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RELEVANCE OF PERIANASTOMOTIC SATURATION BIOPSY SCHEME IN THE DIAGNOSIS OF LOCAL RECURRENCE AFTER RADICAL PROSTATECTOMY

Lucio Dell' Atti, Gian Rosario Russo

Urologia, Azienda Ospedaliero-Universitaria Arcispedale S. Anna, Ferrara, Italy

Introduction: The perianastomotic biopsy is indicated in patients with clinical suspicion of local recurrence, that of course cannot be diagnosed only by serum PSA, digital rectal examination or imaging techniques. This study evaluated the optimization of the detection rate in a standardized manner using a scheme perianastomotic biopsy transrectal ultrasound with 8 biopsies for the diagnosis of local recurrence in patients with prostate cancer who underwent radical prostatectomy (RP), compared to 4 or 6 conventional biopsies. *Patients and Methods:* Between July 2007 and May 2012 we evaluated 62 patients (range 56-76 years) who underwent consecutive RP (48 with the open technique and 14 with the laparoscopic technique) with recovery of biochemical disease (PSA >0.2 ng/ml). The pathologic stages of patients were: 27pT2, 33pT3 and 2pT4 respectively. All patients had negative lymph nodes and only one pT4 had positive surgical margins. All patients with suspected local recurrence were subjected to rectal examination and transrectal ultrasound-guided biopsy perianastomotic (BTP) using an "end-fire" multi-frequency convex probe under local anesthesia with lidocaine spray (10g/100ml). *Results:* Patients were divided into two groups. Group A: 33 patients with mean PSA 2.3 ng / ml, subjected to BTP: 14/33 (42%) and 19/33 (57%) respectively four and six biopsies. Group B: 29 patients with mean PSA 1.4 ng / ml underwent a standard eight biopsies. Among patients in the latter group, three had already undergone four biopsies. One patient belonging to group B did not complete the entire biopsy procedure because of discomfort. In the first group signs of local recurrence were observed in 11/33 (33%), while in 22/33 (66%) residual benign prostate tissue was found in six biopsies and fibrous tissue and scar in sixteen. In Group B: 22/29 (76%) were found with prostate cancer relapsed, whereas 7/29 (24%): prostate tissue residue was found in two biopsies fibrous tissue and scar in five biopsies. *Discussion and Conclusion:* The present study raises the possibility that residual and benign tissue, resulting from unintentional disruption of the prostatic capsule during surgery, may be responsible for a detectable postoperative PSA. The clinical significance of prostatic residual tissue in follow-up is most important since it can be responsible for biochemical failure and can increase in size, simulating in this way a local recurrence. Although there was no evidence of a significant correlation between PSA levels to local recurrence, Gleason score and positive biopsy, the BTP conducted in a standardized manner with 8 biopsies in patients with biochemical recurrence of disease has enabled us to increase the detection rate of local recurrence of 43% and certainly avoid radiation therapies for prostate bed in cases of detection of benign prostatic residual tissue.

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ROLE OF HIGH GRADE INTRAEPITHELIAL NEOPLASIA AS A RISK FACTOR FOR PROSTATIC CANCER

Lucio Dell' Atti, Gian Rosario Russo

Urologia, Azienda Ospedaliero-Universitaria Arcispedale S. Anna, Ferrara, Italy

Introduction: High grade prostatic intraepithelial neoplasia (HGPIN) is traditionally considered as a precancerous conditions. The majority of patients with diagnosed HGPIN are expected to develop prostate cancer (PC) within 10 years (1). The degree of association between HGPIN and PC in different sources of literature ranges between 22% and 80% (2, 3).There is a controversy regarding the role of HGPIN as a risk factor for PC. The aim of the present study was to evaluate the role of HGPIN in prediction of adverse pathology in patients undergoing a radical prostatectomy (RP). *Patients and Methods:* We retrospectively analysed 210 patients who underwent a RP (open or laparoscopic) between July 2007 and December 2010 at a single referral center. Exclusion criteria were any preoperative treatment protocol, active surveillance, hormone therapy and radiotherapy. The relationship between HGPIN and the presence of positive surgical margins (PSM), extracapsular disease (ECD), seminal vesicle invasion (SVI) and lymph node invasion (LNI) was analysed. Patients were stratified into low (PSA <10 ng/ml, cT1, biopsy Gleason sum ≤6), high (cT3 or biopsy Gleason 8-10 or PSA >20 ng/ml) and intermediate risk (all the remaining patients). The prognostic value of HGPIN was estimated in each risk group separately. *Results:* The median age was 66.7 years (range 48-77) and median PSA was 8.5 ng/ml (range 2.5-16). Based on the preoperative clinical staging, 139 (66%) patients were T1c, 51(24%) T2a, 17(8%) T2b and 3(1.5%)T2c. HGPIN was found

in 41(19.5%) speciments. PSM were identified in 64(30.5%), ECD in 23(11%) and SVI in 14(6.6%) patients. A pelvic lymph node dissection was conducted in 186 patients and from those a malignant invasion was found in 22 (10.4%) patients.Concerning the preoperative risk stratification: 72(34.2%) patients were considered low risk, 113(53.8%) medium risk and 25(11.9%) high risk. A statistically significant correlation was found between HGPIN and preoperative PSA (p=0.025) and patients'age (p=0.030). No significant differences were found, regarding the presence of adverse pathological findings, between the patients with or without HGPIN, irrespective of the preoperative risk stratification. *Conclusion:* The results of our study showed that patients with HGPIN were younger and they had lower levels of preoperative PSA. However, there was no significant difference in the tumor grade and pathological stage between groups. HGPIN did not reach significance for the prediction of PSM, ECD, SVI and LNI. Similar findings were shown when patients were divided into risk categories regarding Gleason score. Based on our results, we suggest that there is no benefit by the application of HGPIN as predictor of worse pathological and clinical outcome following radical prostatectomy.

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MIR-501 DEPLETION INDUCES CELL CYCLE INHIBITION BY MTOR AND P53 MODULATION IN RENAL CARCINOMA

Alessandra Mangolini[1], Lucio Dell'atti[1], Anna Bonon[2], Giovanni Lanza[3], Gian Rosario Russo[1], Gianluca Aguiari[2]

[1]Urologia, Azienda Ospedaliero-Universitaria Arcispedale S. Anna, Ferrara;
[2]Biologia Molecolare, Dip. Scienze Biomediche e Chirurgiche Specialistiche Università Ferrara;
[3]Anatomia Patologica, Dip. Scienze Morfologiche e Medicina Sperimentale, Università Ferrara, Italy

Introduction: MicroRNAs (miRs) are small noncoding RNAs that regulate gene expression at post-transcriptional level. The abnormal expression and mutation of miRs has been observed in most urologic cancers including renal cancer, thus they may contribute to development and progression of kidney carcinoma. In fact, their impaired function could trigger a series of altered signalling resulting in abnormal differentiation, proliferation and apoptosis. In the last years, the necessity to use miRs as biological biomarkers is emerging in order to improve diagnosis, prognosis and therapy response in renal carcinomas. Furthermore, miRNAs might be potential targets for novel therapeutic strategies, especially in patients with tumour subtypes that do not respond to currently available therapies (1, 2). Here, we have focalized our study on the role of miR501-5p in kidney carcinomas because it has been found differently expressed in kidney cancer tissues compared with the normal kidney of the same patients. *Materials and Methods:* Analysis of miR501-5p expression was performed by real time RT-PCR. Depletion or enrichment of this miR was conducted by specific antagomiRs and plasmid expressing miR-501-5p specific sequences, respectively. Protein activity was analyzed by immunological and cell imaging techniques. Apoptosis was studied through caspase-3 activity and cell cycle analysis was performed by propidium iodide staining. *Results:* We have analyzed the expression of miR501-5p in 36 clear cell (ccRCC) and 11 papillary (pRCC) kidney carcinomas. The expression of miR501-5p was higher in ccRCC (3.72 fold) and lower (3.76 fold) in pRCC tissues compared with normal kidneys derived from the same subjects, respectively. However, the distribution of miR501-5p expression values in ccRCC was found strongly variable. Follow up data of 25 ccRCC and 5 pRCC patients suggest that subjects who showed lower expression of miR-501 in cancer tissues with respect to control (normal kidney), exhibited a good prognosis compared with patients with unchanged or high levels of this small RNA. In order to evaluate the role of miR501-5p in renal cancer, we have depleted it by a specific antagomiR in KJ29 kidney cancer cell line (3). KJ29 cells expressed higher levels of miR501-5p than normal immortalized tubular kidney cells. The transfection of KJ29 cells with antagomiR caused a 50% reduction of miR501-5p expression compared with untransfected cells. Furthermore, the reduction of miR501-5p induced an increase in G_0/G_1 phase of cell cycle and a decrease of mTOR activity in KJ29 cells. In addition, the treatment with antagomiR caused an increase in caspase-3 activity, suggesting that this miR may regulate apoptosis. Moreover, miR-501-5p depletion enhanced the expression of p53, data also observed in kidney cancer tissues expressing lower levels of this miR than controls. The activation of p53 was also observed by its nuclear translocation in KJ29 treated with antagomiR. KJ29 cells were also transfected with a plasmid expressing miR-501-5p sequences and these cells showed an increased level of miR-501 compared with untranfected cells. *Conclusion:* Our findings show that miR501-5p was differentially expressed in ccRCC. High or

unchanged levels of miR501-5p do not seem to be related with grading and metastasis in ccRCC; however, when it is downregulated it could promote a good prognosis. Data reported suggest an anti apoptotic role for miR501-5p, making it a likely risk factor for a poor prognosis in renal carcinoma. Therefore, the expression of miR501-5p could be considered as a potential biomarker for the prognosis of clear cell kidney carcinoma.

