPACT OF SKIN METASTASES FROM RENAL CELL CARCINOMA

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Background: Renal cell carcinoma (RCC) is the most common primary neoplasm of the kidney, accounting for 3-4% of all adult malignancies; about 25% of patients is found with metastatic disease at the time of diagnosis, while another 30% will develop distant metastases following the surgical treatment of a localized primary. The most common sites of metastases from RCC are lungs, lymph nodes, bone, adrenals, liver and brain, even though rarer metastatic sites are relatively common, as compared to other malignancies; according to the literature, metastases to the skin are observed in only 6% of all RCC cases. *Materials and Methods:* We reviewed our data base of 879 consecutive RCC patients evaluated at our Center between 2004 and 2013 (data cut-off at 31-12-2013), isolating 33 patients with skin metastases, thus confirming the prevalence reported in the literature (3.8% in our series). *Results:* Of the 33 patients with skin metastases collected, the vast majority (*i.e.*, 30 patients, 90.9%) developed metachronous skin metastases, with a median time from first RCC diagnosis to the development of skin metastases of 25.5 months (mean: 48.3, range: 1-272); only 3 patients (9.1%) had skin metastases that were synchronous to the primary. The most common sites of skin metastasis were the trunk (14 cases, 42.4%), the head (13 cases, 33.3%), the limbs (7 cases, 21.2%), the neck (1 case, 3%), the fingers (1 case, 3%) and the gluteus (1 case, 3%); 54% of the patients had thus more than one site of skin metastases. As far as the morphology of the lesions, the vast majority of patients had either nodular or fungoid lesions, with two patients only presenting with diffuse, shell-like, lesions. As far as the histology of the primary, a classical clear cell histology was evidenced in 28 cases (84.8%), while 2 other patients showed a papillary or a prevalent sarcomatoid histology, respectively; as far as the Fuhrman's grade of the primary, it was G3 or 4 in 17 cases (51.5% of the available graded tumors). In 13 cases (39.4%) a skin biopsy was performed to confirm the metastatic nature of the skin lesion; in the remaining cases, the diagnosis was clinical, mainly driven by the progressive growth of the lesions and by their high vascularization; notably, no cases of discrepancy between the histology and the grading of the primary and those of the skin metastases were evidenced. One-, 3- and 5-year mortality rates in our patients with skin metastases were 78.8%, 90.9% and 96.9%, respectively, while median overall survival (calculated from the time of the development of the first skin metastases to death) was 5 months (mean: 12.9±24.2 SD, range: 1-128). *Discussion and Conclusion:* In Conclusion, skin metastases from RCC account for about 3% of all metastatic sites, are usually metachronous and related to a more aggressive tumor phenotype (at least in terms of grading), and are endowed by a dismailing poor prognosis.

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ADVANCED UROTHELIAL CANCER WITH NODAL DISEASE: THE IMPACT OF SURGERY AFTER CHEMOTHARAPY

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Background: Based on available information urothelial cancer patients with metastases would benefit from surgery. However, heterogeneity of surgery, treatment, and disease characteristics, as well as the limited sample size hamper the level of evidence. We aimed to analyze the contribution of post-chemotherapy (CT) lymphadenectomy just on survival outcomes in patients of our center. *Patients and Methods:* Between 1986 and 2012, 157 patients with locally advanced or metastatic urothelial cancer received first-line combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Of them, only patients experiencing at least a stable disease of subdiaphragmatic nodal disease/local recurrence were selected. For the sake of parsimony, the prognostic effect of singly taken covariates (surgery of tumor primary, site of nodal disease, extent of nodal sites [single *vs*. multiple]) upon survival was investigated using Cox proportional hazard regression models, with and without adjustment by treatment group (post-CT surgery *vs*. observation). *Results:* 59 patients were identified, 31 (52.5%) had regional nodes and 28 (47.5%) had metastatic disease. 42 (71.2%) had multiple nodal sites, 15 pts (25.4%) had an upper tract tumor primary, 24 (40.7%) had received major surgery. Twenty-eight pts underwent post-chemotherapy pelvic (N=14) or retroperitoneal lymphadenectomy (N=14) after achieving a complete response (CR, N=7) or a partial response-stable disease (PR+SD, N=21). 8/28 pts (28.6%) achieved a pathologic-CR. Median follow up was 88 months (IQR: 24-211). Median progression-

free (PFS) survival by treatment group (surgery *vs.* observation) was 18 (95% CI, 11-N.E.) and 11 (95% CI, 5-19) months, respectively (logrank test p=0.009). Median overall survival (OS) was 37 (95% CI, 20-N.E.) and 19 (95% CI, 9-38) months, respectively (p=0.004). Surgical consolidation was associated with better PFS (HR: 0.43, 95% CI, 0.22-0.84, p=0.013) and OS (HR: 0.36, 95% CI, 0.17-0.76, p=0.007) in univariable analysis (UVA). This was the only significance in UVA and it was retained in multivariable analysis when adjusting for each of the other covariates. No effect of pathologic status was found. Results are limited by small numbers. *Conclusion:* In well-selected patients with UC like those achieving a clinical benefit from chemotherapy and having exclusive nodal metastatic disease, there was a clear survival advantage when removing disease residuals.

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IMMUNOHISTOCHEMISTRY-BASED PROGNOSIS FOR METASTATIC UROTHELIAL CANCER UNDERGOING CHEMOTHERAPY

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Background: Knowledge of the expression of molecular drivers and potentially druggable targets may enhance prognostic classification of metastatic UC. We aimed at assessing the expression of multiple key molecular biomarkers (BMK) by IHC and their potential to enhance prognostic allocation of patients (pts) with UC. *Materials and Methods:* We analyzed formalin-fixed paraffin embedded tumors from pts with UC undergoing st 1 -line CT with MVAC for locally-advanced unresectable (LA, T3-4±N+) and metastatic (M) disease between the years 2000 and 2013. The expression of the following panel of BMKs by IHC was evaluated using conventional protocols: ERCC1, EGFR, HER2/neu, VEGFR, PDGFR, p53, p63. Expression levels were dichotomized as positive (2+,3+) or negative (≤1+). Fisher exact test was used to evaluate the association with response and setting (LA *vs.* M). Cox regression multivariate (MVA) models evaluated the association with PFS and OS of each biomarker, adjusted for recognized prognostic variables (setting [LA *vs.* M], Bajorin score [0 *vs.* 1-2], primary site). *Results:* Since 06/2009, tissues of 88 pts (27 LA, 61 M) underwent IHC. Samples were from primary tumor (N=67) or metastases (N=21). Rates of positive IHC/number evaluable were as follows: ERCC1: 30/66 (45%); HER2: 24/52 (46%); EGFR: 31/54 (57%); VEGFR: 50/66 (76%); PDGFR: 10/63 (16%); p53: 25/56 (45%); p63: 46/53 (87%). HER2 trended for a significant association with higher stage (p=0.079). Median follow up was 41 months (IQR, 15-64). On MVA, significant results were obtained for VEGFR and PDGFR, in addition to Bajorin score (Table). The c-index was 0.68 for both PFS and OS.

Table I.

	PFS			OS		
Variable	HR	95% CI	*p*	HR	95% CI	*p*
VEFGR						
Pos *vs.* Neg	0.45	0.21-1.01	0.054	0.36	0.15-0.85	0.019
PDGFR						
Pos *vs.* Neg	3.32	1.28-8.58	0.013	2.66	0.96-7.42	0.060
Bajorin score						
1-2 *vs.* 0	4.24	1.94-9.26	<0.001	4.49	1.91-10.56	<0.001

Conclusion: VEGFR and PDGFR expression appears to confer a divergent prognostic impact in pts receiving st 1 -line cisplatin-based CT for advanced UC. These data warrant external validation and underline the difficulties in defining the role of angiogenesis as a molecular driver and therapeutic target.

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PHASE TWO NEOADJUVANT SORAFENIB PLUS CISPLATIN AND GEMCITABINE FOR MIBC AND RESULTS AT THE END OF STAGE ONE

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Background: The small, yet significant, survival advantage with neoadjuvant chemotherapy in MIBC needs to be improved. A rationale exists for inhibiting the RAF/MEK/ERK pathway and investigating S-CG combination in an ongoing open-label, single-group, Phase 2 trial. *Methods:* Patients (pts) with T2-4N0 MIBC received 4 cycles of cisplatin 70 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on day 1 and 8, every 3 weeks. Sorafenib 400 mg q12h was administered daily from day 1 to cystectomy. An optimal 2-stage Simon's design was applied. 6 pathologic complete st responses (pT0, primary endpoint) should be observed in the 1 stage before moving to full enrollment of 45 cases. Residual carcinoma *in situ* with no evidence of invasive tumor was considered as pT0. Intention-to-treat (ITT) analysis was

applied. Circulating biomarker and circulating tumor cell (CTC) analysis is ongoing. *Results:* 24 pts were enrolled from 04/11 to 10/13. Thus far, 22 completed the treatment and are evaluable for ITT analysis. Median age was 61yrs (IQR: 54-66). 12 had T2, 9 T3, and one a T4 disease. 6 pts had hydronephrosis at presentation; 20 pts underwent radical cystectomy. Nine pts (40.9%, 95%CI: 20.7-63.6%) had a pT0 and 2 pts a pT<2. G3-4 side effects consisted of hematologic toxicity in 8 pts (36.3%), hand-foot syndrome (HFS) in 3 pts, hypertension and asthenia in 2 pts each. 9 pts (40.9%) needed a temporary interruption of sorafenib, 7 (31.8%) a dose reduction, and 2 suspended the drug. After a median follow up of 12.6 months, 3 pts (13.6%) had a recurrence or progression and died, the remaining are disease-free. nd Median increase from baseline to day 8 of 2 cycle was observed for VEGF levels (85.8 to 119.5 pg/mL). All pts had a stepwise reduction of CTC count/7.5 mL blood by ScreenCell® (median baseline of 8 [0-40] to 2[0-6]). Three pT0 pts starting with cT3b disease had a decrease from baseline 21, 10, and 40 cells to ≤3 cells. An increase in circulating EpCAM±Muc-1 levels by CTC was observed in accordance with disease progression (PD). *Conclusion:* We observed a positive effect of Sorafenib in enhancing the activity of CG in this setting. If confirmed, research should delineate the mechanisms behind clinical benefit in this patient population, and characterize unresponsive patients.

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CTC IN UROTHELIAL CANCER PATIENTS UNDERGOING SYSTEMIC TREATMENTS

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Background: CTCs from patients (pts) at different clinical stages were analyzed by a never-explored experimental approach based on a combination of two techniques. Provision of this information may contribute to the optimization of tailored therapies. *Methods:* 3 cohorts were analyzed, partly enrolled in clinical trials: pts with muscle-invasive bladder cancer receiving neoadjuvant (NA) sorafenib + chemotherapy (CT) (NCT01222676), and metastatic (M1) pts receiving first-line MVAC, and second-line (M2) anti-TGFβ receptor ALK1 PF-03446962 in a phase 2 trial (NCT01620970). 5 ml of whole blood were filtered by ScreenCell® Cyto devices and CTC status was assessed with centralized scoring by referral pathologists. Additional 5 ml of whole blood were processed by immunomagnetic beads (AdnaTestSelect® kit) and the expression level of a panel of markers (including EPCAM and MUC1) was studied using RT-multiplex PCR. Our objective was the association with clinical endpoints (pathologic/clinical response, disease relapse). *Results:* From 07/2012 to 1/2014, 65 pts (20 NA, 31 M1, and 14 M2) were enrolled. Rates of baseline CTC+ were: 92, 75, 91%, and 31, 50, 64% with the 2 techniques, respectively. NA setting: all pts had a stepwise reduction of CTC count/5 ml blood by ScreenCell® (median baseline of 14 [0-40] to 0 [0-9] – end of treatment). Increase in circulating EPCAM±MUC1 levels by CTC was seen in accordance with the 3 disease progressions (PD). M1 setting: While there was a discrepancy between CTC signals and partial/complete response (PR/CR), a trend towards an increase in CTC levels was observed in 7/9 evaluable relapsers. Pts who relapsed had a median of 43 CTC/5 ml (IQR: 17-51.5) at the end of CT, while all the others had levels <13. EPCAM profile was not concordant in all cases (median 1.01 *vs*. 1 ng/ul). Interestingly, an increase in both CTC signals anticipated relapse in 5/9 evaluable responders (CR+PR). M2 setting: an increase in CTC was documented by both Methods in each case, in accordance with PD. *Conclusion:* This combined technique was endowed with promising utility to anticipate the detection of clinical relapse. Refining molecular characterization might help design informed clinical trials.