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THE PATIENT'S AGE MAY INFLUENCE THE DECISION OF AN ANESTHETIC TECHNIQUE DURING TRANSRECTAL PROSTATE BIOPSY

Lucio Dell'Atti[1], Deidania Medici[2], Carmelo Ippolito[1], Giovanni Pietro Daniele[1], Gianni Ughi[1], Gian Rosario Russo[1]

[1]Urologia, Azienda Ospedaliero-Universitaria Arcispedale S. Anna, Ferrara;
[2]Clinica Neurologica, Università Politecnica delle Marche, Italy

Introduction: In literature there are numerous studies that compare various local and general anesthetic techniques for transrectal ultrasound-guided prostate biopsy (TBP), analyzing different variables of discomfort in patients undergoing this procedure. (1) None has so far considered the effect of aging on the perception of acute pain. Acute pain of recent onset decreases with age while increasing the chronic and chronic pain syndrome (clinical condition that involves the mind and behavior by influencing the experience of illness and quality of life). The purpose of this study was to evaluate how the age factor might influence the tolerance biopsy examination, and then choose the modality of a local or general anesthetic technique. *Patients and Methods:* 362 consecutive patients, between November 2008 and December 2011, underwent TBP. Patients were excluded if they had a history of previous prostate biopsy, had chronic pelvic pain syndrome, anal surgery, or any other medical condition that could potentially interfere with pain assessment. All procedures were performed to empty the bladder, since we believe that even the state of bladder repletion may be an element of discomfort during the performance of TBP. Each patient was treated under local anesthesia with lidocaine spray (10gr/100ml)(2). Patients were divided into two groups according to age: Group A) 175 patients with age range ≤65 years, Group B) 187 patients with age range > 65 years. Our first aim was to obtain a schedule of 14 biopsy samples in both groups. After the procedure each patient was given a verbal numeric pain scale (VNS), which was designed with 0 representing absence of pain and 10 the maximum pain they perceived in life. *Results:* Only four patients were not able to undergo the procedure with the introduction of the probe: in four the reason was the presence of anal stenosis and in two because of the presence of a severe hemorrhoidal prolapse. The average age of patients in Group A was 59 years (44-64), the average value of total PSA was 8.7 (3.4-15.3), while average total volume of the gland was 54ml (28-79). In Group B the average age was 72 years (65-77), the average PSA was 9.4 (3.2-18.3), while the total glandular volume was 64ml (34-115). The number of biopsies performed in the first group was 9.7 (4-14), while in the second group 13.1 (7-17). The average pain assessed with VNS was around 4.5 (2- 8) and 2.6 (0-6) for the patients in Group A and Grioup B, respectively . The two groups appear to be homogeneous in terms of pain perception regarding PSA value and gland volume, and appeared to have different pain scores with regard to age. *Discussion and Conclusion:* Age dependent differences in pain perception are probably not the expression of a receptor damage, or abnormal stimulation of accommodation, but are the consequence of a more complex process involving the pathways of transmission, the representations and cognitive evaluations, social status and the history of pain, a mutual integration between cognitive and affective component, behavioral anatomical areas with the participation of cortical somatosensory prefrontal and limbic system and hypothalamic pituitary mediation of the autonomic nervous system (3). In conclusion, we can say that since the reliability of multiple prostate biopsy is directly proportional to the number of needle biopsies, a local anesthetic in clinical practice in the course of TBP is more sensitive if performed in a person aged 65 years, for the reasons listed above, while in a young adult to perform the examination in sedation would result in better compliance by the patient, increasing the detection rate.

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GATA3 AND P63 IMMUNOSTAINING ANALYSIS IN HIGH GRADE BLADDER CARCINOMA

Carlo Patriarca, Alessandra Cavallero

Anatomia Patologica, Azienda Ospedaliera Sant'Anna, Como, Italy

p63 immunostaining, in conjunction with high molecular weight cytokeratins and PSA, belongs to a widely applied panel that is often specific enough in supporting the differential diagnosis between bladder urothelial carcinoma and high grade prostate adenocarcinoma (1). However, in metastatic poorly differentiated carcinoma of unknown primary site, more immunostaining are frequently necessary to identify a bladder carcinoma origin. GATA3 regulator of T-cell development is a nuclear antigen specific for breast and bladder carcinoma (2). Hence, in case of unknown metastasis, it represents a useful candidate in supporting the identification of a possible bladder origin, together with p63, high molecular weight cytokeratin, cytokeratin 20, thrombomodulin, S100P and uroplakin III (3). Nevertheless, a few data are available concerning the sensibility of GATA3 immunostaining in comparison with p63 particularly when dealing with high grade poorly differentiated carcinoma (4). We selected 14 high grade urothelial carcinomas and 1 small cell bladder carcinoma. Step sections underwent immunohistochemical staining with p63 mouse MoAb (clone 4A4) and GATA3 mouse MoAb (clone L50-823). The range of nuclear immunostaning was subdivided as + (> 10% <50% positive cells), ++ (>50% < 75% positive cells) and +++ (>75% positive cells). 13 out of 14 cases were GATA3 positive (92.8 %: 10 cases +++ and 3 cases ++), while 12/14 cases were p63 immunoreactive (85.7 %: 10 cases +++, 1 case ++ and 1 case +). The two p63 negative cases were GATA3 (+++) immunoreactive, while the only GATA3 negative case showed wide squamous differentiation and was p63 (+++) immunoreactive. Finally both GATA3 and p63 were negative in the small cell bladder carcinoma. Accordingly, both antigens are useful in an ideal panel.

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IMAGE GUIDED (IGRT) HYPOFRACTIONATED INTENSITY-MODULATED SIMULTANEOUS INTEGRATED BOOST (IMRT-SIB) RADIOTHERAPY IN HIGH-RISK PROSTATE CANCER PATIENTS: PRELIMINARY REPORT

Maurizio Valeriani, Alessia Carnevale, Mattia Falchetto Osti, Vitaliana De Sanctis, Linda Agolli, Stefano Bracci, Riccardo Maurizi Enrici

Department of Radiation Oncology, "La Sapienza" University, Sant'Andrea Hospital of Rome, Italy

Background: Hypofractionated "dose escalation" intensity-modulated radiotherapy (IMRT) might be able to improve locoregional control in prostate cancer without an increase in OAR toxicity. Image guidance is a widely accepted approach to increase the therapeutic ratio in external radiotherapy (IGRT). If IGRT and IMRT are combined it is even possible to use SIB approach in order to reduce the number of fractions and therefore the treatment time length. *Materials and Methods:* Between December 2009 and January 2012 in our institution we treated 61 patients with high risk prostate carcinoma (≥T3 or Gleason score ≥ 8or PSA ≥ 20 ng/ml). The median age was 73 years (range 61–88). All patients underwent a neoadjuvant, concomitant and adjuvant hormonal therapy with antiandrogen (bicalutamide 150 mg) in 19 patients (31.1%) and LHRH analogous in the other 42 patients (68.9%) for a total of 2 years overall starting 3 months before radiotherapy. Stage was cT1c in 3 patients (4.9%), cT2a in 5 patients (8.2%), cT2b in 10 patients (16.4%), and cT2c in 6 patients (9.8%), cT3a in 17 patients (27.9%), cT3b in 18 patients (29.5%) and cT4 in 2 patients (3.3%). Gleason score was 5 in 3 patients (4.9%), Gleason 6 in 15 patients (24.6%), Gleason 7 in 19 patients (31.1%), Gleason 8 in 17 patients (27.9%) and Gleason score 9 in 7 cases (11.5%). All patients performed a simulation CT scan with 2.5 mm slice thickness to execute 3D conformal planning IMRT (intensity-modulated radiation therapy) developed with Eclipse System. Patients were immobilized with a footlocker in supine position. All patients underwent proper rectal and bladder preparation. MR imaging was fused with planning CT to help clinical target volume (CTV) delineation. The CTV1 included the pelvis, CTV2 included the seminal vesicles and CTV 3 only the prostate. The margins for the planning target volume (PTV) were 5 mm in all directions. The total dose to PTV1 was 45 Gy in 25 fractions (1.8 Gy each fraction), the total dose to PTV2 was 55 Gy (2.2 Gy each fraction) and the total dose to PTV3 was 68.75 Gy in 25 fractions (2.75 Gy each fraction), 5 days per week. Patients were controlled during treatment with Cone-Beam (ChiloVoltage) CT. Follow-up evaluations were performed at 1, 3, 6, 9 and 12 months after treatment, and every 6 months thereafter. Acute side effects were evaluated according to the

RTOG/EORTC late morbidity Scoring Scale. *Results:* Median follow-up was 14 months (range 2-29 months).The acute toxicities during the treatment were: grade 1-2 gastrointestinal (GI) toxicity in 7 patients (11.5%), grade 1-2 genitourinary (GU) toxicity in 15 patients (24.6%); grade 3 GU toxicity in 1 patient (1.7%). The toxicities, 1 month after the end of the treatment, were grade 1-2 GI in 1 patient (1.7%), grade 1-2 GU in 10 patients (16.4%). The toxicities, 3 months after the end of the treatment, were grade 1-2 GI in 1 patient (1.7%), grade 1-2 GU in 4 patients (6.6%). The median PSA at diagnosis was 10.1 (range 2.92-45.4) and that at the last follow-up was 0.06 ng/ml (range 0-1.1 ng/ml). *Conclusion:* Technological progress enables the implementation of new technologies such as intensity-modulated radiation therapy (IMRT) and image guided radiotherapy (IGRT). IMRT allows to minimize the volume of irradiated normal tissue and reduce acute toxicity in all patients.

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IMAGE GUIDED (IGRT) HYPOFRACTIONATED RADIOTHERAPY IN LOW-RISK PROSTATE CANCER PATIENTS: RESULTS OF ACUTE TOXICITY

Maurizio Valeriani, Alessia Carnevale, Giuseppe Minniti, Mattia Falchetto Osti, Enrico Clarke, Claudia Scaringi, Giovanna Scalabrino, Vitaliana De Sanctis, Teresa Falco, Riccardo Maurizi Enrici

Radioterapia, Università "La Sapienza" Roma Az. Osp. S. Andrea; Roma, Italy

Introduction: Hypofractionation presents crescent interest in the treatment of prostate cancer. We have evaluated the acute toxicity in patients with low-risk prostate cancer treated with hypofractioneted IGRT in our institution. Materials and Patients. Between March 2007 and April 2012 we have treated 45 patients with low- risk prostate cancer (T1-T2 and Gleason score ≤6 and PSA ≤ 10 ng/ml)). The median age was 71 (range 58–82). All patients underwent prostate biopsy. Stage was cT1c in 18 patients (40%); cT2a in 14 patients (31,1%) ; cT2b in 10 patients (22.2%); cT2c in 3 patients (6.7%). Gleason score was 6(3+3) in all patients. All patients performed a simulation CT scan with 2.5 mm slice thickness to execute 3D conformal planning. They were immobilized in supine position with a footlocker. 28 patients (66.7%) were treated with a total dose of 45Gy on the first 1.5 cm of seminal vescicles and 60 Gy on prostate; 3 Gy for fraction 5 times a week and a total time of 4 weeks. 14 patients (33.3 %) were treated with a total dose of 46.5 Gy on the first 1.5 cm of seminal vesicles and 62 Gy on prostate; 3.1 Gy for fraction 5 times a week and a total time of 4 weeks. Margin from CTV to PTV was 5 mm in all directions. The external beam radiation therapy was performed with image guided technique (IGRT), with daily cone-beam TC. Follow-up evaluations were performed at 3, 6, 9 and 12 months after treatment, and every 6 months thereafter. Acute side effects were evaluated according to the RTOG/EORTC late morbidity Scoring Scale. *Results:* Median follow-up was 20 months (range 3-62 months). The acute toxicities during the treatment were: grade 1-2 gastrointestinal (GI) toxicity in 7 patients (15.6%), grade 1-2 genitourinary (GU) toxicity in 19 patients (42.2%)%; grade 3 GU toxicity in 1 patient (2.2%). The toxicities 3 month after the end of the treatment were grade 1-2 GI in 4 patients (8.9%), grade 1-2 GU in 12 patients (26.7%). The toxicities 6 months after the end of the treatment were grade 1-2 GI in 2 patient (4.4%), grade 1-2 GU in 6 patients (13.3%). The median PSA before the start of radiotherapy was 5 (range 1.74-8.43) and at the last follow-up was 0.83 ng/ml (range 0-5.05 ng/ml). *Conclusion:* This study showed that the hypofractionated radiation therapy was well tolerated with a low grade of toxicity, but it needed a longer follow-up to determine possible late toxicity and local control.