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PAZOPANIB IN CHEMORESISTANT PATIENTS WITH GERM CELL TUMORS (GCT): UPDATED RESULTS OF THE OPEN-LABEL, SINGLE-GROUP, PHASE 2 PAZOTEST-01 TRIAL

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Background: Patients (pts) with GCT who fail to be cured following multiple chemotherapy (CT) courses (± high-dose CT) have an extremely poor prognosis and long-term remissions are anecdotal. Pazopanib (PZP) is a potent and selective, orally available, TKI of VEGFR1, 2, and 3, PDGFRα, PDGFRβ, and cKit. We updated the initial results of the ongoing open-label, single-group, phase 2 study which is sponsored by INT Milano (ClinicalTrials.gov NCT01743482). *Methods:* Patients failing at least 2 platinum-based CT (including high-dose CT) received

PZP 800 mg/day orally until disease progression (PD) or evidence of unacceptable toxicity/side effects. All pts underwent measurement of serum tumor markers (STM), a computed tomography and a FDG-PET after 1 month and q2 months thereafter. In a Simon's 2-stage design, the primary endpoint is 3-month progression-free survival (PFS). In stage 1, 18 evaluable patients will be accrued. If ≥3 pts will be progression-free at 3 months, enrolment will be extended to the 2nd stage. *Results:* From 06 to 12/2013, 9 patients have been enrolled, 6 in fourth and 3 in fifth-line. Median age was 38 yrs (IQR: 32-42). Eight patients had nonseminomas, 3 had a teratoma with malignant transformation, 3 had failed HDCT, 2 had liver metastases. Seven pts (77.8%) showed an early response after 4 weeks of treatment, and it was a marker +/- dimensional partial response (RECIST, PRm+). One had a stable disease, one a PD. In addition, patients showed a densitometric response (N=3) or a reduction of FDG uptake (N=2). At +3 month-restaging, 3 patients (33.3%) were progression-free. Two patients (22.2%) had G3 AST/ALT increase and needed temporary discontinuation of PZP. One case had G2 hypertension and diarrea. *Conclusion:* The study has already met the PFS requirements (3 progression-free patients at +3 months) to complete the full accrual of 43 patients.The activity of pazopanib was mainly seen as a reduction of STM, as expected. However responses were also seen in patients yielding divergent histologies. Additional considerations on non-conventional response (densitometric and metabolic) assessment will require more cases.

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DEVELOPMENT OF A PHASE 2 STUDY OF THE AURORA KINASE-A INHIBITOR ALISERTIB (MLN8237) IN PRE-TREATED PATIENTS (PTS) WITH UROTHELIAL CANCER (UC)

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Background: Progress in developing new effective therapies for advanced and relapsing urothelial cancer has been stagnant in the last few decades and a paradigm shift is desperately needed. Aurora kinase-A overexpression has been previously described in bladder cancer and spindle checkpoint dysregulation is a common feature of human UC. Alisertib (Millennium Inc.) is an orally available, selective small molecule inhibitor of Aurora A kinase. Single agent and combination treatment of MLN8237 with either paclitaxel (TXL) or gemcitabine synergistically reduced UC cell viability compared with either drug alone. Hence, sequential application of MLN8237 and TXL warrants clinical investigation. Phase 1 trials of both single agent and the combination with TXL defined the recommended doses for phase 2 trials. *Methods:* A multistep approach will be adopted for this Phase 2 trial. A single-group run-in phase will be conducted first with Alisertib 50 mg orally BID for 7 days, followed by 14d rest until disease progression. In case of activity, a confirmatory randomized (1:1) trial of weekly TXL plus either Alisertib or Placebo will follow, incorporating efficacy and futility boundaries for early stopping. In a single-blind design, TXL will be given on days 1,8,15 q4wks at the dose of 60 mg/m^2 with alisertib and 80 mg/m^2 with placebo. Alisertib dose will be 40 mg BID days 1-3, 8-10 and 15-17, q4wks. In the single-arm phase, primary endpoint (EP) will be RECIST 1.1 response-rate. 20 pts will be accrued, ≥3 responses will be required (10% type I and 20% type II error costraints). An accrual of 110 pts is foreseen in the randomized phase. Primary EP: progression-free survival (PFS), assuming an improvement in PFS from a median of 2.5 months (H0) to a median of 4.5 months (H1) (44% hazard rate reduction, 10% drop out rate). Eligibility will include diagnosis of metastatic UC and failure of 1-2 CT regimens (singlearm) or 1 prior CT only (randomized phase). A relapse within 6 months of a peri-operative CT will be counted as 1 line. Computed tomography and PET will be done every 2 cycles (2 months). Additional pharmacodynamic and translational analyses are planned on prepost- blood and tissue samples.

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THE IMPACT OF PROSTATE VOLUME ON BIOCHEMICAL RECURRENCE IN PROSTATE CANCER PATIENTS TREATED WITH RADICAL PROSTATECTOMY

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Introduction: Evidence is conflicting regarding the role of prostate volume (PV) on the risk of biochemical recurrence (BCR) in patients with prostate cancer (PCa) treated with radical prostatectomy (RP). While retrospective studies relying on historical cohorts indicated a possible impact of PV on

BCR-free survival rates, others failed to confirm these observations. We aimed at evaluating the role of PV in our large cohort of patients treated with RP at a referral institution. *Methods:* Overall, 5,637 patients with PCa treated with RP between January 1993 and August 2013 were identified. All patients had available preoperative and pathological data. Multivariable Cox regression analyses tested the association between prostate volume (PV, continuously coded) and the risk of experiencing BCR after surgery in the overall population, and after stratifying patients according to the D'Amico risk groups (low- *vs*. intermediate- *vs*. highrisk). Covariates consisted of surgical margin status, pathological Gleason score, pathological stage, lymph node invasion, and the administration of adjuvant therapies. *Results:* Mean patient age was 64.8 years (median: 65). Mean PV was 50.6 ml (median: 46). Overall, 1,789 (31.7%), 2,657 (47.1%), and 1,191 (21.1%) patients had low-, intermediate-, and high-risk PCa, respectively. Mean (median) PV was 51.7 (48), 49.8 (45), and 50.6 (46) in patients with low-, intermediate-, and high-risk PCa, respectively (p=0.04). Overall, the 5-year BCR-free survival rate was 87.9%. In the entire population, PV was associated with lower risk of BCR (Hazard ratio [HR]: 0.99, 95% Confidence Interval [CI]: 0.99-1.00; p=0.03), after accounting for confounders. When patients were stratified according to D'Amico risk groups, PV represented an independent predictor of BCR only in patients with intermediate-risk disease (HR: 0.62, 95% CI: 0.99-1.00; p=0.04). Conversely, PV was not associated with reduced risk of experiencing BCR in patients with low- and high-risk disease (all p≥0.4). *Conclusion:* Smaller PV is significantly associated with increased risk of BCR after surgery only in men with intermediate-risk PCa. In this patient category, PV might be used to identify patients at higher risk of BCR after surgery, in order to individualize follow-up schedules and administer adjuvant or salvage treatments in a timely fashion.

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INCIDENCE AND PREDICTORS OF READMISSION AFTER ROBOT-ASSISTED RADICAL PROSTATECTOMY IN PATIENTS WITH PROSTATE CANCER

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Introduction: Although several studies reported advantages related to the adoption of robot-assisted radical prostatectomy (RARP) in terms of postoperative pain, blood transfusions, and length of hospital stay, evidence is scarce regarding the incidence and predictors of readmission in prostate cancer (PCa) patients treated with this minimally invasive approach. *Methods:* Overall, 1,402 patients treated with RARP at a single tertiary referral center between February 2006 and August 2013 were identified. All patients had preoperative and follow-up data available. Baseline comorbidities were categorized according to the Charlson comorbidity Index (CCI). The ClavienDindo classification system was used to categorize postoperative complications which occurred during the first hospital stay. Patients experiencing 30day readmission were identified. Uni- and multivariate logistic regression analyses tested the association between 30-day readmission and age at surgery, the receipt of pelvic lymph node dissection, CCI, and the severity of postoperative complications classified according to the Clavien-Dindo system. *Results:* Mean patient age was 62.7 years (median: 63). Overall, 38 patients (2.7%) needed a new hospitalization within 30 days after discharge. The proportion of patients who experienced 30-day readmission was significantly higher among patients who had a complication during the first hospitalization compared to those who did not experience a complication during the first hospitalization (6.2 *vs*. 2.3%, respectively; p=0.01). At univariate analyses, the occurrence of a complication during the first hospitalization (odds ratio [OR]: 2.87; 95% confidence interval [CI]: 1.36-6.02; p<0.001) and its severity (OR: 1.56; 95% CI: 1.28-1.91; p<0.001) represented the only significant predictors of 30-day readmission after surgery. This was confirmed at multivariable analyses, where the occurrence of a complication during the first hospitalization and its severity represented independent predictors of 30-day readmission, after accounting for confounders (all p<0.01). Particularly, patients experiencing a complication during the first hospitalization had 3-fold higher risk of 30-day readmission (p=0.004). Of note, age, comorbidity status, and the receipt of pelvic lymph node dissection did not represent independent predictors of 30day readmission (all p≥0.1). *Conclusion:* Our observations show that patients undergoing RARP have a relatively low risk of 30-day readmission (2.7%). Of note, the occurrence of a postoperative complication represented the only independent predictor of 30-day readmission. Our findings highlight the need for better patient management when a complication occurs during hospitalization for RARP.

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BIOCHEMICAL RECURRENCE IN MISCLASSIFIED ACTIVE SURVEILLANCE CANDIDATES TREATED WITH RADICAL PROSTATECTOMY

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Introduction: Although candidates to active surveillance are generally considered at low-risk of recurrence, the rates of unfavorable pathological characteristics after radical prostatectomy (RP) in these patients are not negligible. The aim of our investigation was to test the effect of unfavorable pathological characteristics on the risk of recurrence after RP in patients who could have been selected for active surveillance. *Methods:* The study included 330 patients treated with RP between 1994 and 2013 who could have been selected for active surveillance according to the van der Bergh *et al*. criteria. The rates of unfavorable disease at final pathology were examined. Additionally, patients were categorized in three groups according to the final pathology results: men with organ confined disease, pathological Gleason score ≤6, and pN0 (Group 1), men with organ-confined disease, pathological Gleason score 3+4, and pN0 (Group 2), and patients with non-organ-confined disease, pathological Gleason score ≥4+3 or pN1 (Group 3). Biochemical recurrence was defined as the detection of PSA ≥0.2ng/ml after surgery. The Kaplan-Meier curves were used to assess the time to BCR after surgery. The long-rank test was used to compare the rates of BCR according to pathological features. *Results:* Mean patient age was 64.4 years (median: 65). Overall, 306 (92.7%), 19 (5.8%), 5 (1.5%), and 3 (0.9%) of the patients included in the study had organ-confined disease, extracapsular extension, seminal vesicle invasion, and lymph node invasion, respectively. Pathological Gleason score was ≤6, 3+4, and ≥4+3 in 247 (74.8%), 62 (18.7%), and 21 (6.4%) patients, respectively. When patients were stratified according to the presence of unfavourable characteristics at final pathology, 243 (73.6%), 62 (18.8%), and 25 (7.6%) were included in Group 1, Group 2, and Group 3, respectively. Overall, 12 (3.6%) patients experienced BCR during follow-up. The BCR-free survival rate at 60-month follow-up was 95.6%. When patients were stratified according to the pathological features, individuals with worse characteristics (Group 3) had lower BCR-free survival rates compared to their counterparts with favourable disease (Group 1) at final pathology ($p<0.001$). However, no differences were observed in the BCR-free survival rates when patients with organ-confined disease and pathological Gleason score ≤6 (Group 1) were compared to those with organ-confined disease and pathological Gleason score 3+4 (Group 2; $p=0.4$). *Conclusion:* A non-negligible proportion of potential active surveillance candidates harbors unfavorable disease at final pathology. Of note, in these patients the upgrade from biopsy Gleason score ≤6 to pathological Gleason score 3+4 does not significantly increase the risk of BCR.

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TUMOR VOLUME IS A PREDICTOR OF UNFAVORABLE DISEASE CHARACTERISTICS IN PROSTATE CANCER PATIENTS

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Introduction: Previous studies showed that the tumor volume (TV) might increase the ability to identify patients with insignificant prostate cancer (PCa). However, these results were obtained using preoperative imaging modalities, which might lead to an under- or overestimation of the actual TV. The aim of our study was to test the role of pathological TV on the risk of unfavorable characteristics at final pathology in patients treated with radical prostatectomy (RP). *Methods:* Overall, 3,193 patients with PCa treated with RP between February 2003 and August 2013 at a single tertiary referral center were identified. All patients had available preoperative and pathological data. TV was calculated by visual inspection, according to the College of American Pathologists guidelines. Uni and multivariable logistic regression analyses tested the impact of tumor volume (continuously coded) on the risk of pathological Gleason score 8-10, seminal vesicle invasion (SVI), and lymph node invasion (LNI) in the overall population, and after stratifying patients according to the D'Amico risk groups. Covariates consisted of preoperative PSA, clinical stage, and biopsy Gleason score. *Results:* Mean patient age was 62.5 years (median: 63). Mean tumor volume was 4.8 ml (median: 2.8). Overall, 1,200 (37.6%), 1,406 (44.0%), and 587 (18.4%) patients had low-, intermediate- and high-risk PCa, respectively. Overall, 392 (12.3%), 367 (11.5%), and 325 (10.2%) patients had pathological Gleason score 8-10, SVI, and LNI, respectively. In multivariate logistic regression analyses, TV was associated with increased risk of pathological Gleason score 8-10, SVI, and LNI, after accounting for confounders (all $p<0.001$). This held true after stratifying patients according to the risk groups (all $p<0.001$). Particularly, TV represented an independent predictor of pathological Gleason score 8-10, SVI, and LNI even in patients with low-risk PCa, after accounting for preoperative PSA (all $p<0.001$). *Conclusion:* Pathological TV represents an independent predictor of unfavorable pathological characteristics in PCa patients. These results support the role of preoperative assessment of tumor volume in order to identify patients at higher risk of more aggressive disease at final pathology. On the other hand, preoperative TV evaluation might help to select the best candidates for active surveillance among patients with low-risk PCa.