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

R. Schiavina[1], G. Passaretti[1], D. Romagnoli[1], A. Bertaccini[1], E. Brunocilla[1], F. Manferrari[1], M. Garofalo[1], V. Vagnoni[1], G.C. Rocca[1], M. Cevenini[2], F. Chessa[1], L. Bianchi[1], M. Borghesi[1], M. Fiorentino[2], G. Martorana[1]

[1]University of Bologna, Dept. of Urology, Bologna, Italy; [2]University of Bologna, Dept. of Pathology, Bologna, Italy

Introduction & Objectives: A consistent rate of patients who are classified as "node-negative" after radical prostatectomy and pelvic lymph-node dissection (PLND) experience a nodal disease relapse. Routine pathological examination can miss micro-metastatic tumor foci in the lymph nodes (LN) of patients with prostate cancer (PCa), resulting in confused tumor staging and clinical decision-making. The aim of the present perspective study was to evaluate the impact of micro-metastasis assessed by serial section (SS), immunohistochemistry (IHC) and real time-Polymerase Chain Reaction (RT-PCR) in patient submitted to radical prostatectomy with extended PLND. *Patients and Methods:* Fifty-two consecutive patients submitted to radical prostatectomy with extended PLND for intermediate (clinical T1c-T2 and PSA: 10-20 ng/mL and clinical Gleason Score=7) or high (clinical stage T3 or PSA>20 or clinical Gleason Score=8-10) grade PCa were enrolled. The average probability of nodal invasion with the Briganti pre-operative nomogram of the whole population was 26.9% (SD=13.4). Extended PLND included obturator, internal/external and distal 2 cm common iliac lymph-nodes (LN). The nodes were processed by one uro-pathologist both according to the routine pathological examination (analysis of the central section for 4 mm nodes or every 2 mm for LN>4 mm, which served as comparative method, both according to SS, IHC with antibodies against PSA and spectrum-cytokeratins (BSCK) and quantitative RTPCR targeting PSA, PSMA (PS Membrane Antigen) and Glucuronidase-S-Beta (GUSB) mRNA, that are over-expressed in prostatic cancer cells. *Results:* A total of 1041 LN were analyzed, with a mean number of LN removed of 20 (SD=7.7). Applying the routine pathological examination, 11 (21.2%) patients and 28 (2.7%) LN resulted positive for nodal involvement, with mean positive LN of 2.5 (SD=1.8). After applying the SS and the molecular method of analysis (IHC and RT-PCR), micro-metastases were found in 16 LN (SS showed micro-metastases in 9 of them, IHC in 14 of them and RTPCR in 16 of them) and a total of 5 (9.6%) node negative patients at routine pathological examination showed micro-metastasis (3 patients with RTPCR , 1 with IHC and 1 with SS). *Conclusion:* Molecular analysis of the LN can detect a not negligible percentage of patient who harbor micro-metastatic PCa missed at routine pathological examination and can enhance the accuracy of lymphadenectomy as a staging method. Cost-effective analysis is needed. The significance of the micro-metastasis in PCa and the potential therapeutic role of PLND is not yet clarified but the removal of micro-metastases can reduce the rate of nodal disease relapse.

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HYPOFRACTIONATED RADIOTHERAPY IN INTERMEDIATE PROSTATE CANCER

Stefano Bracci, Maurizio Valeriani, Vitaliana De Sanctis, Giuseppe Minniti, Mattia Falchetto Osti, Linda Agolli, Teresa Falco, Riccardo Maurizi Enrici

Radioterapia, Università "La Sapienza" Roma, Az. Osp. S. Andrea, Roma, Italy

Aim: To evaluate the tolerance and the clinical efficacy of hypofractionated radiotherapy in patients affected by intermediate risk prostate cancer. *Patients and Methods:* Between March 2007 and November 2011, 106 patients with intermediate risk prostate cancer were treated with 3-dimension conformal hypofractionated radiotherapy. Intermediate risk was defined as clinical stage T1–T2 and pre-radiotherapy PSA between 10 and 20 ng/mL, and Gleason Score equal to <7 or clinical stage T1–T2 and pre-radiotherapy PSA between ≤20 ng/mL, and Gleason Score equal to 7. Prostate biopsy was performed to all patients to confirm the diagnosis. A total dose of 43.8 Gy was delivered to seminal vesicles and 54.75 Gy to the prostate, 3.65 Gy per fraction, three times a week for a total of 5 weeks. All patients underwent neoadjuvant, concomitant and adjuvant hormonal therapy (OT) for a total duration of 9 months. Acute and late toxicities were evaluated according to RTOG scale. The nadir PSA after radiotherapy plus 2 ng/mL was used for defining biochemical relapse (Phoenix criteria). *Results:* Median follow-up was 25 months (range 4-55 months). Five patients (4.7%) developed biochemical failure: of these patients were found to have metastasis to regional lymphnode, while two patients developed bone metastasis. Six patients (5.9%) died from causes different from prostate cancer without biochemical failure, while patients died due to disease progression. Acute toxicities (within 3 months from the end of RT) were as follow: Grade 1 Genitourinary (GU) toxicities were 43.2%, while 10% presented Grade 2 toxicities; Grade 1 Gastrointestinal (GI) toxicities were 9.6 %, Grade 2 GI toxicities were 10.8%. Late GU and GI toxicities ≥ Grade 2 recorded at the last follow-up were 3.3% and 4.6% respectively. No patient developed grade 4 toxicity. 2-year BFS and 4-year BFS were 94.4% and 92%, respectively. *Conclusion:* The hypofractionated schedule used was well tolerated with a low rate of acute and late grade ≥2 gastrointestinal and genitourinary toxicities. Hypofractionation is useful to obtain high rate of tumor control also if longer follow-up is needed.

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BIOPSY AND RADICAL PROSTATECTOMY PATHOLOGICAL PATTERNS INFLUENCE PROSTATE CANCER GENE 3 (PCA3)

Stefano De Luca[1], Roberto Passera[2], Enrico Bollito[3], Angela Milillo[4], Roberto Mario Scarpa[5], Mauro Papotti[6], Renato Coda[7], Donato Franco Randone[1]

[1]Divisione di Urologia, Ospedale Gradenigo di Torino; [2]Medicina Nucleare 2, Ospedale Molinette E Universita' di Torino;

[3]Servizio di Anatomia Patologica, Ospedale San Luigi di Orbassano;
[4]Laboratorio Analisi, Ospedale Gradenigo di Torino;
[5]Divisione di Urologia, Ospedale San Luigi di Orbassano E Universita' di Torino;
[6]Servizio di Anatomia Patologica, Ospedale San Luigi di Orbassano E Universita' di Torino;
[7]Servizio di Anatomia Patologica, Ospedale Gradenigo di Torino, Italy

Background: The assumption that higher PCA3 scores are associated with more aggressive cancer is based on the hypothesis that with increasing dedifferentiation, neoplastic cells become more invasive and could therefore more easily be shed into the ductal system of the prostatic gland after DRE or that larger tumours simply have more surface area over which to shed PCA3. The aim of this study was to evaluate the relationship between PCA3 score and prostate cancer as assessed by Gleason's Score (GS) and pathological stage in a series of Italian patients, with elevated PSA undergoing radical prostatectomy (RP). *Patients and Methods:* 222 patients underwent RP for clinically localized prostate cancer; total PSA, free-PSA (%fPSA) and PCA3 score were collected and the possible associations among PCA3 and histological grade/pathological stage at biopsy and RP were investigated. *Results:* median PCA3 scores by GS at radical prostatectomy were 51 *vs*. 67 (GS <7 *vs*. GS ≥7, p=0.007) while at the biopsy 56 *vs*. 67 (GS <7 *vs*. GS ≥7, p=0.007), and in pT2 *vs*. pT3 patients 54 *vs*. 80 (p=0.001). Positive digital rectal examination (OR 5.47, p=0.026), pT3 pathological stage (OR 3.68, p=0.006) and PCA3≥35 (OR 2.04, p=0.030) were the main risk factors for the presence of an aggressive disease (GS≥7 at RP). *Conclusion:* PCA3 might not only be helpful for diagnostic purposes, but also for prognostic estimation for its possible capability to predict cancer aggressiveness. Unfortunately, focusing on the latter topics, the results are still conflicting. Some studies revealed a clear association between PCA3 and GS, while others didn't. In our experience PCA3 could play an interesting role to predict significant disease: we observed that a unit increase of PCA3 score would enhance the risk of aggressive cancer by 0.7%.

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CHRONIC PROSTATITIS AND HIGH-GRADE PROSTATE INTRAEPITHELIAL NEOPLASIA (HG-PIN) DO NOT INFLUENCE URINARY PCA3 SCORE

Stefano De Luca[1], Roberto Passera[2], Angela Milillo[3], Renato Coda[4], Maria Sara Squeo[4], Donato Franco Randone[1]

[1]Divisione di Urologia, Ospedale Gradenigo di Torino;
[2]Medicina Nucleare 2, Ospedale Molinette e Universita' di Torino;
[3]Laboratorio Analisi, Ospedale Gradenigo di Torino;
[4]Servizio di Anatomia Patologica, Ospedale Gradenigo di Torino, Italy

Aim: To evaluate if histological chronic prostatitis and HG-PIN influence PCA3 score in patients with elevated PSA and negative digital rectal examination (DRE) undergoing a first or repeat prostate biopsy. *Patients and Methods:* Urinary PCA3 test was prospectively performed in 432 consecutive patients admitted in Gradenigo Hospital of Turin between January and December 2011 and scheduled for first and repeat prostate biopsy because of elevated PSA and negative DRE. Comparison of PCA3 score and patients with negative biopsy (normal parenchyma, benign prostatic hyperplasia, chronic prostatitis, HG-PIN) and positive biopsy was performed. *Results:* PCA3 median scores varied significantly (p<0.001) in men with a negative *versus* positive biopsy, 33 (range 2-212) and 66 (range 5-324) respectively. On the contrary men with chronic prostatitis and HG-PIN had no significant difference in PCA3 score with other negative biopsy patients. No correlation was found between the number of positive cores for chronic prostatitis, HG-PIN and PCA3 value. Twenty percent (23/114) of all patients with a positive biopsy had a PCA3 score ≤35. Forty percent (79/197) of men with a negative biopsy had normal parenchyma and PCA 3 score superior to 35. *Conclusion:* at this early stage of clinical evaluation, cancer specificity of the urinary PCA3 test in Italian patients with elevated PSA and negative DRE undergoing a first or repeat prostate biopsy, seems to be maintained in the face of the major cause of noncancerous PSA elevations: chronic prostatitis and also in the face of HG-PIN, the only accepted precursor of prostatic adenocarcinoma. References: 1. Benign prostatic hyperplasia BPH), 37.5% (24/64) of men with chronic prostatitis and 39.6% (19/48) of HG-PIN had PCA3 score Ploussard G, Durand X, Xylinas E *et al*. Prostate cancer antigen

3 score accurately predicts tumour volume and might help in selecting prostate cancer patients for active surveillance.

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THERMOABLATION OF SMALL RENAL TUMORS. OUR EXPERIENCE WITH RADIOFREQUENCY AND MICROWAVES

Alessandro Della Melina[1], Stefano Nerozzi[1], Giuseppe Canovaro[1], Enrico Trinci[1], Luca Carmignani[2], Alfredo Trippitelli[1]

[1]U.O. Urologia, AUSL N°3 Pistoia;
[2]U.O. Radiologia Diagnostica ed Interventistica, AUSL N°3 Pistoia, Italy

Aim: The gold standard for treatment of small renal tumors (<4 cm), confined to the kidney, remains the enucleation or enucleoresection (laparoscopic or open) of the neoplasm. Nevertheless thermoablation is a possible therapeutic option in selected cases. The aim of the study is to describe our experience in using of Radio Frequency (RF) and Microwave (MW) in the treatment of this group of tumors. Materials and Methods From January 2006 to December 2012 56 ablation procedures (40 RF, 16 MW) were performed on many renal neoplasms. The average age of the 54 patients (32 men, 22 women) was 72.3 years (range: 49-87). 36 nodules were exophytic and 20 were intraparenchymal with a maximum diameter between 13 and 37 mm. The histological examination, performed on needle biopsy, showed 49 RCC, 2 leiomyosarcomas and 1Kaposi's sarcoma. In 4 cases the histology was not conclusive. No benign neoplasm were detected. In 18 patients the surgical treatment was excluded for comorbidities, in 10 for advanced age, in 8 cases for poor performance status, in 4 for a solitary kidney, in 3 cases for bilaterality and in 10 cases for patient refusal. 51 procedures (91,1%) were performed percutaneously (ultrasound guided in 35 cases and CT guided in 16 cases) using local anesthesia, analgesia and sedation (discharge after 24 hours). In two cases the approach was laparoscopic. In another case it was mixed: percutaneous and open for bilaterality. All patients were evaluated by CT with contrast at 1, 3, 6 and 12 months, then once a year. Complete necrosis was defined as a lack of contrast enhancement in the treated area. Results The mean follow-up is 45,3 months (range 1-83). Two patients (3,7%) had a partial enhancement to the first control and underwent a second ablation. No major complications were observed. 2 cases of perirenal hematoma (1 immediate and 1 after 1 month) required only observation. In 22 patients treated with RF (55,0%) and 3 with MW (18,7%) arose transient abdominal pain with moderate discomfort. Discussion The thermal ablation with MW is more indicated in the treatment of large/exophytic lesions while the use of RF is preferable in small/intraparenchymal lesions. In any case, for masses with diameter <4 cm, the percentage of incomplete treatment is negligible with both methods. A significant lower incidence of post ablation syndrome is observed with the use of microwaves. Conclusions Although there are no long-term prospective studies, the thermal ablation of small renal tumors, in selected patients, turns out to be a minimally invasive treatment, safe and effective with low costs.

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CRM1-SELECTIVE INHIBITORS OF NUCLEAR EXPORT (SINE) REDUCE THE INCIDENCE OF TUMOR SPREADING AND IMPROVE OVERALL SURVIVAL IN PRECLINICAL MODELS OF PROSTATE CANCER

Giovanni Luca Gravina[1], Monica Tortoreto[2], Andrea Mancini[3], Paola Muzi[4], Luca Ventura[5], Alessandro Addis[6], Yosef Landesman[7], Dilara Mccaluey[7], Michael Kauffman[8], Sharon Sacham[9], Nadia Zaffaroni[2], Claudio Festuccia[10]

[1]Dipartimento Si Scienze Cliniche ed Applicate E Biotecnologiche, Università Dell'Aquila;
[2]Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milano;
[3]Biochimica, Dipartimento di Scienze Cliniche Applicate e Biotecnologiche;
[4]Immunoistochimica, Medicina Clinica, Sanità Pubblica, Scienze Della Vita E Dell'Ambiente;
[5]Anatomia Patologica, Ospedale San Salvatore L'Aquila;
[6]Veterianaria, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy;
[7]Preclinical Development, Karyopharm Therapeutics, Natick, MA, USA;
[8]Chief Executive Officer and Director, Karyopharm Therapeutics, Natick, MA, USA;
[9]Chief Scientific Officer and President of R&d, Karyopharm Therapeutics, Natick, MA, USA;
[10]Preclinical Studies, Dipartimento di Scienze Cliniche Applicate E Biotecnologiche, Università Dell'Aquila, Italy

Background: The human nuclear export protein, chromosomal region maintenance/exportin 1/Xpo1 (CRM1) is the sole exportin mediating transport of many multiple tumor suppressor proteins (TSP) including p53, pRb, FOXO, APC and p21 out of the nucleus, abrogating their function. *Aims and Methods:* To verify the hypothesis that CRM1 inhibition could be beneficial for the treatment of prostate cancer metastases, we tested the effects of the orally available, potent and selective, clinical stage SINE

compound, KPT 330. Male SCID mice were subjected to orthotopic intra-prostatic inoculation of the high aggressive DU145 prostate cancer cells, known to produce highly metastatic tumors with visceral metastases. In parallel, male CD1-nu/nu mice were subjected to intra-cardiac and intratibial injection of the high aggressive/bone-derived prostate cancer cells PC3, known to produce prominent osteolytic bone lesions. Animals were treated with KPT-330 administered by oral gavage. The effects of treatment with KPT330 on metastatic spreading, in terms of visceral and bone secondary incidence, were compared with another SINE inhibitor, the KPT251. *Results:* We previously demonstrated that SINE CRM1 antagonists have antitumor effects on prostate cancer cell lines at submicromolar range with KPT330 and KPT251 showing a profound antitumor effect in *in vivo* models. Here, we demonstrate that KPT330 reduces intra-prostatic DU145 tumor burden as well as the incidence of macroscopic metastases to lymph nodes, liver and lung, in a dose-dependent manner. The DU145 tumor burden was reduced by 41% with KPT-330 (4 mg/Kg qd/5 days) and 61% (10 mg/Kg q 3-4 d x 7) when compared to controls. The incidence of PC3derived bone metastases were significantly reduced upon KPT330 treatment when this inhibitor was administered at 10 mg/Kg (q 2d x 3 weeks). At 50 days after cell injection, 80% (8/10) of controls and 0% (0/10) of the KPT330-treated animals developed X-Ray evidence of bone lesions ($p<0.05$). The burden of bone metastasis, measured by lytic bone area, was significantly higher in controls than in KPT330-treated animals. Similarly, after intra-tibial injection, the lytic areas were higher in controls than in the KPT330 group ($p<0.05$). Analogously, the amount of osteoclast markers, measured in the serum and including TRAP and type I collagen fragment (CTX), was significantly higher in controls than in KPT330-treated animals. The comparison with a second CRM1 inhibitor, KPT251 (administered at 100 mg/Kg q 2d x 3 weeks), confirmed the reduction in incidence of bone metastasis after CRM1 inhibition (2/10 animals showed lytic lesions on X-ray in KPT251-treated animals, $p<0.05$). Importantly, the overall survival probability, evaluated at 170 days after tumor injection, was significantly higher in KPT330- and KPT251-treated animals when compared to controls ($p<0.0001$). Similar results were obtained also when disease-free probability was considered as endpoint ($p<0.0001$). The *in vitro* analyses performed on PC3 and DU145 cells revealed that the secretion of proteolytic enzymes (MMP-9, MMP-2 and uPA) was significantly reduced after KPT330 treatment, which, in turn, decreased the ability of tumor cells to migrate and invade matrigel. Impairment of secretion of pro-angiogenic (VEGF, IL6, IL8) or pro-osteolytic (RANKL , IL6) cytokines was also observed. Together these findings suggest that CRM1 is a key modulator of the metastatic process, inhibiting both tumor cell seeding and neo-angiogenetic events. *Conclusion:* These data show that selective blockade of CRM1-dependent nuclear export represents a completely novel, tumor metastasis-selective approach for the treatment of advanced/metastatic prostate cancers. KPT-330 is now in Phase 1 clinical trials in patients with advanced solid tumors (clinicaltrailas.gov: NCT01607905).