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BEVACIZUMAB PLUS INTERFERON AS FIRST LINE: TREATMENT IN RENAL CELL CARCINOMA

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Introduction: Renal cell carcinoma is the most common kidney cancer. Up to 30% of patients have metastases at the time of the initial diagnosis (1). The 5-years survival for patients who present with metastatic renal cell carcinoma (mRCC) or locally advanced disease is 10-15%. The mortality estimate for RCC, in 2013, is 13,680/year (2-4). Systemic treatment for patients who have mRCC with clear cell histological component has shifted from a cytokines to drugs targeting angiogenesis. There are seven targeted agents approved by the FDA: sorafenib, sunitinib, benacizumab, temsirolimus, everolimus, pazopanib and axitinib. These agents come from two unique targeted pathways for RCC, tyrosine kinase inhibitors (TKis) of vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) inhibitors. The standard first line treatment options for mRCC are sunitinib, bevacizumab plus interferon and pazopanib for disease with a good or intermediate prognosis, while temsirolimus is recommended for untreated in poor risk setting. However, the treatment with bevacizumab plus interferon is not the common choice. We present 12 patients with mRCC who were treated with bevacizumab plus interferon as in first line of treatment. We retrospectively evaluate the median treatment duration, overall survival (OS) and treatment-related toxicities. *Materials and Methods:* Between January 2009 and January 2014, 12 patients with mRCC, 11 men and 1 woman, were treated with bevacizumab in combination with interferon-α2a (IFNα) as first line therapy. The median age at the diagnosis was 58 years. All patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0, histologically clear cell carcinoma, except for a case of papillary disease; in 66% (8 patients) grade of Fuhrman was 3 or 4, 5 patients (41%) had a IV stage at diagnosis, 100% of patients had prior nephrectomy and a prognostic favorable or intermediate risk according to the criteria of Motzer. The main sites of metastases were lymphnodes and lung. Patients received bevacizumab, 10 mg/kg intravenous (*i.v.*) every 2 weeks, plus IFN, 9MIU subcutaneously (*s.c.*) three times weekly, until disease progression or unacceptable toxicity; all patients were premedicated with paracetamol (500 mg oral). The median line treatment at the progression after first line was 1.6 (range 0-5). We retrospectively evaluate the median treatment duration, overall survival (OS) and treatment-related toxicities. *Results:* IFNα was administered at 9MIU *s.c.* three times weekly in 6 patients (50%), but only 2 patients maintained the dose until the end of the treatment; in 5 patients (41%), IFNα was administered at 6MIU *s.c.* three times weekly, but 2 patients completed treatment with 3MIU of IFNα because of toxicity. Only in one patient, IFNα was administered at 3MIU *s.c.* three times weekly, for all the duration of the treatment. Bevacizumab and IFNα were temporarily interrupted and/or reduced of dosage in 6 patients (50%). The most common grade 3 toxicities observed were fatigue (50%), hypertension (41%) and fever (33%). Four patients (33%) discontinued treatment because of important toxicity: 2 patients for gastrointestinal toxicity, 1 patient for proteinuria and hypertension, 1 patient for cerebral hemorrhage, without neurological outcomes. 10 patients underwent at least one line of therapy represented by TKIs: 9 patients were administered sunitinib at the progression, in one patient pazopanib. The median treatment duration was 9.5 months. At the time of the analysis 4 patients had died, only one patient is still in treatment. The median OS was 50.9 months. In 41% of the patients partial response of disease was observed; stable and progression disease were observed in the 50% of patients: 25% and 25% respectively. No complete response was found. *Discussion:* Most patients with clear-cell carcinoma have mutations or epigenetic changes in the von Hippel-Lidau (VHL) tumour suppressor gene, leading to increased transcription of several hypoxia-inducible genes, including VEGF. On the basis of this observation, the treatment of mRCC has been transformed in recent years with the approval of several novel therapies that directly or indirectly inhibit VEGF, the key mediator of tumour angiogenesis. In the multi-centre, randomized, double-blind, phase III AVOREN trial (Avastin and Roferon in Renal Cell Carcinoma), combining bevacizumab with IFN significantly improved progression-free survival (PFS) with 10.2 months *versus* 5.4 months (HR 0.63) compared IFN with placebo. The recent final analysis of this trial reported longer median overall survival (OS) in patients treated with bevacizumab plus IFN than in those receiving IFN plus placebo: 23.3 months *versus* 21.3 months respectively. However, this difference was not statistically significant. In fact, at the progression the most of patients were treated with TKIs: this is a possible explanation of the absence of statistical significance in OS. In our own clinical practice, in case of patients with a good performance status and "limited disease", bevacizumab plus interferon is a possible choice of treatment. *Conclusion:* Bevacizumab plus Interferon is a good opportunity as first line treatment with an acceptable profile of toxicity.

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Table.

Patients characteristics	No. of patients
Median age, years (range)	58 (51-81)
Gender	
Male	11
Female	1
ECOG PS	12 (100%)
Previous nephrectomy	12 (100%)
MSKCC prognostic groups	
Favorable	4
Intermediate	8
Poor	0
Fuhrman	
1	3
2	3
3	1
4	5
Stage TNM	
I	1
II	3
III	5
IV	3
Histology	
Clear cell	11
Papillary	1
Median no. of metastatic sites	
0	0
1	4
2	7
3	1
Sites of metastatic disease	
Lung	6
Lymphnodes	7
Pancreas	2
Adrenal	2
Others	4

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IS PROSTATE HEALTH INDEX USEFUL FOR DIAGNOSTIC ACCURACY IN PATIENTS UNDERGOING REPEAT PROSTATE BIOPSY?

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Introduction and Objectives: Indication for prostate biopsy (Bx) is mainly based on prostate-specific antigen (PSA) and digital-rectal examination. In view of their unsatisfactory accuracy, research has focused on novel markers to improve pre-Bx prostate cancer (PCa) detection, such as prostate health index (phi) and prostate cancer antigen 3 (PCA3). We assessed the diagnostic performance of these biomarkers and %fPSA in Italian men undergoing first or repeat prostate Bx for suspicion of PCa. *Patients and Methods:* Three hundred forty male subjects of two Institutions were enrolled in this prospective observational study. phi and PCA3 score were assessed in the same laboratory between Sept. 2011 and Sept. 2013 before patients undergoing first or repeat Bx. At least 12 standardized peripheral zone Bx cores were taken at first Bx, and 18 peripheral and transition zone Bx cores at re-Bx. All specimens were evaluated by an experienced pathologist, according to the 2005 consensus conference of the International Society of Urological Pathology. *Results:* Median PSA, %fPSA, phi and PCA3 scores were 7 ng/ml (range 2.5-51), 15% (3-40.4), 42 (10-605) and 40 (2-264), respectively. In first Bx group 34 of the 89 men (38.2%) had cancer; in repeat one, 54 of 215 patients (25.1%) had PCa. Phi and PCA3 median values were significantly higher in patients with PCa compared to PCa-negative group (phi: 64 *vs*. 38, $p<0.001$; PCA3: 49 *vs*. 38, $p=0.011$). Phi had the largest accuracy at the re-Bx (AUC=0.82/0.62/0.63 for phi, %fPSA and PCA3), conversely from the first biopsy (AUC=0.66/0.73/0.55). No linear relationship was found between either PCA3 and phi or PCA3 and %fPSA, while there was an inverse one between phi and %fPSA ($p<0.001$). At the multivariate logistic analysis, Phi>40 (OR 3.33 $p<0.001$), PCA3>50 (OR 1.83 $p=0.053$), age>65 (OR 1.98 $p=0.039$) and DRE+ (OR 8.48 $p<0.001$) were the main PCa risk factors with an overall accuracy of 68.8%, while %fPSA (OR 1.59 $p=0.228$) was not. *Conclusion:* Among first Bx patients, phi and PCA3 did not perform better than conventional %fPSA, while being obviously more expensive. On the contrary, phi significantly improve cancer diagnostic accuracy in patients undergoing re-Bx. Among the three biomarkers, only phi>40 and PCA3>50 were the main PCa risk factors.

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THE ROLE OF CELL CYCLE PROGRESSION (MULTI-GENE ASSAY) IN PATIENTS WITH PROSTATE CANCER: PRELIMINARY DATA IN A LARGE ITALIAN SITE

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Introduction and Objectives: Recent studies aiming at identifying prostate cancer (PCa) aggressiveness have been focused on molecular analysis, in particular using gene-profiling methods. We focused our interest on the cell-cycle progression (CCP) gene expression assay, developed and marketed by Myriad Genetics Laboratories (Salt Lake City, USA). This CCP assay has been previously validated retrospectively in specimens following radical prostatectomy or transurethral prostate resection (1) and, more recently, on prostate biopsy specimens (2). In these studies, the CCP Score™ was shown to predict the biochemical failure after radical prostatectomy and PCa specific mortality. In this preliminary study, we assessed the CCP score data in an Italian case series, evaluating the distribution of the scores and correlating it with other prognostic factors. *Materials and Methods:* An open-label, observational study started on January 2013 at our Institution, after IEC/IRB approval. Ninety-four patients presenting with localized PCa confirmed by biopsy, with WHO Performance Status <2, were enrolled. The CCP score was performed measuring the expression of 31 genes involved in CCP in combination with 15 housekeeping genes with quantitative RT-PCR on RNA extracted from formalin-fixed paraffin-embedded tumor samples from prostate biopsy. All tests were carried out at Myriad Genetic Laboratories and a CCP score, derived from the ratio between normal and abnormal genes, was calculated for each case. Scores ranging between –1.3 to 4.7 (3) were expected by this assay. Finally we assessed the association of CCP score with bioptic Gleason Score, % positive cores on prostate biopsy, clinical and pathological TNM stage, tumor volume, and surgical margins. *Results and Conclusion:* To date, 78 out of 94 patients (83%) have completed CCP scores (final results awaited), of whom 46 patients (59%) were submitted to radical prostatectomy. Pathological data from surgical specimens were available for all of them. Median CCP score was –0.3 (IQR: –0.7; 0.2). Median CCP score was significantly different according to clinical stage (Kruskal-Wallis p=0.013) and Gleason score (p=0.017), while it was not different according to margins status (p=0.084) and pathological stages (p=0.429). Conversely, no significant (p<0.05) correlations were found between Prolaris and age (r Spearman=0.30 p=0.061), % positive cores (r=0.25 p=0.119), tumor volume (r=0.138 p=0.499) or PSA (r=–0.02 p=0.876). At this very early stage of clinical evaluation, CCP score is different in patients with different clinical stage and Gleason score at biopsy. The study is ongoing and more data are expected in a larger sample size and will be presented.

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ROBOTIC-ASSISTED EXTENDED PELVIC LYMPH-ADENECTOMY FOR HIGH-RISK PROSTATE CANCER: TECHNICAL FEASIBILITY AND RESULTS. OUR EXPERIENCE WITH 118 CASES

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Introduction and Objectives: In patients with prostate cancer (PCa), extended pelvic lymphadenectomy (EPLA) yields a higher number of lymph node metastases than limited pelvic lymph node dissection (LPLA) of the external iliac vein and obturatory fossa only. To date, there is still a paucity of data in the literature on robotic-assisted extended pelvic lymphadenectomy (RAEPLA) in patients with PCa. The aim of the study was to describe the technical feasibility of RAEPLA in patients with high-risk PCa. We also evaluated the number, the locations of positive lymph nodes and the morbidity of our surgical technique. *Patients and Methods:* From April 2010 to September 2013, we performed RAEPLA in 118 patients prior to robotic-assisted radical prostatectomy. Table I presents the patient demographics. Indications for RAEPLA were defined according to a nomogram based on pre-treatment prostate-specific antigen (PSA), clinical stage, primary and secondary biopsy Gleason score, and percentage of positive cores according to Briganti *et al*. The transperitoneal approach was used in all cases by placing six ports. The lymphatics covering

the distal tract of the common iliac artery, the medial portion of the external iliac artery, the external iliac vein and the internal iliac vessels, the obturator and the presacral lymphatic packets were removed on both sides.The total lymph node yield, the frequency of lymph node metastases, and the complication rate were evaluated retrospectively.

Table I.

No. of patients	118
Median age, yr (IQR)	64 (59-68)
BMI (IQR)	26 (24-28.1)
Preoperative PSA, median, ng/ml (IQR)	7.47 (5.54-11.50)
Clinical T stage, No (%)	
T1	66 (55.9)
T2a	20 (16.9)
T2b	25 (21.2)
T2c	4 (3.4)
T3	3 (2.6)
Preoperative Gleason Score, No (%)	
5	2 (1.7)
6	17 (14.4)
7a (3+4)	31 (26.3)
7b (4+3)	30 (25.4)
8	34 (28.8)
9	4 (3.4)
10	0

Results: The median patient age was 64 yr (IQR: 59-68 yr). The median preoperative PSA level was 7.47 ng/ml (IQR: 5.54-11.5 ng/ml). Mean number of lymph nodes retrieved was 25.02+8.45/patient (median: 25; IQR: 19-30). The left and right side accounted for a mean number of 11.69+4.74 (median 11; IQR: 8-15) and mean 13.39+4.9 (median 12; IQR: 11-15.25) lymph nodes retrieved, respectively. 13 patients (11.02%) had lymph node metastasis, their mean PSA level was 10.12+7.99 ng/ml. The mean number of positive lymph nodes was 2.69+2.02 /patient (median: 1; IQR: 1-5). The location and number of metastases per anatomic region are reported in the Table II. Median hospital stay was 5 days (IQR 4-9.85). Complications occurred in 4 patients (3.38%). One patient had a temporary and reversible neurapraxias (ischiatic nerve and obturator nerve). In 3 patients (2.54%), a symptomatic lymphocele was treated conservatively.

Table II.

Anatomic region	Total lymph nodes, No	Metastatic lymph nodes, No (%)	Exclusively metastatic in this region
Iliac-obturator left	1202	17 (1.4)	10
Hypogastric-presacral left	171	1 (0.6)	0
Iliac-obturator right	1135	15 (1.3)	4
Hypogastric-presacral right	419	2 (0.5)	0
Total	2927	35 (1.2)	-

Conclusion: RAEPLA is feasible, and its lymph node yield is widely comparable to open series. The robotic-assisted approach does not seem to limit surgeon's ability to perform a complete EPLA.