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BELINOSTAT POTENTIATES HORMONAL THERAPY AND PREVENTS THE ONSET OF CASTRATION-RESISTANT PHENOTYPE MODULATING ANDROGEN RECEPTOR, HSP90 AND CRM1 IN PRECLINICAL MODELS OF PROSTATE CANCER

Giovanni Luca Gravina[1,2], Francesco Marampon[1,2], Paola Muzi[3], Andrea Mancini[4], Margherita Piccolella[5], Paola Negri Cesi[5], Marcella Motta[5], Andrea Lenzi[6], Vincenzo Tombolini[7], Emmanuele Jannini[8], Claudio Festuccia[1]

[1]Laboratory of Radiobiology, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy;
[2]Division of Radiotherapy; Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy;
[3]Laboratory of Genaral pathology, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy;
[4]Laboratory of Biochemistry; Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy;
[5]Department Of Endocrinology, Center Of Endocrinological Oncology, University Of Milano, Milan, Italy;
[6]Laboratorio of Endocrinology, Department Of Experimental Medicine, University La Sapienza, Rome;
[7]Division of Radiotherapy, Department Of Experimental Medicine, University La Sapienza, Rome;
[8]Course of Endocrinology and Medical Sexology, Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, L'Aquila, Italy

Aims: Aberrant activation or "reactivation" of androgen receptor in the course of androgen-ablation therapy shows a potential cause for the development of castration-resistant prostate cancer. This study tested the hypothesis that Belinostat (PXD101), a potent pan histone deacetylase inhibitor, may potentiate hormonal therapy and prevent onset of castration resistant phenotype. *Materials and Methods:* A panel of human prostate cancer (PCa) cells with graded castration resistant phenotype and *in vivo* models were used to verify this hypothesis. *Results:* We demonstrated that hormonal manipulation favors the onset of castration resistant phenotype by the increase of HDAC expression and activity as well as by the increased expression and activity of AR, EGFR, HER2 and Akt. Consistent with these observations, the functional knockdown of HDACs by Belinostat

prevented the onset of castration resistant phenotype with a significant down-regulation of AR, EGFR, HER2 and Akt expression/activity. The deregulation of functional cooperation between HDAC-6 with hsp90, on one hand, and between GSK-3β with CRM1, on the other hand, may explain the biological effects of Belinostat. In this regard, the HDAC-6 silencing or the functional knockdown of hsp90 by 17AAG resulted in the selective down-regulation of AR, EGFR, HER2 and Akt expression/activity, while the decreased phosphorylation of GSK-3β mediated by Belinostat increased the nuclear expression of CRM1 which in turn modified the AR and survivin recycling with increased caspase-3 activity. *Conclusion:* HDAC inhibitors retain the ability to prevent the onset of castration resistant phenotype and, therefore, merit clinical investigation in this setting. However, further information is necessary to develop clinical treatment strategies for this disease.

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SOLITARY FIBROUS TUMOR OF THE KIDNEY: A CASE REPORT

Alessandro Della Melina[1], Giuseppe Silvestri[2], Lodovico Viganò[2], Francesco Muzzillo[2], Stefano Nerozzi[2], Silvia Tozzini[3], Alfredo Trippitelli[2]

[1]U.o. Urologia, AUSL3 Pistoia;
[2]U.o. Urologia, AUSL N°3 Pistoia;
[3]U.o. Anatomia Patologica, AUSL N°3 Pistoia, Italy

Introduction: The solitary fibrous tumor (SFT) is a rare mesenchymal spindle cell neoplasm. Most frequently it is found arising from the pleura but it has also been described in extrapleural sites. Its retroperitoneal localization is unusual and only 39 cases of renal or perirenal localization have been described. The neoplasm tends to be slow-growing and is most often diagnosed in middle aged adults. In a low percentage of cases it is associated with hypoglycemia because of the overproduction of insuline-like growth factor. *Patients and Methods:* We describe a case of SFT in the left kidney of a 59-years-old female. The patient performed CT for left low back pain. A tumor localized in the upper part of the front lip of the kidney with contrast enhancement and colliquative areas. An abnormal hilar lymph node was detected . A transperitoneal nephrectomy with enlarged lymphectomy was performed. Gross examination revealed a solid mass at the hilum of the kidney, measuring 9x8x8.5 cm. No nodal involvement was detected. The tumor was gray-brownish in colour, including some cystic space of different size, had pushing edges and it appeared to displace the renal pelvis and medullary without infiltrating them. A well defined fibrous capsule was not observed. Histological sections showed a hypercellular proliferation of spindle/ovoid cells, which were placed around numerous dilated and branching vesels in a typical hemangiopericytoma-like pattern. Moderate nuclear pleomorphism was detected, as well as scattered foci of tumor necrosis, while the mitotic rate was low (2 mitosis/10 HPF). Immunohistochemical stains were performed: the tumour was strongly and diffusely positive for Vimentin, CD34 and Bcl-2, weakly positive for Actin and it was negative for CK AE1/AE3, CD10, EMA, S100, HMB45 and Desmin. According with these data the diagnosis of extra-pleural SFT with atypical features was done. The follow up at 6 month after surgery showed no recurrence or distant metastasis. *Discussion:* The literature show that the clinical behavior of the pleural or extrapleural SFT is unpredictable. In all sides some factors are associated with an aggressive clinical behavior even though they are not predictive. They are hypercellularity, cellular atypia, mitotic rate > 4/10 HPF and tumor necrosis. The SFT can give local recurrence or metastasis even after 5 years from surgery regardless the presence of these factors so that a long accurate follow-up, is necessary.

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SALVAGE RADIOTHERAPY WITH VOLUMETRIC MODULATION ARC THERAPY AND HYPOFRACTIONATION FOR RECURRENT PROSTATE CANCER AFTER HIFU FAILURE

Filippo Alongi, Rocco Luca Emanuele Liardo, Cristina Iftode, Tiziana Comito, Angelo Tozzi, Pierina Navarria, Pietro Mancosu, Stefano Tomatis, Marta Scorsetti

Radioterapia e Radiochirurgia, Manzoni Istituto Clinico Humanitas, Milano, Italy

Background: In the controversial management of low risk prostate cancer, high-intensity focused ultrasound (HIFU) has been used usually in salvage therapy for recurrence after external beam radiotherapy or as optional primary treatment. Conversely, but less frequently, radiotherapy is a therapeutic option for recurrences after HIFU treatment. *Objectives:* Our aim was to evaluate tolerance, feasibility and acute and addictional toxicity in patients undergoing salvage radiotherapy after HIFU failure. *Patients and Methods:* Fifteen patients were treated with HIFU as primary radical treatment from 2005 to 2011. Six out of 15 were treated twice. Between September 2011 and February 2013, all patients, presenting biochemical relapse after HIFU, underwent salvage EBRT with moderate Hypofractionation schedule in 28 fractions. Treatments have been performed with V-MAT technique (RapidArc® Technology). Genito-urinary (GU) and gastrointestinal (GI) toxicity were scored using the Common Terminology Criteria for Adverse Events (CTCAE V.4) scale before and after the treatment. Biochemical response was assessed by ASTRO Phoenix criteria (+2 from Nadir of PSA during follow-up). *Results:* The median age of the patients was 67,5 years (range:

53-85). The median Gleason Score was 7 (range: 6-9). The mean prostate specific antigen (PSA) before radiotherapy was 4.59 ng/mL (range: 0.18-64.2). Six out of 15 patients received adjuvant androgen deprivation therapy (ADT). The treatment was well tolerated and completed by all patients with a median dose of 71.4 Gy (range: 71.4-74.2 Gy) in 28 fractions and without radiation related major gastrointestinal and genito-urinary toxicity. For GU, acute grade 1 and grade 2 toxicities were 6/15 and 4/15; for GI acute grade 1 and grade 2 toxicities were 4/15 and 3/15 respectively. No grade 3 or greater toxicities were found. Biochemical control was assessed in 12/15 patients. Three out of 15 patients, with biochemical relapse, showed lymph-nodal recurrence and were treated with salvage hormonal therapy and radiotherapy on local lymph nodal recurrence (included in a protocol of study for oligometastatic patients). *Conclusion:* Our early clinical results and biochemical data confirm the feasibility and show a good tolerance of the salvage radiation therapy after HIFU failure. The findings of low acute toxicity is encouraging, but longer follow-up is needed to assess late toxicity and definitive outcomes.

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FIVE FRACTIONS LINAC BASED SBRT FOR LOW – INTERMEDIATE RISK PROSTATE CANCER: PRELIMINARY REPORT OF A PHASE II STUDY WITH FLATTENING FILTER FREE DELIVERY AND SPACE OAR

Filippo Alongi[1], Cristina Iftode[1], Stefano Arcangeli[1], Rocco Luca Emanuele Liardo[1], Rodolfo Hurle[2], Tiziana Comito[1], Elisa Villa[1], Angelo Tozzi[1], Pierina Navarria[1], Pietro Mancosu[1], Stefano Tomatis[1], Gianluigi Taverna[1], Pierpaolo Graziotti[1], Marta Scorsetti[1]

[1]Radioterapia E Radiochirurgia, Istituto Clinico Humanitas, Milano;
[2]U.o. Urologia, Istituto Clinico Humanitas, Milano, Italy

End point of the present study is to evaluate the technical feasibility and early side effects of a short course hypofractionated high dose LINAC based SBRT delivered with Flattened Filter Free (FFF) beams, and SpaceOAR as a spacer between rectum and prostate. *Patients and Methods:* This is a prospective phase-I-II pilot feasibility study, started on February 2012. Inclusion criteria were: age ≤ 80 years, WHO PS ≤2 PSA ≤20 ng/ml, histologically proven prostate adenocarcinoma(risk of microscopic nodal involvement ≤15%), T1-T2 stage, no distant metastases, no previous prostate surgery other than TURP, no malignant tumours in the previous 5 years, IPSS 0-7. The schedule was 5×7 Gy=35 Gy, delivered in 5 alternative days(NTD2 between 70 and 85 Gy for an α/β between 3 and 1.5 Gy, respectively). SBRT was delivered using the volumetric modulated arc technique by RapidArc, with photon beam energy of 10 MV FFF(Filter Flattening Free) and maximum dose rate of 2400 MU/min. Physical examinations and toxicity assessments were performed during and after SBRT according to CTCAE v4.0 toxicity scale. EPIC questionnaires were used for Quality of Life assessing. Tumour response was evaluated on ASTRO PHOENIX definition (+2 from Nadir of PSA). Neo-adjuvant/concomitant hormonal therapy was prescribed based on the risk according to NCCN classification. SpaceOAR was implanted by intraperineal injection as a spacer to enlarge the minimum distance between prostate and anterior rectal wall. The SpaceOAR implant was optional and based on clinician decision for each case. *Results:* With a median follow-up of 6 months (1-9), 40 patients were treated with this schedule and were evaluable for the current analysis. 34/40 patients were officially recruited in the protocol and met perfectly all inclusion criteria. Other 6/40 'out of trial' were treated with the same protocol. In the trial, according to NCCN criteria, 21/34 patients were low-risk and 12/34 were intermediate risk. Median Age was 69.6(56-80), median initial PSA was 6.33 ng/ml (range: 0.50-12 ng/ml). Median Gleason score was 6.33 (6-7). Median treatment duration was 11.8 days (9-22). All patients completed the treatment as programmed. Acute toxicities were as follow: Rectum G0 in 21/34 cases (62%), G1 in 11/34 (33%); G2 in 2/34 (5%). Genito-urinary G0 in 15/34 cases (45%), G1 in 7/34 (20%), G2 in 12/34 (35%). In two G2 urinary retention cases, the placement of intermittent catheter was needed (in both cases prostate dimension was superior than100cc). No acute G3-5 was found in the trial and 'out of trial'patients. Median treatment time was 126 seconds (120-136). SpaceOAR was implanted in 9 patients with a single case of rectal fascia infection resolved with antibiotics. During Follow-up, PSA reduction was documented in all treated patients. *Conclusion:* Our early findings suggest that LINAC based SBRT FFF treatment for prostate cancer in 5 fractions is feasible, fast and well tolerated in acute setting for the first 40 treated patients. Longer follow-up is needed for definitive assessment of late toxicity and clinical outcome.