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THE MULTIPARAMETRIC MRI IN PATIENTS WITH PROSTATE CANCER: ITS ROLE IN THE CHOICE OF THERAPEUTIC APPROACH

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Introduction: Nowadays, prostate cancer is mostly diagnosed in the localized stage. This has led to the development of minimally invasive surgical approaches, able to get the best result in terms of the "trifecta": oncological radicality, sexual potency and urinary continence conservation. Robotic assisted radical prostatectomy (RARP) is one of the most important actors in this scenario. The prostatic multiparametric MRI (mp-MRI) has developed rapidly and is increasingly used in clinical practice for the PC staging and, on the basis of its findings, surgeon can use a "tailored" surgical technique. The aim of this study was to evaluate if this "tailored" approach can modify oncologic and functional outcomes after RARP. *Patients and Methods:* We retrospectively reviewed our prospectively maintained database of RARP and extracted data of patients treated from January 2011 to March 2013. The patients were divided into two groups, depending on whether they did (group A, 203 pts) or did not (group B, 100 pts) perform a pre-operative mp-MRI. In group A the mp-MRI consisted of a T1, T2 weighed study, and diffusion images acquired after administration of contrast medium. In this group, mp-MRI information was used for tailoring of the surgical technique (*i.e.* intra/inter/extrafascial prostatectomy) for each patient. In group B mp-MRI was not performed for reasons that were independent of prostate disease (*i.e.* claustrophobia, implanted metallic devices, cardiac pace-makers) and surgical technique was based on clinical and biopsy findings. mp-MRI, RARP and pathological analysis were performed by the same uro-radiologist, surgeon, and uro-pathologist, respectively. The two groups were compared regarding preoperative, intra-operative (type of nerve-sparing approach [extra-, inter- or intra- fascial]) and pathological data. Primary endpoint was the comparison of

the trifecta defined as: positive surgical margin rate (PSMr), urinary continence at catheter removal and one month after RARP, sexual potency at one month after nerve-sparing RARP. *Results:* The two groups were comparable in terms of preoperative, intraoperative and pathological characteristics. The PSMr was 20.8% for group A and 27.1% for group B (p=0.29). Urinary continence at catheter removal was 62% in group A and 49.4% in group B (p=0.05), while at one month was 62.2% and 54.4% respectively (p=0.25). Sexual potency at one month amounted to 30.6% in group A and 27.9% in group B (p=0.95). *Conclusion:* The results showed a favorable trend toward a reduction of PSMr and a faster recovery of urinary continence and sexual potency. The statistical significance of these results is probably reduced by the small sample size.

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IS PROSTATE CANCER GENE 3 (PCA3) SCORE A VALID AND STABLE MARKER ON REPEATED MEASURES OVER TIME? A FIRST EXPERIENCE

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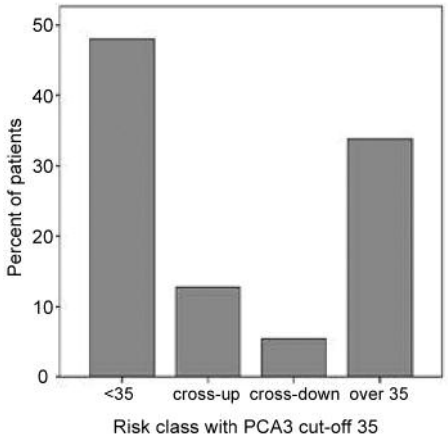
Introduction and Objectives: PCA3 is a genetic marker: so it would be expected to be a stable score on repeated measures, and not modified by the main patient characteristics (age, prostate volume, BPH and prostatitis, finasteride/dutasteride administration). To our knowledge this is the first study to evaluate the variability of PCA3 repeated measures in men with elevated PSA undergoing a first or repeat prostate Bx. *Patients and Methods:* 369 males of two Italian Institutions who had undergone at least two PCA3 assessments in the same laboratory between October 2008 and August 2013, were selected. 97.5% of these patients were scheduled for first or repeat prostate Bx because of elevated PSA and/or positive digital rectal examination (DRE). Comparison of PCA3 score in patients with negative Bx (normal parenchyma, benign prostatic hyperplasia BPH, chronic prostatitis, high-grade prostate intraepithelial neoplasia HG-PIN) and positive Bx was performed. The evaluation of biological variability of PCA3 on repeated measures and its possible association with main patient characteristics (age, family history for prostate cancer, DRE, prostate volume, BPH, prostatitis and HG-PIN) were also performed. Patients characteristics were tested using the Fisher's exact test for categorical variables, while for continuous ones the Mann-Whitney and Kruskal-Wallis tests (for independent measures) and the Wilcoxon and Friedman tests (for repeated measures). In order to easily describe PCA3 repeated measures behavior, all the patients were divided in 4 groups: stable PCA3-low risk, stable PCA3-high risk, upgrading PCA3-from low-to-high risk, downgrading PCA3-from high-to-low risk. All reported p-values were obtained by the two-sided exact method, at the conventional 5% significance level. Data were analyzed as of October 2013 by SPSS 21.0.0 (IBM Corp., USA). *Results:* PCA3 median scores varied significantly (p<0.001) in men with a negative *versus* positive Bx, 25 (range 2-276) and 43 (range 7-331) respectively. Men with chronic prostatitis and HG-PIN had no significant difference in PCA3 score compared with other negative biopsy patients. The variability on PCA3 repeated measures was about 25%.



Dichotomizing PCA3 scores at the classical level of 35, the repeated measures analysis demonstrated that 302 patients (81.8%) had not changed their risk category: 177 of them had PCA3 ≤35, while the remaining 125 had PCA3 >35. The rates of "cross down" (downgrading PCA3 from >35 to ≤35) and "cross up" (upgrading PCA3 from ≤35 to >35) were 5.4% and 12.7%, respectively. *Conclusion:* PCA3 score can be considered a stable over time marker in most cases. Anyway, there is a group of patients (about 20%) having a clinically notable risk class change, needing deeper investigations on the genesis of this phenomenon.

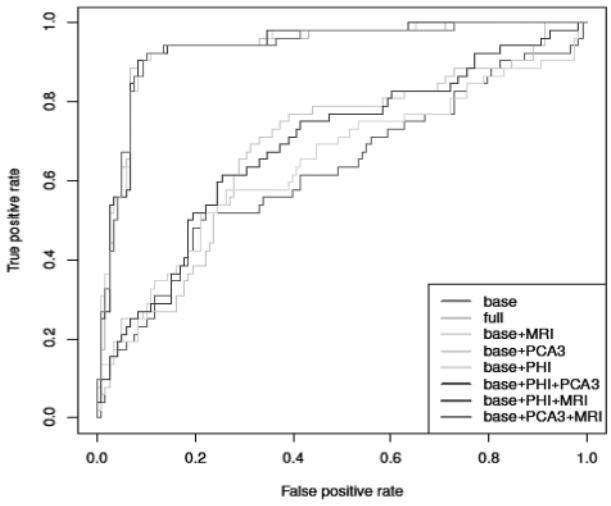


Figure 1.

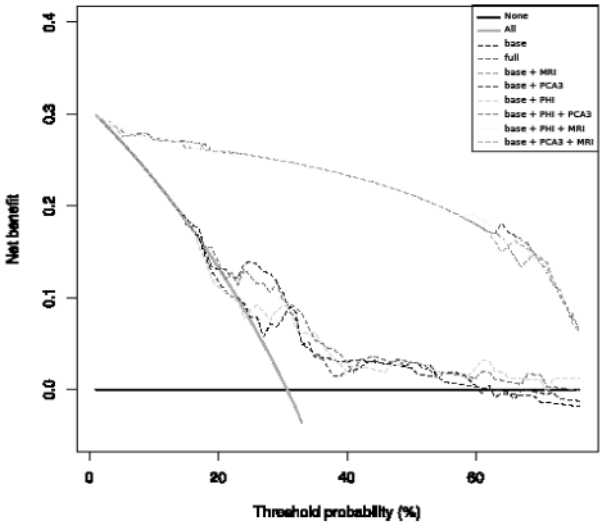


Figure 2.

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A COMPARISON BETWEEN MULTIPARAMETRIC MRI, PCA3, AND PHI IN THE PREDICTION OF PROSTATE CANCER AFTER AN INITIAL NEGATIVE BIOPSY

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Introduction and Objectives: Additional analyses such as the PCA3 score, Prostate Health Index (PHI) and prostate multiparametric Magnetic Resonance Imaging (mp-MRI) have been proposed for reducing the number of unnecessary repeated biopsies (RB) in patients with a negative prostate biopsy (PB) and persistent suspicion of prostate cancer (PCa). We conducted this study to evaluate the diagnostic accuracy of PCA3, PHI, mp-MRI, and different combinations of these tests in the RB setting. *Patients and Methods:* After Ethics Committee approval, 170 patients with an initial negative PB and persistent suspicion of PCa were enrolled in this prospective study. The patients underwent serum measurements of the total PSA and free PSA rate, along with PHI, PCA3 tests, and mp-MRI prior to standard (18- or 24-core) RB that was performed by urologists blinded to the mp-MRI results. Multivariable logistic regression models with different combinations of PCA3, PHI, and mp-MRI were used to identify the predictors of PCa with RB, and the performances of these models were compared using ROC curves, AUC analysis, and decision curve analysis (DCA). *Results:* In the ROC analysis, the most significant contribution was provided by mp-MRI (AUC value of 0.936), which was greater than the contribution of the PHI+PCA3 model ($p<0.001$), as shown in Figure 1. In the multivariate logistic regression analysis, only mp-MRI was a significant independent predictor of PCa diagnosis with RB ($p<0.001$). The results of the DCA confirmed that the most significant improvement in the net benefit was provided by mp-MRI (Figure 2).
Conclusion: Our results indicate that mp-MRI has high diagnostic accuracy in identifying patients with PCa in the RB setting compared with PCA3 and PHI. For this reason, mp-MRI should be considered as a valid tool for avoiding unnecessary biopsies in this clinical scenario.

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SERTOLIFORM CYSTOADENOMA OF THE RETE TESTIS: A CASE REPORT

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Introduction: Neoplastic and non neoplastic proliferations of the testicular collecting system may be a source of diagnostic difficulty as they are very rarely encountered (1). Here we present a case of a sertoliform cystoadenoma of the rete testis, a benign tumour which, to our knowledge, has been described in only 7 previous cases. *Patients and Methods:* A 18 year old man came to our attention for left testicular pain. Ultrasound examination demonstrated a 0.5 cm hypoechogenic partially cystic nodule in a zone belonging to the rete testis. Tumour markers alpha-fetoprotein and human chorionic gonadotropin were not increased. Under the assumption of a dermoid cyst a conservative surgery with frozen section assessment was performed in order to prevent radical orchiectomy. *Results:* Macroscopically the tumour was 5 mm in maximum diameter and had a grey/white color at the cut surface, with small cystic spaces. Histologically it was made by two compartments: a solid area with sertoliform epithelial like tumour cells growing within a sclerotic stroma, and a cystic part. The latter represented dilatated lumen of the rete testis filled with islands of uniform cells arranged in tubules and acini, with eosinophilic cytoplasm, prominent nucleoli and no obvious mitotic activity. Frozen section diagnosis was questionable but in agreement with the urologist a testicular sparing surgery was done. Immunohistochemistry was performed in order to achieve a correct definitive diagnosis. Tumour cells showed intense positivity for inhibin, calretinin and vimentin both in the solid and in the polypoid masses of the cystic areas, while pancytocheratins were focally positive in the former and totally negative in the latter. Sclerotic tissue around tubules of the sclerotic area expressed smooth muscle actin. Proliferative index (Ki67) was very low and reached 3%. A final diagnosis of sertoliform cystadenoma of the rete testis was made and attested by a special opinion MC; patient was submitted to follow-up. *Discussion and Conclusion:* To our knowledge this is the 8th case of sertoliform cystoadenoma of the rete testis to be described, and the only one treated with testicular spearing surgery. Previously reported cases occurred in adult patients but one was observed in a 6 years-old boy; all these cases were treated with orchifunicolectomy because frozen sections were not performed. The main histological differential diagnosis is testicular Sertoli cell tumor. The distinction between them is important because Sertoli cell tumors have a malignant potential in 12% of patients, whereas sertoliform cystadenomas of the rete testis described to date have behaved in a benign fashion.

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ADJUVANT AND SALVAGE RADIOTHERAPY AFTER PROSTATECTOMY:OUTCOME ANALYSIS OF 307 PATIENTS WITH PROSTATE CANCER

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Aim: In men with adverse pathology after radical prostatectomy, the most appropriate timing to administer radiotherapy (RT) remains a topic of debate. We analyzed in terms of efficacy, prognostic factors and toxicity the two therapeutic strategies: immediate postoperative radiotherapy (PORT) and salvage radiotherapy (SART). *Patients and Methods:* Between January 1995 and November 2010, 307 patients underwent adjuvant or salvage radiotherapy, after prostatectomy. *Results:* In the PORT group, 42 patients (20.7 %) had biochemical failure, with a median time to biochemical failure of 1.8 years; two parameters (age at diagnosis and PSA pre-RT) resulted to be significant at the survival analysis for overall survival (p=0.003 and p=0.046, respectively). In the SART group, 33 patients (31.7 %) had biochemical relapse; sixteen patients died of prostate cancer; postoperative hormones therapy, conformal radiotherapy and level of PSA pre-RT >1.0 ng/ml resulted to be significant at the survival analysis, p=0.009, p=0.039 and p=0.002, respectively. *Conclusion:* Our study is limited by its retrospective and nonrandomized design. As such, decisions to treat with adjuvant or salvage radiotherapy and the time to initiate therapy were based on patient preference and physician counseling. Our recommendation is to suggest adjuvant radiotherapy for all patients with adverse prognostic

factors and to reserve salvage radiotherapy for low-risk patients, when biochemical recurrence occurs.