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COMPARISON OF ACUTE TOXICITY BETWEEN MODERATE HYPOFRACTIONATION WITH VOLUMETRIC MODULATION ARC THERAPY AND CONVENTIONAL FRACTIONATION WITH THREE DIMENSIONAL CONFORMAL RADIATION THERAPY IN POST-OPERATIVE PROSTATE CANCER PATIENTS

Filippo Alongi[1], Cristina Iftode[1], Tiziana Comito[1], Elisa Villa[1], Rocco Luca Emanuele Liardo[1], Angelo Tozzi[1], Pietro Mancosu[1], Stefano Tomatis[1], Antonella Fogliata[2], Luca Cozzi[2], Gianluigi Taverna[3], Pierpaolo Graziotti[3], Marta Scorsetti[1]

[1]Radioterapia e Radiochirurgia, Istituto Clinico Humanitas, Milano, Italy;
[2]Fisica Medica, IOSI, Bellinzona, Switzerland;
[3]U.o. Urologia, Istituto Clinico Humanitas, Milano, Italy

Objectives: To retrospectively evaluate and compare the incidence of acute genito-urinary(GU), upper gastrointestinal (uGI) and rectal (lGI) injuries of hypofractionation by volumetric modulation arc therapy (Hypo-RapidArc group) and conventional fractionation by three dimensional conformal radiotherapy(3DCRT group) in patients with localized prostate cancer treated with prostatic bed irradiation, after radical prostatectomy. *Patients and Methods:* Between 2007 and 2012, 84 consecutive patients with clinically localized prostate, submitted to radical prostatectomy, were also irradiated to prostate bed in our Institute. of the 84 patients 41 had undergone 3DCRT and 43 patients were treated with RapidArc (after its clinical use for prostate bed in 2009/2010). The median age was 67 and 68.5 years for 3DCRT and HypoRapidArc group respectively. The median dose to the prostatic bed was 70 Gy (70-76) with 2 Gy per fraction in 3DCRT group and 70 Gy (70-72.4) with 2.5Gy (2.5-2.55) per fraction in the Hypo-RapidArc group. After radical prostatectomy, the median time to RT was 15 and 16 months respectively in 3DCRT and Hypo-RapidArc group. Acute GU, uGI e lGI toxicities after radiation treatment were evaluated using Radiation Therapy and Oncology Group/European Onganization for Research and Treatment of Cancer (RTOG/EORTC) medical scoring system. *Results:* Acute GU G2 was recorded in 17% of cases in 3DRCT group and in 12% in Hypo-RapidArc group. No acute G2 uGI toxicities were found in 3DCRT *versus* 7% in Hypo-RapidArc group. Regarding lGI G2 toxicities were 7% in 3DCRT *versus* 18% in Hypo-RapidArc group. No G3 or greater toxicities was found in both groups. In both groups the PTV coverage was suitable: PTV mean dose was 99.4±1.0% and 99.8±0.9% and V95% 96.3±3.6% and 95.7±8.9 for 3DRCT and RA group respectively. For 3DRTC group the rectum received a mean dose of 42.1±9.4 Gy (with V65Gy equal to 26.9±10.0%) and the bladder received 69.3±17.2 Gy in mean (with the V65Gy equal to 45.0±19.5%); and for RA group the dose decreased to 37.2±5.2 Gy (V65Gy 9.6±5.1%) and 39.2±13.4 (V65Gy 25.2±14.4%) for rectum and bladder. *Conclusion:* The results of our study of 84 patients have shown that acute G2 GU are reduced using hypofractionation by RapidArc compared to conventional fractionation by 3DCRT, while acute G2 GI toxicities remain better for the last one. Remarkable is the absence of G3 using hypofractionation by RapidArc as well as recorded previously with conventional fractionation by 3DCRT. Longer term data are awaited for late toxicity profiles and clinical efficacy in HypoRapidArc group of patients.

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PROGNOSTIC FACTORS AND RISK GROUPS IN T1G3 PATIENTS INITIALLY TREATED WITH BCG: RESULTS OF A MULTICENTER RETROSPECTIVE SERIES IN 1743 PATIENTS

P. Gontero[1], R. Sylvester[2], F. Pisano[1], S. Joniau[3], Kathy Vander Eeckt[3], V. Serretta[4], S. Larre'[5], S. di Stasi[6], B. Van Rhijn[7], A. Witjes[8], A. Grotenhuis[8], R. Colombo[9], A. Briganti[9], M. Babjuk[10], V. Soukup[10], P.U. Malmstrom[11], J. Irani[12], N. Malats[13], J Baniel[14], R. Mano[14], T. Cai[15], E. Cha[16], P Ardelt[17], J. Vakarakis[18], R. Bartoletti[19], M Sphan20, G. Dalbagni[21], S.F. Shariat[16], J karnes[22], J Palou[23]

[1]Dept of Urology, MolinetteHospital, University of Turin, Italy;
[2]EORTC Data Center, Bruxelles;
[3]Oncologic and Reconstructive Urology ,Dept of Urology. University Hospitals Leuven, Belgium;
[4]Dept of Urology, Paolo Giaccone General Hospital, Palermo, Italy;
[5]Dept of Surgical Science, John Radcliffe Hospital, University of Oxford, UK;
[6]Policlinico Tor Vergata-University of Rome, Italy;
[7]Dept f Urology, Netherland Cancer Institute, Amsterdam;
[8]Dept of Urology, Radboud University Nijmegen Medical Centre, The Netherlands;
[9]Dipartimento di Urologia, Università Vita-Salute, Ospedale S. Raffaele, Rome, Italy;
[10]Dept of Urology, Motol Hospital, University of Praha, Chech Rep.;
[11]Dept of Urology, Academic Hospital, Uppsala University, Sweden;
[12]Dept of Urology, Centre Hospitalier Universitaire La Milétrie,University of Poitiers, France;
[13]Dept of Urology, Spanish National Cancer Research Centre-Madrid, Spain;
[14]Dept of Urology, Rabin Medical Centre,Tel Aviv, Israel;
[15]Department of Urology, Santa Chiara Hospital, Trento, Italy;
[16]DeptOf Urology, Weill Medical College of Cornell University in New York City, USA;
[17]Facharzt fur Urologie, Abteilung fur Urologie, Chirurgische Universitats klinik. Freiburg, Germany;
[18]Dept of Urology, Sismanoglio Hospital, University of Athens, Greece;
[19]Dept of Urology Unit S.Maria Annunziata Hospital, University of Florence, Italy;
[20]Dept of Urology, University Hospital of Wurtzburg, Germany;
[21]Dept of Urology, Memorial Sloan Kettering, New York, NY, USA;

[22]Dept of Urology, Maio Clinic, Houston, TX, USA;
[23]Dept of Urology, Fundacio Puigvert, University of Barcelona, Spain

Introduction and Objectives: The impact of prognostic factors in T1G3 patients (pts) is critical for proper treatment decision making, however most available data are from small series of pts. The aim of the current study is to assess prognostic factors in a large group of pts who received BCG as initial treatment of T1G3 tumours and identify a subgroup of high risk pts who should be considered for early cystectomy. *Patients and Methods:* Individual pt data were collected for 1743 ptsfrom 20 centers who received induction or maintenance BCG between 1990 and 2008. Using Cox regression analysis, the prognostic importance of the following variables were assessed for time to recurrence, progression to muscle invasive disease and overall survival:age (<70 *vs*. >70yrs), gender, primary T1G3 *vs*. recurrent T1G3 after previous non T1G3 tumour, tumour size (<3 *vs*. >3 cm), multiplicity (single *vs*. multiple), concomitant CIS (no/yes), and maintenance BCG (no/yes). *Results:* Median age was 68yrs, 84% were male, 89% were primary T1G3, 50% had multifocal disease, 67% had tumours less than 3 cm, 24% had concomitant CIS, 30% had a restaging TUR, 52% received some sort of maintenance BCG. With a follow up out to 15 years, 801 pts (46%) recurred, 326 (19%) progressed, 291 underwent cystectomy (17%) and 409 (23%) died, 151 (9%) due to bladder cancer. In multivariate analyses, the most important prognostic factors ($p<0.05$) for recurrence were: tumour size and multiplicity; for progression: age, size and concomitant CIS; for overall survival: age and size. Maintenance BCG had a positive impact on recurrence ($p<0.001$), progression ($p=0.059$) and survival ($p=0.01$). Patients were divided into 4 risk groups according to the number of bad factors for progression among age >70, size >3 cm and presence of CIS. Progression free rates at 10 yrs were 84%, 75%, 66% and 28% for patients with 0, 1, 2 and 3 bad factors while the corresponding overall survival rates were 78%, 56%, 45% and 6%, respectively. *Conclusion:* T1G3 patients treated with BCG have a heterogeneous prognosis, with overall survival at 10 yrs ranging from 78% to 6%. Although maintenance BCG improves outcome as compared to induction alone, fit pts over 70 yrs of age with tumours greater than 3 cm and concomitant CIS should be considered for an early cystectomy.