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PROGNOSTIC ASSESSMENT OF NEOPLASTIC INVOLVEMENT OF THE PROSTATIC APEX IN RADICAL PROSTATECTOMY

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Aim: To evaluate the prognostic role of prostatic apex tumor invasion in patients undergoing radical prostatectomy for prostate cancer (pca) clinically organ-confined, and to define its correlation with clinical and pathologic variables (age, clinical stage, preoperative psa,% frustules positive biopsy, Gleason score, surgical margin status). *Patients and Methods:* From our database of 1693 patients who underwent rp between 2000 and 2012 for clinically localized pca, data from 498 patients with pathological stage t2 were retrospectively evaluated. The entire prostate was examined with 2-4 mm intervals transections in a plane perpendicular to the urethra. The apical prostate was separately sectioned and examined in parallel slices and "apical involvement" was defined as the presence of neoplastic glands in the last 8 mm of the prostate. Patients with lymph nodes involvement were treated with early adjuvant hormonal therapy. Biochemical relapse was defined as the evidence of psa>0.2 ng/ml in two consecutive measurements. The probability of biochemical recurrence was estimated by the Kaplan-Meier method, with the log-rank test used to evaluate differences among levels of the analyzed variables (apical involvement, preoperative psa, gleason score, pathological stage, surgical margins status). The multivariate Cox proportional hazard model was used to estimate the relative importance of the variables in predicting survival. *Results:* Overall 280 patients (56.2%) had neoplastic involvement of the prostatic apex. The mean follow-up was 40 months (range 6-154). In 30 patients (6.02%) a biochemical relapse was observed, with a mean time of 30 months (range 3-149). Positive surgical margins were observed in 34 patients (6.8%), of whom, 26 (76.4%) presented involvement of the prostatic apex. The number and the percentage over the total of neoplastic biopsy cores were predictor factors of tumor apex involvement (p=0.018). The biochemical recurrence-free survival (brfs) for patients with positive apex was lower than in patients with negative apex (91.9% *vs*. 95.9% at 36 months, 88 % *vs*. 92.8 % at 60 months and 86% *vs*. 92.8% at 120 months, respectively) (p=0.05). Positive surgical margins, the apex involvement and pathological stage were significantly correlated with biochemical relapse at univariate analysis. Multivariate analysis confirmed the statistical independence of positive surgical margins (p=0.0004, rr=5.17) and apex involvement (p=0.0536, rr=2.47). *Conclusion:* The prostatic apex represents a crucial anatomical structure during radical prostatectomy for both oncological and functional outcomes. The absence of a well anatomically defined capsule at this level suppose the risk of understaging at final pathological analysis. Our data showed that tumor invasion into the prostatic apex is a significant prognostic factor regardless of the status of surgical margins.

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A PROPOSED SCORE FOR ASSESSING PROGRESSION IN PT1 HIGH-GRADE UROTHELIAL CARCINOMA OF THE BLADDER

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Aim: We tested a selected series of patients with single urothelial high-grade pT1 stage (pT1 HG) or urothelial carcinoma *in situ* (CIS) with a set of immunohistochemical markers to elaborate a risk score for progression. *Patients and Methods:* We retrospectively reviewed all first diagnoses of single, <3 cm, urothelial papillary carcinoma pT1 HG or isolated CIS between 2006 and 2009. Galectin-3, CD44, E-cadherin, CD138, p16, survivin, HYAL-1, and topoisomerase-II α were used. A grading score 0 or 1 for each immunohistochemical staining was assigned to obtain a total score for assessing progression. The median "progression score" was selected as cut-off value for statistical analysis. Overall, 23 patients (19 pT1 HG and 4 CIS) were included in the study. *Results:* After a median follow-up of 21 months (range, 12 to 34 mo), 9 patients (39.1%) showed disease recurrence whereas 4 patients (17.4%) showed tumor progression. Topoisomerase-II α, p16, survivin, galectin-3, and CD138 were significantly associated with progression. Progression score ranged from 0 (best prognosis) to 7 (worst prognosis). Using a score ≥5 as a threshold, specificity was 78.9%, sensitivity 100%, positive predictive value 50%, and

negative predictive value 100%. ROC area (a 95% confidence interval, 0.807-1.000; $p<0.001$). *Conclusion:* This immunohistochemistry-based progression score using a threshold ≥5, might help the clinician to focus on patients with HG pT1 or extended CIS at high risk for disease progression. These patients might benefit from a more intensive follow-up program or early cystectomy.

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CHARACTERISTICS OF LONG-TERM BIOCHEMICAL RELAPSE IN PATIENTS WHO UNDERWENT RADICAL PROSTATECTOMY FOR PATHOLOGIC STAGE T2

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Aim: To evaluate the characteristics of long term biochemical relapse in a cohort of patients undergoing radical prostatectomy for clinically localized prostatic disease with pathologic stage t2. *Patients and Methods:* From our database of 1628 patients who underwent radical prostatectomy from 2000 to 2012 we analyzed data from 727 patients, mean age 65.1 aa (range, 43-78 yr), with organ-confined disease at the definitive histopathological examination. Biochemical relapse of disease was defined as the relief of psa>0.2 ng/ml in two consecutive samples. Survival was assessed using the Kaplan-Meyer method with the log rank test for univariate analysis and the Cox method for multivariate analysis. We analyzed: the characteristics of biochemical relapse, the need and response to treatment and clinical and pathologic variables which correlate most with the relapse. *Results:* Surgical margins were positive in 64/727 patients (8.8%) and negative in 663/727 (91.2%). Nerve sparing technique (bilateral or unilateral) was performed in 480 of the 727 patients. The mean follow-up was 34.6 months (range 6-154). A biochemical relapse of disease was observed in 73/727 patients (10.04%). The mean time of relapse was 23.9 months (median 23.5, range 3-149). Of these 73 patients, 34 underwent delayed treatment (19 hormonal therapy, 15 radiotherapy). The opportunity of a treatment was evaluated according to patient age, comorbidities and time of relapse. Thirty-nine patients (53.4%) presented an elevation of psa >0.2 ng/ml, which remains stable in a range between 0.2 and 0.5 ng/ml over the years without any radio or hormonal therapy. The disease-free survival was significantly higher for patients with negative margins ($p<0.0001$). Pathological stage (pt2a, pt2b pt2c) and the presence of positive surgical margins (both $p<0.0001$) significantly correlate with the biochemical relapse, and were both confirmed as predictor factors at the multivariate analysis ($p=0.04$ and <0.001, respectively). *Conclusion:* An important rate of patients (>50%) presented a stable value of psa between 0.2 and 0.5 ng/ml over the years without any additional therapy. These data show that radical prostatectomy provides control of the disease in almost all patients with organ-confined disease, and, despite the occurrence of biochemical relapse, a treatment is not always necessary.

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NUCLEAR MATRIX PROTEIN NMP22 ANCILLARY TEST IN THE DETECTION OF UROTHELIAL CARCINOMA

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Introduction: Morphological CTM detection in voided urine samples is a cheap and universally adopted exam, though affected by a relatively low sensitivity, because of the usual challenge represented by the interpretation of the "atypical" category. Hence, new analytical methods of cancer detection like abnormal level of NMP22 matrix protein obtained a lot of attention in the last decade. NMP22 is an enzyme linked immunoassay performed in fresh collected urine, aimed to identify the NuMA matrix protein of the neoplastic urothelial cells. The exam is a time (30' to get the answer) and cost effective approach to the problem of splitting the wide "atypical" category of urine sediment. *Methods:* We analyzed 43 fresh voided urine samples both for cytology (one sediment as opposed to the conventional 3 days/3 sediment approach) and NMP22 of 43 patients submitted to TURB resection in the following hours (same day). *Results:* 36 out of 43 patients were positive for papillary urothelial carcinoma (18 low grade and 18 high grade), while 7 cases were affected by cystic cystitis. 19/36 (overall sensitivity: 52%) positive cases were CTM+ (4/18 low grade and 15/18 high grade); 8/36 cases were NMP22+ (overall sensitivity: 22%): 4/18 low grade and 4/18 high grade. None of the 7 negative cases showed morphological or NMP22 positivity. 15/19 cases of CTM+ cases were NMP 22 negative. 4/8 cases of NMP22+ cases were CTM negative (low grade papillary carcinoma). Comments: In the present experience, NMP22 is a test affected by a low sensitivity. Nevertheless, in combination with cytology it may increase the sensitivity of tumor detection, particularly in low grade tumors. Nevertheless, a limitation of our comparison between the two methods is due to the single sediment analysis of the CTM morphological investigation method, that might have further affected its sensitivity (52%).

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INVERTED PAPILLOMA OF THE KIDNEY: A SYSTEMATIC REVIEW OF LITERATURE

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Introduction: Inverted Papilloma (IP) of the bladder is an infrequent event (2.2% of all cancers of the bladder) (Picozzi, Urol Oncol 2012). The IP of the upper urinary tract and in particular of the renal pelvis is exceptionally rare. We performed a systematic review of the literature on this unusual pathological findings. *Materials and Methods:* We carried out a systematic research from January 1974 to January 2013 on the Medline, Embase and Cochrane Library using the key words: "renal inverted papilloma", "inverted papilloma of the upper urinary tract" "inverted papilloma kidney", restricted to English articles. *Results:* We identify 39 articles in literature and 14 are included in this review, for a total of 19 clinical cases. The mean age of presentation of renal IP was 65.1 years (range 49 to 89), with a male/female ratio of 18/1. In 1 case (5.3%) the clinical presentation of the IP is synchronous with a carcinoma of the bladder (3) and in another case with an urothelial neoplasm on the controlateral kidney (2). The finding of IP in the kidney was incidental in 10 cases (52.6%), in 5 cases (26.3%) there was documented hematuria and flank pain in 2 cases (10.5%). The lesion was identified by CT in 13 cases (68.4%) and by urography in 6 cases (31.6%). In 15 cases (79.0%) a nephrectomy or nephroureterectomy was performed, and in 3 cases (15.78%) a local excision of the lesion by ureterorenoscopy or pielotomy. In 3 cases (15.8%) local relapse has been described, and in one case (5.3%) worsening of the disease in a urothelial cancer (4). *Discussion:* An analysis of the literature on this rare disease has shown that, despite IP is classified as a benign lesion, in 10% of cases it may be associated with other carcinoma of the urinary tract and in one case out of five may recur or develop into malignancy. Instrumental investigation can not suggest any distinctive features of these lesions such as to allow a differential diagnosis with urothelial carcinoma. In fact in the most of the cases the patients were subjected to nephrectomy or nephroureterectomy. Considering the possible association with malignancy, the tendency of these lesions to relapse and the rare malignant progression, a close follow-up is recommended like the model used for the conventional renal tumor. *Conclusion:* The IP of the kidney is an uncommon disease, which requires accurate characterization by the pathologist for the risk of malignant lesions and close monitoring by the urologist for the risk of local recurrence or malignant degeneration.

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DEGARELIX INHIBITS CELL GROWTH OF THREE HUMAN PROSTATE CANCER CELL LINES

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Background and Aims: Gonadotropin-releasing hormone (GnRH) agonists are used in the standard treatment of advanced prostate cancer. More recently, GnRH antagonists have been developed and compared *versus* GnRH agonists in clinical trials. GnRH analogues act *via* specific GnRH-receptors and block the pituitary-gonadal axis. Nevertheless, it has been widely demonstrated *in vitro* that GnRH agonists exert a direct effect on tumor cells. There are fewer data on the antagonists, but no information is available about the direct effect of a new analogue of third generation named Degarelix. In this study, the antiproliferative effect of Degarelix on three human prostate cancer cell lines (LNCaP, androgen-sensitive; DU145 and PC3, androgen-independent) was explored. *Methods:* Cells were grown in their standard culture

conditions, *i.e.* medium containing 5% or 10% foetal bovine serum (FBS). Degarelix at the concentrations ranging from 10^{-11} to 10^{-5}M was added. The effect of the analogue on LNCaP cell growth was also evaluated in medium containing charcoal-treated FBS (CH-FBS), deprived from steroids and other small molecular weight peptides. Preliminary experiments have been performed on DU145 treated with 50 ng/ml EGF in the presence of Degarelix to explore the ability of the analogue of counteracting the growth factor mitogenic activity. Cell counts were performed with a hemocytometer, after 3 and 6 days of exposure to hormone and/or growth factor. A Student's *t*-test was carried out to assess the statistical significance of the data. *Results:* Degarelix showed anti-proliferative effects on all cell lines cultured in their standard conditions. In both LNCaP and PC3 cells, the antagonist reduced the growth (about 15%, $p<0.05$) starting from the concentration of 2×10^{-8}M. The inhibitory effect gradually increased reaching the maximum at the highest concentration used (10^{-5}M, >60%, $p<0.0001$). In DU145 cells, Degarelix was also effective when low doses were used. In fact, it inhibited DU145 cell growth (about 25%, $p<0.01$) starting from the concentration of 10^{-10}M. This effect was seen up to the concentration of 10^{-7}M, increased slightly at 10^{-6}M (about 35%, $p<0.01$) and was maximum at 10^{-5}M (>60%, $p<0.0001$). In preliminary experiments, EGF increased DU145 cell proliferation (about 45%, $p<0.01$) and the addition of Degarelix seemed to reduce the stimulatory effect of the growth factor. Finally, in LNCaP cells cultured in the presence of 5% CH-FBS, inhibition of cell proliferation was obtained only at the highest concentrations tested (10^{-6} and 10^{-5}M). *Conclusion:* Our results clearly show that Degarelix has an inhibitory activity on proliferation of prostate cancer cell lines with different characteristics in terms of androgen sensitivity, differentiation and aggressiveness. Using standard culture conditions, this effect is observed at therapeutic concentrations of the GnRH antagonist. It is worth mentioning that in the androgen-independent DU145 cells Degarelix acts at low doses.

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WHORLED UROTHELIAL CELL CARCINOMA: A LOW-AGGRESSIVE UNDESCRIBED VARIANT

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Introduction: The main principles of the ISUP/2004 WHO grading formulation are based on the morphological concept of architectural order, leading to a low-grade lesion, or disorder, characterizing high grade tumors. The overall orderly appearance of low-grade tumors is based on the presence of a certain degree of nuclear polarity of the cell growth. However, a rare and well characterized variant of urothelial carcinoma may lack the orderly pattern. We collected 12 cases with an undescribed whorled pattern of growth that breaks the usual rules of urothelial carcinoma histology. *Patients and Methods:* From pathological archives of more than 1500 cases of trans-urethral resections or cold biopsies, we selected 12 cases of urothelial carcinoma with an unusual, well characterized, pattern of growth with a peculiar "turbulent", "whorled" aspect present in at least 50% of the neoplastic urothelium. Hematoxylin and eosin stained sections were re-evaluated by 3 of the authors (CP, EC, EB). A cytological grading according to the 1973 WHO classification was applied and the 2004 WHO grading was blindly applied again to the cases. Additional immunohistochemical reactions were done for GATA3 (Mouse-MAb, L50-823, BioCare 1:50 diluted, Concord CA), for Ki-67 (30-9, Roche Ventana prediluted, Mouse MoAb, Tucson, AZ), p53 (Bp53-11, Roche Ventana prediluted MoAb) and p27 (clone IB4 Novocastra 1:30, Wetzlar, Germany). As cut-offs of these biomarkers (Ki-67>20%; p53>10%, p27<30%), we used the criteria validated in the literature and reported by Shariat *et al*. (2). *Results:* As whorled we defined a pattern of growth characterized by concentrically organized cell structures without evidence of keratinization, resembling whorls/whorling structures of transitional meningioma. Although variations in nuclear shape and loss of polarity were constitutively present in the whorling structures, limited nuclear sizes and their homogeneous chromatin pattern allowed a classification of the cases among low grades. Gata3 stains positively in all cases ranging 90-100%; One case only reached 20% of positive nuclei, using Ki-67/Mib1. P53 immunoreactivity was low in all cases but 3. Conversely, p27 immunostaining was 30% or higher in most cases. The combined evaluation did not show cases with alteration of all 3 markers, whereas 2 cases showed alterations of at least 2 markers. *Discussion:* The stage of the tumors (Ta in 12/12 cases), the immunoistochemical results and the follow-up (no progression, 2/12 recurrences) of the patients support the low grade/low aggressiveness of these tumors. Hence, despite their morphological aspect, urothelial tumors with a whorled pattern of growth should be considered as low grade carcinomas.

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PROGNOSTIC ROLE OF DNA REPAIR GENE POLYMORPHISMS ON PROSTATE CANCER OUTCOME AFTER RADIOTHERAPY

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Introduction: Germinal polymorphisms in DNA repair genes play a pivotal role in biological effects of ionizing radiation. Such genetic variations can alter gene expression or protein function, predisposing subjects to disease. The effect of germinal polymorphisms in DNA repair genes on toxicity after radiotherapy (RT) have been reported, but their role on biochemical prostate-specific antigen (PSA) recurrence (BCR) after RT and overall survival (OS) remains unexplored. *Objective:* To evaluate the potential prognostic role of candidate gene polymorphisms in DNA damage response (double strand breaks-DSBs, mismatch repair-MMR, nucleotide excision repair-NER, base excision repair-BER) on BCR after RT and OS in prostate cancer (PCa) patients. *Patients and Methods:* A total of 542 Caucasian PCa patients were enrolled at CRO-National Cancer Institute, Aviano, Italy. All patients received a radiation treatment with a median follow-up of 46 months after RT (BCR) and 68 months from diagnosis (OS). Patients were genotyped for 22 polymorphisms (SNPs) in 15 DNA repair genes selected in agreement with the effects on RT outcome previously reported in literature. Associations between BCR and OS were assessed using the Kaplan-Meier analysis and Cox proportional hazards model. *Results and Limitations:* After adjustment with clinical features in multivariable analysis, hEXO1 (rs4149963) variant and ERCC1 (rs11615) resulted significantly associated with higher risk of BCR (dominant model: hazard ratio (HR)=1.81(1.16-2.82), p=0.0086, and dominant model: HR=1.55(1.01-2.39), p=0.0448 respectively) while ERCC2 (rs1799793) variant determined a decreased PSA relapse risk after RT (dominant model: HR=0.62(0.42-0.92), p=0.0160). Among them hEXO1 (rs4149963) was also associated with a worse OS (dominant model: HR=1.69(1.07-2.65), p=0.0233). Two other SNPs resulted significantly associated with OS: hMSH6 (rs3136228) polymorphism showed better survival (dominant model: HR=0.64(0.44-0.93), p=0.0193), instead RAD51 (rs1801320) variant showed poorer survival (recessive model: HR=4.83(1.39-16.75), p=0.0130). *Conclusion:* This mono institutional study demonstrated a role of DRG polymorphisms on BCR (ERCC1-rs11615, ERCC2-rs1799793, hEXO1-rs4149963) and OS (hEXO1-rs4149963, hMSH6-rs3136228, RAD51-rs1801320) in PCa patients homogenously treated with primary RT.

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EVEROLIMUS AS SECOND-LINE THERAPY FOR METASTATIC RENAL CELL CARCINOMA. AN OBSERVATIONAL, RETROSPECTIVE STUDY FROM THE CAMPANIA REGION

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Background: Everolimus is approved for treatment of patients (pts) with metastatic renal cell carcinoma (mRCC) who have progressed on prior VEGFr-TKI (Vascular Endothelial Growth Factor receptor - Tyrosine Kinase Inhibitors) therapy. However, how a new drug is used in practice may not always reflect the way that drug was used on registrative, randomized study, potentially affecting its broad efficacy and safety profile. Observational studies can provide valuable clinical information about the safety and effectiveness of cancer therapies and represent an additional, real-world source of clinical information. *Patients and Methods:* An observational, retrospective study conducted in Italy by 10 Centres from the Campania Region considered mRCC patients starting Everolimus (Eve) immediately after failure of initial VEGFr-targeted therapy. Study endpoints were activity (according to RECIST 1.1), efficacy (Progression-Free Survival – PFS: time from first dose to progression or death from any cause, estimated with the Kaplan-Meier method), and tolerability

(adverse event type and grade according to CTC-AE v.3.0). *Results:* One hundred pts, progressing after 1st line sunitinib (99%) or pazopanib (1%) were recorded. Seventy-one were males and 29 were females, with median age 64 years (range: 41-75). Nineteen pts had a partial remission of disease, 62 had a disease stabilization, and 19 had a disease progression. Eighteen pts were still on Eve, 67 discontinued Eve for radiologic progression, 12 for clinical progression, and 3 because of untolerable toxicity. The median PFS estimate was 8 months (95% CI: 6.7 to 9.3), with 26.3% of pts estimated to be free from progression at 12 months from Eve initiation. Grade ≥3 adverse events were stomatitis (11%), diarrhea (3%), hyperglycemia (2%), infection (2%), non-infectious pneumonia (2%), fatigue (2%). *Conclusion:* Heeding the possible under-reporting by participating physicians in routine clinical practice, as compared with the randomized RECORD-1 trial, anyway Eve demonstrated a longer median treatment duration and a better safety profile than the pivotal phase 3 trial. The observed 8-month PFS and favourable safety profile were similar to those of the CHANGE Eve real-life study (median PFS: 7 months). Thus, these results support the use of everolimus for patients with mRCC who have failed a single VEGFr-TKI.

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ACTIVE SURVEILLANCE: ADJUSTMENT TO UNTREATED PROSTATE CANCER AND ITS RELATIONSHIP WITH QUALITY OF LIFE

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Introduction: Patients diagnosed with low-risk, potentially non aggressive prostate cancer (PCa) often reported to choose Active Surveillance (AS) in order to avoid impairments in their quality of life (QoL) which may derive from the adverse side effects of radical therapies (commonly, erectile, urinary and bowel dysfunctions) (1). Nonetheless, "living with untreated PCa" was deemed to be related to psychological distress. Studies examining the QoL of patients on AS showed that most patients reported high levels of physical and psychosocial well-being (2). It is still scarcely understood how patients on AS adjust - in terms of cognitive and behavioural responses - to untreated PCa, which could be eventually related to their QoL (3). The aim of this study was to evaluate the association between AS patients' coping strategies and their Health Related Quality-of-Life (HRQoL). *Patients and Methods:* Between September 2007 and October 2013, 324 patients were enrolled in PRIAS study. Of these, 253 (78%) patients consented to participate in the ancillary PRIAS QoL study. Data were collected by administering self-report instruments. For this study, evaluations at entrance in AS protocol (T0) and at 10 months from diagnostic biopsy (T1) were considered. Coping strategies were measured by using the Mini Mental Adjustment to Cancer (Mini-MAC) scales: fighting spirit, helplessness/hopelessness, fatalism, anxious preoccupation and cognitive avoidance. Functional Assessment of Cancer Therapy – Prostate Version (FACT-P) was used to assess HRQoL in terms of: physical wellbeing (PWB), social wellbeing (SWB), emotional wellbeing (EWB), functional wellbeing (FWB). Descriptive analyses were performed. Univariate logistic regression analyses were used to identify the role of coping at T0 and T1 as potential predictor of low (<25th percentile) HRQoL at T1. *Results:* The mean age of the study patients was 64 years old (range 44-83, SD=7,4). Descriptive normalized scores for Mini-MAC at T0 and T1 and FACT-P at T1 are reported in Table I. Patients with high helplessness/hopelessness at enrolment on AS were more likely to report low EWB (OR=2.7585, $p<0.01$, AUC=0.654) and FWB (OR=2.4471, $p<0,01$, AUC=0.614) at T1. Anxious preoccupation at entrance on AS was associated with low EWB (OR=3.3567; $p<0,001$, 0.676) at T1. Both helplessness/hopelessness and anxious preoccupation at T1 were predictive of low EWB (respectively, OR=4.2202, $p<0,001$, AUC=0.661; OR=5.9505 $p<0.001$, AUC=0.748) at T1. *Discussion and Conclusion:* Our findings suggested that men who felt powerless and experienced lack of hope following diagnosis were more likely to report emotional distress and difficulties in carrying out their daily activities. The results also highlighted that feelings of anxiety, fear and apprehension for cancer experienced at entrance on AS could predict poor emotional wellbeing over time. Psychological assessment should be routinely conducted to detect those patients who do not cope well with the diagnosis of cancer and offer tailored psycho-social interventions.

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2 Van den Bergh *et al*: Curr Opin Urol, 2012.
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Table I. *Descriptive normalized scores for Mini-MAC (1-4) at T0 and T1 and FACT-P (0-4) at T1.*

	N	Mean	SD	Median
Fighting spirit_T0	240	2.796	0.5977	2.800
Fighting spirit_T1	196	2.660	0.7371	2.800
Helplessness/hopelessness_T0	240	1.399	0.4741	1.220
Helplessness/hopelessness_T1	196	1.296	0.5070	1.165
Cognitive Avoidance_T0	240	2.348	0.8165	2.250
Cognitive Avoidance_T1	196	2.161	0.8599	2.250
Fatalism_T0	240	2.346	0.6645	2.250
Fatalism_T1	196	2.185	0.7737	2.250
Anxious preoccupation_T0	240	1.933	0.5648	2.000
Anxious preoccupation_T1	196	1.843	0.6541	1.860

	N	Mean	SD	Median	25th-75th percentile
EWB	185	3.165	0.5704	3.330	2.830-3.500
FWB	185	2.605	0.6546	2.570	2.140-3.000
PWB	185	3.871	0.2593	4.000	3.860-4.000
SWB	185	2.618	0.7995	2.710	2.000-3.140

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VALIDATION IN ITALY OF THE QUALITY OF LIFE QUESTIONNAIRE PROSQOLI IN PATIENTS WITH PROSTATE CANCER

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Objectives: Culture adaptation of the validated PROSQOLI questionnaire (Prostate Cancer Specific Quality Of Life Instruments). A questionnaire to evaluate quality of life in Italian patients with prostate cancer. *Patients and Methods:* An observational cross-sectional multicenter study was conducted in 756 patients (21 centers) with locally advanced or advanced/metastatic prostate cancer (according to TNM criteria) who came to the scheduled check-up. Patients were grouped according to primary cancer treatment: prostatectomy, radiotherapy and medical therapy (hormone therapy). Socio-demographic and clinical data of the participants were collected. The subjects filled out the PROSQOLI and SF-12 questionnaires. The final analysis included 472 cases (19 centers), which met the selection criteria. The psychometric characteristics (feasibility, validity and reliability) of the adapted PROSQOLI questionnaire were analyzed. *Results:* Mean age was 73.5 (7.9) years. A total of 60% of the participants had high or very high cancer recurrence risk. In 53.2%, the primary treatment was prostatectomy, in 12.3% it was radiotherapy and for the last 34.5% it was medical therapy. The mean for each scale of the PROSQOLI questionnaire varied from 65.1 to 81.9. The percentage of no response was less than 3% for each scale. The percentage of subjects with minimum score in any scale was less than 1.5%. The percentage of maximum score was equal or less than 11% for each item, except for the adjectival ordinal scale to assess the current intensity of pain where the percentage was 44.7%. Mean time to fill in the questionnaire was 316 (267.6) seconds. Cronbach's α coefficient was 0.91 and only two items showed the item to total correlation less than 0.7. Correlation with the SF12 questionnaire was high (0.81). The responsiveness of the PROSQOLI summary measures was compared across primary cancer treatments, recurrence risk and age. Significant differences were observed in each of these parameters. *Conclusion:* The results show the reliability and validity of the Italian translation of the PROSQOLI questionnaire, supporting therefore its use in the clinical practice as a measure of quality of life in patients with prostate cancer, in the clinical practice and in national clinical trials.