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BLUE LIGHT (PDD) IN THE ENDOSCOPIC RESECTION OF NMIBC: PRELIMINARY RESULTS OF FIRST 200 CASES

Tommaso Brancato[1], Francesca Suriano[2], Gianni Paulis[3], Pietro Nupieri[3], Roberto D'ascenzo[3], Giuseppe Orsolini[3], Rosaria Alvaro[4]

[1]UOC Urologia- Dipartimento Chirurgia, Ospedale Regina Apostolorum;
[2]U.o. Urologia, Rome American Hospital;
[3]U.o. Urologia, Ospedale Regina Apostolorum;
[4]Dip. Igiene, Università di Roma Tor Vergata, Italy

Introduction: Each year 260,000 new cases of bladder cancer in men and 75,000 in women are approximately estimated overall (1). In Italy, diagnosis of bladder cancer concerns almost 14,000 men and 3,000 women, probably due to greater exposure to smoke cigarettes and professional contact involving certain chemicals. (2) Endoscopic resection of bladder (TURBT) is gold standard therapy for NMIBC cancer. High grade superficial tumor (Ta-T1), needs a second look 4-6 weeks after TURBT. This seems to be associated to understaging, and it may reach 40% in this group of patients (3). Photodynamic cystoscopy (PDD) with hexaminolevulinate (HAL) is a diagnosis technique, which effectively aims to improve the accuracy of white light cystoscopy (WLC) in the diagnosis of superficial bladder tumors, especially of flat urothelial lesions (dysplasia and Cis) (4). *Patients and Methods:* Aims of this Open Label study was to evaluate five years long term results of Safety/ Efficacy/Disease free/relapse data in bladder cancer patients, previously treated with HAL instillation, and WL/PDD endoscopic resection of the bladder. From May 2011 to nowadays all patients with superficial bladder cancer (first presentation or recurrence) were treated with WLC/PDD TURB. Preliminary diagnostic procedures, urine cytology, ultrasound, Uro-Tc, were assessed in all patients. Demographics, medical history, risk factors, previous intravesical therapy and the date of the last instillation were recorded. Instillation of HAL was performed in all patients, 1 hour before surgery. Prior white light cystoscopy was done to identify any macroscopic lesion. Later, cystoscopy with PDD was needed to describe the invisible lesions to WL cystoscopy. TURBT was carried out on all visible lesions to PDD vision. Any lesion was collected separately for histological examination and categorized according to the usual cystoscopy bladder scheme. Patients were followed up with the normal crowd-expected superficial bladder cancers (periodic urine cytology, cystoscopy, intravesical instillations) reporting any given follow-up examination and the date of any recurrence. Data were collected in a database; Fisher's test and a multivariate statistical analysis with SPSS (IBM SPSS Data Collection) were used for statistical analysis. *Results:* Since May 2011 to December 2012, 216 patients (163 males and 53 females) were treated with WLC/PDD TURB for NMIBC, by five trained urologist. Mean age was 68,8 years. Median followup was 9,1 months. Bladder cancer was single lesion in 74 patients (Table I), in 103 patients multifocality was observed and 39 patients were negative at WLC. of these, 32 were positive at PDD and 3 (+7.6%) positive for bladder cancer.

Table I

	Sensitivity	Specificity	PPV	PNV
WLC	74.7	91.4	84.8	84.9
PDD	84.0	98.3	96.9	90.6

CIS was detected in 13 of 216 patients (28%): 7 with PDD alone (53.8%, $p<0.01$), 3 (23%) with WL/PDD and 3 (23%) with WL alone. *Conclusion:* In our preliminary experience adding PDD to conventional cystoscopy-bladder resection is useful and requires little training. Additional costs can be reduced by the delay of recurrence rate (5) and the improvement of diagnosis of Ta, T1 and carcinoma *in situ*.

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OLIGOMETASTATIC PROSTATE CANCER AND RADIOTHERAPY ON PRIMARY SITE AND BONE PELVIC RECURRENCE

Filippo De Renzi[1], Tiziana Iannone[1], Marco Micucci[1], Sergio Bissoli[2], Alessandro Testolin[1]

[1]Radioterapia, Ospedale S Martino Belluno;
[2]Medicina Nucleare, Ospedale Castelfranco Veneto, Italy

Introduction: In 2012, three patients affected by prostate cancer with bone pelvic recurrence were treated with three dimensional conformal radiotherapy not only for metastasis but contouring Planning Target Volume (PTV) for primary tumor and recurrence. *Patients and Methods:* First patient (A) was a 72-year-old man, treated with urinary dysobstruction therapy. *Diagnosis:* Prostate-specific Antigen (PSA) 83 ng/ml, Gleason score 3 plus 3, clinical stage T2c N0 M1b, with a right bone pubic lesion (asymptomatic) identified to ^{11}C-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 he started radiotherapy 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 was stopped 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 ^{11}C-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 ^{11}C-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. Now he is continuing therapy with three-monthly LHRH analogue and monthly bisphosphonate. *Results:* Patient A had a four months follow up: PSA 0,05 ng/ml; IPSS 2; no pain referred. Patient B had a five months follow up: PSA 0.05 ng/ml; IPSS 2; no pain. Patient C had a seven months follow up: PSA 44 ng/ml; no pain; asymptomatic for urinary problems. *Conclusion:* In these three cases, clinical and biochemical results seem to confirm that selected patients with oligometastatic prostate cancer can receive more than only palliative radiotherapy. Three dimensional radiotherapy on primary site and bone pelvic recurrence seems to be a satisfactory therapeutic choice.

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HYPOFRACTIONATION WITH TOMOTHERAPY FOR PROSTATE CANCER: TOXICITIES AND OUTCOMES IN 82 PATIENTS TREATED IN MODENA

Alessio Bruni, Ercole Mazzeo, Bruno Meduri, Elisa D'angelo, Biancaluisa Lanfranchi, Paola Barbieri, Cristina Tata, Laroussi Mohammed Lamin, Filippo Bertoni

UO Radioterapia Oncologica, AOU Policlinico di Modena, Italy

Aim: Curative treatment of patients with prostate cancer (PC) comprises surgery and/or radiotherapy (RT) with or without hormonotherapy (OT). Dose escalation using external beam RT seems to improve clinical outcomes and several studies provide strong evidence for a dose-response relation of local tumor

control, biochemical progression free survival and progression free survival. It is commonly known that dose escalation can also be achieved by increasing the dose per fraction above 2 Gy (as in our study) and many different studies showed that prostate cancer cells may be strongly susceptible to this regimen (due to their low alfa/beta ratio). On the other hand, dose escalation and hypofractionation may hypothetically increase acute and late toxicities (such as genitourinary and gastrointestinal) but the introduction in recent years of IMRT and IGRT (such as Tomotherapy®) may allow us to deliver higher doses to targets without increasing side effects. *Patients and Methods:* From February 2008 to December 2012 a total of 82 patients with prostate cancer histologically proven underwent radical RT. Hypofractionated regimen with or without concomitant OT was used for all patients who were treated using image guided RT with Tomotherapy®. Median age was 72 years (range 51-80 years). About clinical stage, all patients underwent rectal ultrasonography, biopsy, abdominal CT scan and pelvis RMN. At the end of staging protocol five of 82 patients (4.5%) had very low risk prostate cancer, 5 pts (4.5%) had low risk, 26 pts (32%) intermediate risk, 27 pts high risk (33%) and 14 pts (17%) very high risk prostate cancer due to NCCN 2013 recurrence risk stratification; abdominal lymphadenopathy were found in only 5 pts (metastatic stage for NCCN classification). Forty-one patients (50%) received neoadjuvant/concomitant and adjuvant OT while 4 pts (5%) just neoadjuvant/concomitant OT. No OT was planned for 28 patients due to their stage and/or comorbidities. Gleason Score was less than 7 in 31 pts, equal to 7 in 26 pts and superior in the other 24 patients; median Gleason score was 7. Radiotherapy was delivered to a median dose of 70 Gy (range: 45-76 Gy). Clinical target volume included prostate +/– seminal vescicles in 41 patients (50%), while in 41 patients (50%) pelvic abdominal radiotherapy was performed: in 36 pts with prophylactic intent due to high risk of lymphatic extension (based on Roach algorithm) while in 5 patients due to radiologically proven lymphatic involvement (cN1 stage). Regarding clinical outcomes only 71 pts were analyzed: overall survival (OS), disease metastases and biochemical free survival (DMFS and BFS) were investigated. *Results:* Regarding clinical outcomes, after a median follow up of 24 months 63 patients of 71 are still free from disease (89%), five pts (7%) are alive with locoregional disease and 2 pts (3%) developed metastatic disease; only 1 pt died due to the disease. All patients with loco-regional or systemic disease were submitted to first line hormonotherapy with LH-RH. Both 1yr and 4-yrs OS were 98% (±1.7SE), 1-yr and 4-yrs DMFS were 98.3% (±1.7SE) and 90.1% (±8.00SE) respectively. BFS was 93% (±3.5SE), 91% (±4.00SE), 83.7% (±6.00SE) and 75.3% (±9.6SE). Radiotherapy treatment was well tolerated with only 4 patients complaining for acute severe urinary toxicity while 1 pt developed grade 3 acute rectal side-effect. Late grade 3 rectal toxicity was reported in 7 patients (7.5%) while grade 2 urinary toxicity was observed in 4 pts; no grade 3 urinary late toxicity was found. No treatment related deaths were encountered in our population. *Conclusion:* Hypofractionated dose escalated radiation treatment using IG-IMRT with Tomotherapy seems to be feasible and safe being able to achieve optimal outcomes reducing total treatment time without increasing loco-regional side effects. Hypofractionation and dose escalation in radical or concomitant (hormonotherapy) setting should be considered in the management of non-surgical prostate cancer.