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SOCIO-DEMOGRAPHIC FACTORS AND COMORBIDITIES AS PREDICTORS OF QUALITY OF LIFE OF MEN ON ACTIVE SURVEILLANCE

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Introduction: Men with low-risk prostate cancer are given the opportunity to choose between active treatments and Active Surveillance (AS), with the aim to monitor clinical conditions and avoid side effects of radical treatments. An important issue the scientific community has addressed is the investigation of the Health- Related Quality of Life (HRQoL) in patients who opted for AS. Although several studies highlighted that most of patients on AS did not experience a decrease of

psychological wellbeing (1), the next challenge is to identify early, ideally at recruitment, those individuals who are likely to show a reduction of HRQoL over time (2). Thus, the aim of the present report is to study the relationships between the patients' socio-demographic data and their level of HRQoL 10 months after the inclusion in the AS protocol. *Patients and Methods:* Between September 2007 and December 2013, 339 patients enrolled in the PRIAS study accepted to participate in an ancillary HRQoL study. An initial assessment was conducted at enrollment, including the collection of demographic data (age, education, partner, work status - employed, unemployed or retired) as well as the perception of impairment due to the presence of severe pathologies. The HRQoL questionnaires were administered after a 10-month period from diagnostic biopsy, about 2 months before the first re-biopsy. For the purpose of the present work, the socio-demographic and clinical information were considered as potential predictors of HRQoL, measured by the Functional Assessment of Cancer Therapy scale - Prostate Version (FACT-P). Multivariate logistic regression analyses were performed to identify the best predictors of each of the FACT-P HRQoL's domains: functional wellbeing (FWB), emotional wellbeing (EWB), physical wellbeing (PWB), social wellbeing (SWB). The subscale related to prostate cancer therapy symptoms (PCS) was not considered, as it was not strictly relevant for AS patients. *Results:* The mean age of the study population was 64 years (SD=7,08; range: 42-79). Table I illustrates descriptive normalized scores for FACT-P; the 15th percentile was considered as the cut-off between high HRQoL *versus* low HRQoL.

Table I.

	N	Mean	SD	15th percentile	No. of patients under cut-off (%)
EWB	186	3.162	0.5701	2.67	33 (17)
FWB	186	2.602	0.6546	2	28 (15)
PWB	187	3.869	0.2582	3.71	36 (19)
SWB	186	2.614	0.7996	1.86	34 (18)

Results showed that patients who had no partner were more likely to report low emotional wellbeing (OR=0.24; $p<0.01$; AUC=0.62); Functional wellbeing was higher for patients who were younger at the time of diagnosis (OR=0.89; $p<0.001$; AUC=0.71); Physical wellbeing was predicted by the age at the time of diagnosis and the presence of severe pathologies at the enrollment: low scores in PWB were more likely associated with older age (OR=0.91) and the presence of a pathology (OR=0.11) ($p<0.01$; AUC=0.77). Social wellbeing was not predicted by any of the socio-demographic and clinical variable. *Discussion and Conclusion:* As a first interesting result, the current study showed that, in general, the HRQoL of the patients on AS was high, as previously reported in literature. According to the present findings, some demographic and clinical variables, such as age and the perception of impairment due to comorbidities, can negatively affect HRQoL; on the other hand, the presence of a partner positively influences wellbeing. These men could benefit from interventions aimed at promoting supportive networks, such as patients peer-support groups. Future research is needed in order to develop more sensitive tools for the assessment of HRQoL in patients enrolled in AS protocols, and in turn, to build more reliable and informative predictive models.

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11-C-CHOLINE PET/CT IN PREOPERATIVE LYMPH-NODE STAGING IN PATIENTS REFERRED TO RADICAL CYSTECTOMY: COMPARISON WITH COMPUTED TOMOGRAPHY

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Aim: To evaluate the accuracy of PET/CT for lymph-node (LN) staging in patients with bladder cancer (BCa) scheduled for radical cystectomy (RC) in comparison with contrast enhanced CT (CECT). *Patients and Methods:* Twenty male patients with high grade or invasive transitional cell carcinoma (TCC) bladder cancer (BCa) were studied with 11C-choline PET/CT and CECT before radical cystectomy (RC) with extended (internal, external, common iliac, presacral, obturator preaortic/precaval LNs) pelvic lymph nodes dissection (ePLND). Histological findings of LN dissection were compared with 11C-choline PET/CT with low-dose CT for attenuation correction and CECT. All PETCT and CECT scan were by two binded form histological results. At PET/CT the node positivity was defined as the presence of focal uptake in a LN, while at CECT the size criterium (>1 cm) was considered. The reference standard was the assessment of LN specimens evaluated by an experienced uropathologist who measured the diameter of the single LN metastasis. *Results:* Pathological examination of bladder specimen showed organ-confined disease in 12 patients (CIS in 1 patients, pT1 in 6, pT2 in 5), while the remaining 8 had non organ-confined

disease (pT3 in 7 and pT4 in 1). Grade 2 TCC was found in 2 patients while 18 had G3. In 18 patients, PET/CT scan visualized the primary tumor. A total of 655 LNs were removed with a mean number of LN removed of 32.75±14.4 (median: 29.0; range: 20-47); 31 (4.7%) LNs harbored metastasis in 4 (20%) patients. PET/CT showed higher AUCs and sensitivity than CECT in particular in patient and region analysis, with similar specificity. 11C-choline PET/TC detection rate was 1/13 (8%) for LNM of 0.9-4.9 mm, 2/11 (18%) for LNM of 5-9.9mm and 2/7 (29%) for LNM ≥10mm. Finally PET/CT visualized suspected one bone metastasis and one lung metastasis in 2 different patients (confirmed by bone scan and CT during follow-up). *Discussion and Conclusion:* Our preliminary data suggest that 11C-Choline PET/CT may be useful in the LN staging of BC before surgery and may give more information than CECT; moreover it can identify lymph node metastases <10 mm. Moreover, PET/CT may identify systemic metastases that can change the therapeutic management in some patients.

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CAN TESTIS-SPARING SURGERY BE A VALID ALTERNATIVE TO RADICAL ORCHIECTOMY IN SELECTED CASES? A PROSPECTIVE STUDY

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Introduction and Objectives: The widespread use of high-frequency ultrasonography (US) has led to an increasing number of incidentally detected small testicular masses (STMs), most of which have been shown to be benign. Testis-sparing surgery (TSS) represents a new option for the treatment of small testicular masses (STMs), and in some cases can be considered a good alternative to radical orchiectomy. Aim of the present study was to evaluate the incidence of malignancy in STMs treated with TSS with intraoperative frozen-section analysis and to assess the safety of this surgical procedure. *Patients and Methods:* From January 2009 to January 2013, 15 consecutive patients underwent TSS for STMs at our Institution. Inclusion criteria for TSS were: size of the mass < 25 mm and a safe distance of the mass from the rete testis; advanced age was not considered as an exclusion criterion. After exteriorization of the testis, the STM was identified by straight palpation of the testis or with intraoperative US. In all patients, we performed cord clamping after the identification of the lesion to reduce the warm ischemia time. After excision of the mass, frozen section examination (FSE) was performed in all patients in association with multiple biopsies of the surrounding tissue. *Results:* The mean age was 44.3±18.7 years. The mean tumor size was 10.5±3.1 mm. The mean operative time was 90±31 minutes. The effective time between the identification of the lesion and its surgical excision (warm ischemia time) was 18±3 minutes. At final pathologic analysis, 6 patients (40%) were negative for tumor (2 inflammation, 1 hemorrhage, 1 abscess, 1 epidermoid cyst, 1 dermoid cyst). The other 7 cases (46.7%) had benign neoplasms. Of these, 5 patients (33%) had leydigiomas, a Sertoli cell tumor was found in 1 patient (6.6%), and 1 patient (6.6%) had an adenomatoid tumor. Only 2 patients (13.3%) had malignant tumor (a paratesticular low-grade fibromyxoid liposarcoma and a seminoma). Surgical margins were negative in all cases. After a mean follow-up of 19.2±11.5 months, all patients are free of disease, without any postoperative complications. *Conclusion:* Testis-sparing surgery has been proposed as an alternative treatment for the surgical management of STMs, in order to spare as much healthy parenchyma as possible, thus allowing to reduce the risk of hormonal failure and to preserve fertility. Our prospective study showed that TSS is a safe and effective procedure, with promising oncological and functional results, and could be a valid alternative to radical orchiectomy in selected cases.

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PRESERVATION OF INTERNAL VESICAL SPHINCTER AND PROXIMAL URETHRA DURING RADICAL PROSTATECTOMY IMPROVES EARLIER CONTINENCE RECOVERY

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Introduction/Aim: The preservation of urinary continence is one of the most important endpoints of retropubic radical prostatectomy (RRP). Numerous mechanisms have been advocated as responsible for male postoperative urinary continence, but the preservation of the integrity of the external urethral sphincter muscle, of the pelvic floor as well as anterior and posterior urethral support, seems to play the most important role. In this study we describe our approach of preservation of smooth muscular internal (vesical) sphincter (MIS) as well as of the proximal urethra (PA) during bladder neck dissection and we present our first results in a prospective case-control study in order to

evaluate the possible influence of the new technique in the early recovery of urinary continence after radical prostatectomy. *Patients and Methods:* 55 consecutive patients with organ confined prostate cancer were submitted to RP with the preservation of muscular internal sphincter and the proximal urethra (group 1) and compared to 55 patients submitted to standard procedure (group 2). Continence rates were assessed using a self-administrated questionnaire at 3, 7, 30 days and 3, 12 months after removal of the catheter. *Results:* Group 1 had a faster recovery of continence than group 2 at 3 days (50.9% *vs*. 25.5%; p=0.005), at 7 days (78.2% *vs*. 58.2%; p=0.020), at 30 days (80.0% *vs*. 61.8%; p=0.029) and at 3 months (81.8% *vs*. 61.8%; p=0.017); there were no statistical differences in terms of continence at 12 months among the two groups. Multivariate logistic regression analysis of continence showed that surgical technique was significantly associated with earlier time to continence at 3 and 7 days. The two groups had no significant differences in terms of surgical margins. *Discussion and Conclusion:* Our modified technique of RPP with preservation of smooth muscular internal sphincter as well as of the proximal urethra during bladder neck dissection resulted in significant increased early urinary continence at 3, 7, 30 days and 3 months after catheter removal. The technique does not increase the rate of positive margins and the duration of the procedure.

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LYMPH NODE DENSITY IN NODE-POSITIVE PATIENTS TREATED WITH RADICAL PROSTATECTOMY AND PELVIC LYMPH NODE DISSECTION

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Introduction/Aim: A lower volume of LNI (Lymph Node Invasion) by Prostate cancer (PCa) is associated with higher survival rates compared with a higher volume of nodal disease, even in the absence of adjuvant therapy. The aim of this study was to assess the prognostic value of Lymph Node Density (LND: percentage of positive lymph nodes to total lymph nodes retrieved) in patients with prostate cancer who underwent Radical Prostatectomy (RP), Pelvic Lymph Node Dissection (PLND) and adjuvant therapy, on overall (OS) and cancer specific survival (CSS). *Patients and Methods:* 1783 consecutive patients with PCa underwent, at our institute, retropubic/laparoscopic RP from November 1995 to January 2011. Of these, 1166 (65.3%) received a PLND and 128 (10.9%) patients had lymph node metastases. Excluding those undergoing neoadjuvant therapy, with incomplete clinico-pathological data and incomplete follow-up and with a PLND with removal of <10 lymph nodes, 77 patients were evaluated. Kaplan-Meier method was used to study graphically both the cancer-specific survival (CSS) and the overall survival (OS). The univariate and multivariate Cox regression were used to predict survival. *Results:* 4 (5.2%) patients had pT2 PCa, 18 (23.4%) were pT3a and 55 (71.4%) pT3b; 38 (49.4%) patients had a pathological Gleason Score (pGS)=7 and 39 (50.6% a) a pGS >7. All patients were subjected to adjuvant or salvage hormonal therapy and 43 (56%) to adjuvant radiotherapy. The mean number of lymph nodes removed was 17.8±8.2 (median 15, IQR 12-19). The best LND-cut-off, predictive for cancer-specific survival and overall, was 20%: 54 patients (70.1%) had LND <20% and 23 (29.9%) had LND ≥20%. At Kaplan-Meier analysis, patients with LND <20% showed a significantly better CSS (log rank test: p=0.013) and OS (log rank test: p=0.034). In multivariate Cox regression, LND was the only factor conditioning CSS (HR 9.4, p=0.022) and OR (HR 3.16, p=0.045). *Discussion and Conclusion:* Our study highlights the role of LND in predicting CSS and OS in PCa patients with LNI after RP and PLND and reinforce the need for a stratification of node positive patients in the pathologic TNM classification.

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ROLE OF NEPHROMETRIC SCORES IN THE PREDICTION OF WARM ISCHEMIA TIME AND POSTOPERATIVE COMPLICATIONS IN PATIENTS WHO UNDERWENT ELECTIVE OPEN OR MINIMALLY INVASIVE NEPHRON SPARING SURGERY FOR RENAL CELL CARCINOMA

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Introduction: Nephron sparing surgery (NSS) is the standard of care for renal masses ≤4 cm. Aim of this study was to evaluate the correlations between nephrometric scores (P.A.D.U.A. and R.E.N.A.L. score), warm ischemia time (WIT) and postoperative complications in patients treated with NSS for renal cell carcinoma (RCC). *Patients and Methods:* A cohort of 96 consecutive patients who

Table I. *Clinical, demographic and pathological characteristics of 96 patients evaluated in the study.*

Variable	Value
Age	
Mean (SD)	59.8 (11.7)
Median (IQR)	61 (50-68)
Gender	
Males (%)	74 (77.1)
Females (%)	22 (22.9)
Operative time (min)	
Mean (SD)	132.3 (48.1)
Median (IQR)	118 (102-156)
Surgical approach (%)	
Open	75 (78.1)
Laparoscopic	21 (21.9)
WIT (min)	
Mean (SD)	14 (9)
Median (IQR)	14 (8-20)
Side of the tumor	
Right (%)	43 (44.8)
Left (%)	49 (51)
Bilateral (%)	4 (4.2)
Clinical size (cm)	
Mean (SD)	3.2 (1.65)
Median (IQR)	3 (2.4-3.7)
Pathological stage (TNM) (%)	
pT1a	78 (81.3)
pT1b	13 (13.5)
pT2	3 (3.1)
pT3a	2 (2.1)
Fuhrman grade (%)	
Grade 1	8 (8.3)
Grade 2	53 (55.2)
Grade 3	29 (30.2)
Grade 4	2 (2.1)
N.A.	4 (4.2)
Histological subtype (%)	
clear cell	66 (68.8)
papillary	20 (20.8)
chromophobe	8 (8.3)
others	2 (2.1)
Positive surgical margins, no. (%)	
negative	87 (90.6)
positive	9 (9.4)

N.A=not available; BMI=Body Mass Index; WIT=warm ischemia time; TNM=Tumor, Necrosis, Metastasis.

underwent open or laparoscopic NSS for RCC between 2006 and 2012 at our Institution was retrospectively evaluated. Risk group categories identified according to nephrometric scores and Clavien-Dindo grades of postoperative complications were used to stratify patients. Two-tailed $p<0.05$ was considered statistically significant. *Results:* Patients' clinical and pathological characteristics are summarized in Table I. The mean P.A.D.U.A. and R.E.N.A.L. scores were 7.6±1.31 and 7.02±1.58, respectively. Forty-nine (51%), 36 (37.5%) and 11 (11.5%) patients were classified into low, intermediate and high risk categories according to the P.A.D.U.A. classification, respectively; conversely, 29(30.2%), 62 (64.6%) and 5 (5.2%) patients were classified at low, intermediate and high risk according to the R.E.N.A.L. score, respectively. The median WIT was 14 (IQR: 8-20) minutes, and was found to be >20 minutes in 21 (21.8%) cases. The median WIT was significantly longer in laparoscopic (21.0 min) than open procedures (12.1 min, $p<0.001$). Thirty-five out of 96 patients (36.4%) experienced postoperative complications of any grade; in the vast majority of them (82.9%) we observed low grade (grade 1-2) complications. P.A.D.U.A. and R.E.N.A.L. risk group categories were found to be significant predictors of WIT >20 minutes ($p=0.04$) and of high grade (Clavien 3-4) complications ($p=0.04$). *Conclusion:* The classification of patients into risk group categories allow urologists to predict the surgical outcomes after NSS for RCC. More complex cases, included into high risk groups, reflect a more challenging procedure, with a longer expected WIT and higher grade of postoperative complications. In our cohort of patients, P.A.D.U.A. and R.E.N.A.L. scores demonstrated to be equivalent predictors of longer WIT and postoperative complications.

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PATIENTS WITH LYMPH-NODE METASTASIS AFTER RADICAL PROSTATECTOMY AND PELVIC LYMPH-NODE DISSECTION ARE NOT ALL SUBJECT TO THE SAME RISK OF CANCER DEATH: IDENTIFYING DIFFERENT RISK-CATEGORY ACCORDING TO THE NUMBER OF POSITIVE NODES AND GLEASON SCORE

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Introduction and Objectives: Lymph node metastasis usually predict a poorer prognosis in patients with prostate cancer when compared with those without positive nodes, and represents the most important prognostic parameter after radical prostatectomy together with the pathological Gleason score. Not all the patients with LN invasion (LNI) are at the same risk of cancer recurrence and death: actually, some patients with node-positive disease have long-term survival

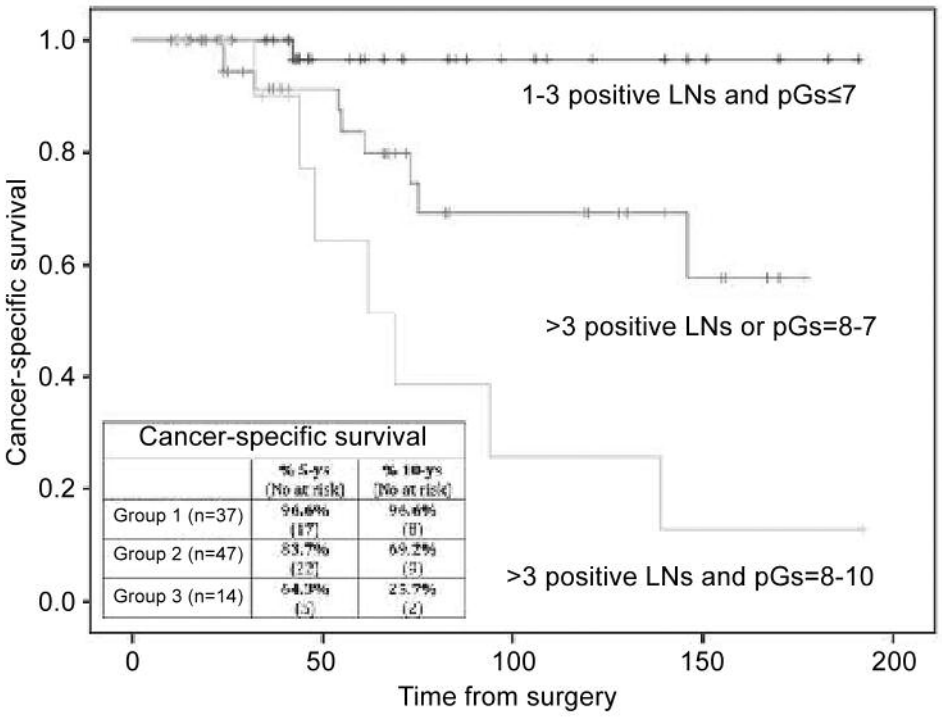

Figure 1. *Kaplan-Meier estimates of cancer-specific survival after surgery according to the new risk-category (Group 1: 1-3 positive LNs and pGs≤7 vs. Group 2: >3 positive LNs or pGs=8-10 vs. Group 3: >3 positive LNs and pGs=8-10; log rank test: p<0.001).*

even in the absence of adjuvant therapy. Aim of our study was to evaluate the outcomes in node-positive patients after radical prostatectomy and pelvic lymph node dissection (PLND) for prostate cancer (PCa) according to the number of positive LNs, and to identify different risk-groups categories. *Patients and Methods:* We evaluated 98 pN1M0 consecutive patients who underwent radical prostatectomy for prostate cancer between November 1995 and May 2011 at our Institution. Kaplan-Meier and Cox proportional univariable and multivariable regression models were used to analyze the survival rates. Number of positive nodes was dichotomized according to the most informative cut-point predicting survival. *Results:* Mean follow-up was 68.4 months (range: 10-192). Patients with 1 to 3 positive LNs (n=75; 76.5%) had significantly better cancer-specific survival (CSS) and overall survival (OS) compared to those with more than 3 positive nodes (n = 23; 23.4%), (p<0.01). Patients with 1 to 3 positive LNs and pGs≤7 (Group 1) had significantly better CSS compared to those with more than 3 positive LNs or pGs=8-10 (Group 2) (p=0.015). Group 2 patients, moreover, had significantly better cancer-specific (p=0.019) survival when compared to those with more than 3 positive LNs and pGs=8-10 (Group 3) (Figure 1). *Conclusion:* Patients with less than 3 positive LNs experience higher CSS and OS than those with more than 3 metastatic LNs. Considering the Gs as well as the number of positive nodes, three risk-group categories with considerable differences in terms of survival can be found. Lymph-nodes positive patients should be stratified in different groups according to these two parameters, in order to obtain a better prediction of oncological outcomes.

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18F-FACBC PET/CT *vs.* 11C-CHOLINE FOR THE DETECTION OF PROSTATE CANCER RELAPSE AFTER RADICAL TREATMENT

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Introduction/Aim: Approximately 40% of all patients who undergo radical treatment for localized prostate cancer (PCa) develop biochemical relapse (BCR) during their lifetime but only 10% to 20% of them will show clinically detectable recurrences. Current imaging techniques have some potential but many limits are yet encountered in the localization of disease relapse. In recent years, the new PET radiotracer anti-1-

amino-3-18F-fluorocyclobutane-1-carboxylic acid (anti-3-18F-FACBC) was tested for the detection of prostate cancer relapse with very promising results. In this study we compare the detection rate of 18F-FACBC and 11C-Choline in patients with biochemical relapse after radical prostatectomy for prostate cancer. *Patients and Methods:* 55 patients with BCR and rising PSA levels after radical treatment for prostate cancer were consecutively and prospectively enrolled. All the patients were free from androgen deprivation therapy at the time of the scans for at least 3 months. All the patients underwent 11C-Choline PET/CT and 18F FACBC PET/CT within one week. The results of the two imaging techniques were compared in terms of detection rate on a patient basis and lesion basis. Furthermore, a more detailed analysis regarding local, lymph-node, and bone relapse was performed. *Results:* At the time of PET scan, mean age was 67 years and mean serum PSA value was 3.2 ng/ml. No adverse reactions to 18F FACBC were recorded. 33 patients turned out negative with both tracers. 11 patients were positive for disease relapse with both tracers, exactly at the same sites. Six patients were positive with 18F FACBC but negative with 11C-Choline. No patients had a positive 11C-Choline scan with a negative 18F FACBC scan. On a patient based analysis, the detection rate of 18F FACBC was 34%, while the detection rate of 11C-Choline was 22% ($p<0.000001$). This result was also true on lesion analysis and lymph node, bone local relapse analysis (all $p<0.0001$). *Conclusion:* In conclusion, in our experimental study, 18F FACBC provides a statistically significant better performance in terms of lesion detection rate as compared to 11C-Choline, in patients with biochemical relapse after radical treatment for prostate cancer. However, more studies are required to evaluate the clinical significance of these results in terms of sensitivity, specificity and accuracy.

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PROS-IT CNR: A PROJECT TO MONITOR PROSTATE CANCER IN ITALY

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Aim: The Pros-IT CNR project aims to monitor patients with prostate cancer in Italy by systematically collecting data on men ≥18 years of age who have been diagnosed at the participating centers with incident prostate cancer, and by analyzing their demographic/clinical features, their treatment protocols and results in terms of quality of life. *Patients and Methods:* Pros-IT CNR is an observational, prospective, multicenter, cohort study. The CNR, Neuroscience Institute, Aging Branch (Padua) is the promoting center while the Sant'Anna Hospital (Como) is the coordinating center. One hundred sixteen Italian centers located throughout Italy will be involved, including 69 Urology, 25 Radiotherapy, and 22 Oncological facilities. Subjects eligible for recruitment are males ≥18 of age, attending one of the participating hospitals, who have been diagnosed with biopsy verified prostate cancer after September 1, 2014 (the date enrollment officially begins), naïve, who have agreed to participate. The project started on July 1, 2013, will last for a total of 48 months and will be organized into three phases. • Phase 1 "Network structures definition and instruments preparation" (July 2013-August 2014): The Steering Committee and Working Group were defined, the protocol was finalized, the Collection Data Form (CDF) was formulated, the web site where the data will be registered was developed and the protocol will be examined by the Ethics Committees. • Phase 2 "Enrollment" (September 2014-April 2015): Centers belonging to the Working Group will identify cases of incident prostate cancer considering the inclusion criteria. Recruitment will last for six months. A sample size of 1500 subjects was calculated, and each center will be asked to enroll at least 20 consecutive patients. A CDF, which gathers demographic details, anamnestic data, information on comorbidities, the initial diagnosis, risk factors, cancer staging, and quality of life measures using the Italian UCLA Cancer Index (1) and the SF-12 Standard V1 Scale (2) will be completed at the time that an incident case is identified. • Phase 3 "Follow-ups" (March 2015-June 2017): Six months after the initial diagnosis is made each patient will be evaluated and a second CDF will be completed, evaluating his health status, the treatment that was carried out and his quality of life (Italian UCLA-PCI; SF-12). A third CDF, which will evaluate the patient's state of health, the treatment follow-up and quality of life, will be completed 12 months after the initial diagnosis. The 4th CDF, similar to the third, will be completed 24 months after the initial diagnosis. *Results:* The study will furnish information on the quality of life and on variations over time in patients who have been diagnosed

with prostate cancer, also considering subgroups based on the various types of treatments received. *Discussion:* A multidisciplinary management of patients with prostate cancer for whom a variety of therapeutic options are available, is considered the best approach in all phases of the disease. For this reason Pros-IT CNR intends to take a multidisciplinary approach and the project's Steering Committee includes urologists, radiotherapists, oncologists, anatomopathologists and epidemiologists.

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