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SINGLE-DOSE ORAL CIPROFLOXACIN COMPARED WITH PLACEBO FOR PROPHYLAXIS DURING TRANSURETHRAL RESECTION OF BLADDER

Lucio Dell' Atti, Giovanni Daniele, Stefano Papa, Gianni Ughi, Gian Rosario Russo

Urologia, Azienda Ospedaliero-Universitaria Arcispedale S. Anna, Ferrara, Italy

Introduction: Transurethral resection of bladder tumour (TURB) is the treatment of choice for low-grade, low-stage bladder tumours and the routine procedure for biopsy and staging of higher-stage, higher-grade bladder tumours. In the absence of antimicrobial prophylaxis, patients with previously sterile urine commonly develop bacteriuria, usually due to Gram-negative bacilli (1, 2). The use of prophylactic antimicrobial agents for these procedures remains controversial, especially in patients whose urine is sterile pre-operatively (3). This study summarizes data from a single clinical trial that compared the efficacy of a single pre-operative dose of oral ciprofloxacin with placebo in the prevention of post-operative bacteriuria in patients requiring TURB. *Patients and Methods:* This prospective, randomized, placebo-controlled study was conducted at a single center of Urology. A total of 158 patients, male or female >40 years of age, between November 2010 and December 2012 were enrolled in this study and underwent TURB. Patients were excluded based on any of the following criteria: history of hypersensitivity to quinolones; valvular heart disease requiring prophylaxis for bacterial endocarditis; significant gastrointestinal disease or inability to tolerate oral medication; presence of bacteriuria (>104 cfu/mL) at pre-procedure urine culture; history of endoscopic manipulation of the urinary tract within 7 days of study enrolment. One group received 500 mg of ciprofloxacin orally, the second group placebo. Patients were evaluated for adverse events at the time of each post-surgical visit. Repeat urine cultures and urinalysis were obtained between 5 and 20 days following the surgical procedure, usually at the time of catheter removal. *Results:* The 158 patients enrolled in the study were divided: Group A, 89

patients treated with a single dose of ciprofloxacin as prophylaxis; while Group B, 69 patients received no treatment (placebo) during TURB. Nine patients (Group A) were excluded from the efficacy and safety analyses because of failure to receive study medication. There was no statistically significant difference among the treatment groups with respect to age, sex race, health status, accompanying diseases, type of resection, time of dosing to start of surgery and antimicrobial use before study entry.The mean age was 67.9 and 69.6 years in A and B groups, respectively. Mean duration of surgery, urinary bladder catheterization and post-surgical length of hospitalization were not significantly different among the two treatment groups. Observed rates of post-operative bacteriuria in the efficacy-valid population were 17.5% (14/80) for ciprofloxacin-treated patients compared with 24.6% (17/69) for those receiving placebo. The difference in post-operative bacteriuria rates between ciprofloxacin and placebo was estimated at 7.1%, demonstrating that the two treatments were not equivalent. Organisms responsible for post-operative bacteriuria included *Enterococcus faecalis* (n:3), *Staphylococcus* (n:4), *Enterococcus faecalis* (n:7) for ciprofloxacin; *Candida albicans* (n:3), *Escherichia coli* (n:9), *Enterobacter* (n:3), *Staphylococcus* (n:2) for placebo. No patient in the ciprofloxacin group compared with 4 in the placebo group (5.8%) valid for efficacy required hospitalization for urosepsis. Three of the 4 patients in the placebo group were categorized as having severe urosepsis; all 4 patients developed urosepsis within 3 days of the TURB. Two of the 4 placebo-treated patients had *E. coli* isolated from the blood; all 4 patients had more than 105 CFU/mL of *E. coli* cultured from the urine. All four episodes resolved or improved without serious sequelae after institution of appropriate antimicrobial therapy. *Conclusion:* Despite the lack of statistical significance, the observed rates of post TURB bacteriuria in this study were lower following a single 500 mg dose of ciprofloxacin than they were with placebo. This study, although unable to show that antimicrobial prophylaxis was superior to placebo, demonstrated that single-dose oral ciprofloxacin (500mg) was an efficacious and cost-effective alternative to placebo for antimicrobial prophylaxis during transurethral resection surgery, even if the rates of prolonged hospitalization for urosepsis reported are low.

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INVESTIGATING THE RELATIONSHIP BETWEEN TYPE OF SURGERY AND SURVIVAL IN PATIENTS WITH LOCALLY-INVASIVE SQUAMOUS CELL CARCINOMA OF THE PENIS

Andrea Guttilla[1], Giovanni Lughezzani[2], Mario Catanzaro[3], Tullio Torelli[3], Silvia Stagni[3], Davide Biasoni[3], Nicola Nicolai[3], Luigi Piva[3], Andrea Necchi[3], Patrizia Giannatempo[3], Daniele Raggi[3], Roberto Salvioni[3]

[1]Urology Clinic, Department of Surgical Oncological and Gastroenterological Sciences, University of Padua; [2]Department of Urology, Vita-Salute San Raffaele University; [3]Urology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy

Introduction: We evaluated whether type of surgery has an impact on the survival outcomes in a population of patients with penile squamous cell carcinoma surgically treated at our Institution between 1980 and 2012. *Methods:* The study population consisted of 275 patients treated with partial penectomy (PP), total penectomy (TP) or emasculation for locally-invasive penile cancer. We determined the pathological characteristics of the disease and the oncological outcomes of these individuals. The Kaplan-Meier method was used to depict cancer-specific survival (CSS) rates. Univariable and multivariable Cox regression models were fitted to test the predictors of CSS. *Results:* Overall, 202 (73.5%), 53 (19.3%) and 20 (7.3%) patients were treated with PP, TP and emasculation, respectively. Tumor stage ($p<0.001$) and grade ($p=0.024$) were significantly higher in patients subjected to TP or emasculation relative to individuals treated with PP. For example, 9 (45.0%) and 12 (22.6%) patients subjected to emasculation and TP had pT3-4 disease compared to 21 (10.4%) patients who underwent PP. The 5-and 10year CSS rate were 76.1% and 72.0%, respectively. In univariable Cox regression models, pT stage, pN stage, tumor grade and type of surgery emerged as significant predictors of CSS (all $p<0.001$). Specifically, patients who underwent a TP or emasculation had a 1.78- (95% CI: 0.98-3.25) and a 3.79- (95% CI 1.86-7.74) fold higher risk of dying of their disease relative to patients subjected to PP. However, in multivariable Cox regression models, after adjustment for pT stage, pN stage and grade, type of surgery did not emerge as an independent predictor of CSS ($p=0.542$). Conversely, both pT stage ($p=0.05$) and pN stage ($p<0.001$) achieved the independent predictor status. *Conclusion:* Different surgical approaches may be adopted for the treatment of locally invasive penile cancer. The most appropriate approach should be chosen after careful evaluation of the disease characteristics and expectations of each patient.

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PREDICTORS OF LOCAL FAILURE AFTER PARTIAL PENECTOMY FOR LOCALLY-INVASIVE PENILE CANCER: A SINGLE-INSTITUTIONAL CASE SERIES

Mario Catanzaro[1], Giovanni Lughezzani[2], Andrea Guttilla[3], Tullio Torelli[4], Silvia Stagni[4], Davide Biasoni[4], Nicola Nicolai[4], Luigi Piva[4], Andrea Necchi[4], Patrizia Giannatempo[4], Daniele Raggi[4], Roberto Salvioni[4]

[1]Urology Unit, IRCSS Istituto Nazionale Dei Tumori; [2]Department of Urology, Vita-Salute San Raffaele University; [3]Urology Clinic, Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua; [4]Urology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy

Introduction: Partial penectomy (PP) is an organ-sparing alternative to total penectomy (TP) in the treatment of locally-invasive penile cancer. In the current study, we investigated the predictors of local failure in a single-institutional population of patients treated with PP. *Methods:* Data from 210 patients treated with PP for penile cancer between January 1980 and June 2012 were retrieved from our institutional database. Local failure was defined as the presence of residual disease (positive surgical margin; R1) or local disease recurrence requiring further surgical intervention. Cox regression models were fitted to test the predictors of local failure. *Results:* Mean patient age was 59.2 years (range 21-92). Positive surgical margins were detected in 13 (6.1%) patients. Seven (25%) out of 21 patients with pT3 disease had positive surgical margins, as compared to 6 (5.3%) out of 108 patients with pT2 disease and 0 (0%) out of 81 patients with pT1 disease. All of these patients were subjected to TP. Overall, 18 (8.6%) patients developed local recurrence at a median follow-up time of 24.8 months (range: 4-47) and required further surgical intervention. At univariable Cox regression analyses, pathological T stage and grade emerged as significant predictors of local failure (all $p \leq 0.001$). Specifically, patients with pT2 and pT3 disease had respectively a 14.17- (95% CI:1.88106.66) and a 42.2-fold (95% CI 5.32-334.8) higher probability of developing local recurrence relative to patients with pT1 disease. Similarly, patients with G2 and G3 disease had respectively a 2.40 (95% CI:0.93-6.94) and a 6.65 (95% CI 2.28-19.45) -fold higher probability of developing local recurrence relative to patients with low grade disease. At multivariable Cox regression analysis, only pT stage emerged as an independent predictor of local failure ($p=0.005$). Conversely, tumor grade did not achieve the independent predictor status ($p=0.150$). *Conclusion:* Partial penectomy represents an oncologically safe option for the treatment of patients with pT1-2 penile cancer. Conversely, patients with pT3 disease are at high-risk of local failure after PP.

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THE RELATIONSHIP BETWEEN LYMPH-NODE DENSITY AND CANCER-SPECIFIC SURVIVAL IN PATIENTS WITH PENILE CANCER: A SINGLE-INSTITUTIONAL EXPERIENCE

Mario Catanzaro[1], Giovanni Lughezzani[2], Andrea Guttilla[3], Tullio Torelli[1], Silvia Stagni[1], Davide Biasoni[1], Nicola Nicolai[1], Luigi Piva[1], Andrea Necchi[1], Patrizia Giannatempo[1], Daniele Raggi[1], Roberto Salvioni[1]

[1]Urology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano; [2]Department of Urology, Vita-Salute San Raffaele University, Milano; [3]Urology Clinic, Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua, Italy

Introduction: Lymph node density (LND; ratio of positive lymph nodes to the total number removed) emerged as a potential significant predictor of survival in several malignancies. In the current study, we evaluated the association between LND and cancer-specific survival (CSS) in a population of patients with penile cancer and pathologically-determined lymph node metastases. *Methods:* We retrieved data from 90 patients with pathologically-determined lymph node metastases who were surgically treated at our Institution between 1985 and 2012. LND was considered both as a continuously-coded and as a categorically-coded variable. The Mazumdar-Glassman method was used to determine the most significant LND cut-off value. The Kaplan-Meier method was used to determine CSS rates. Univariable and multivariable Cox regression models were fitted to test the predictors of CSS. *Results:* Overall, 28 (31.1%), 36 (40.0%) and 26 (28.9%) patients were respectively diagnosed with pN1, pN2 and pN3 disease and 45 (50.0%) patients had extranodal extension (ENE) of the disease. The median number of positive and removed lymph nodes were 2 (IQR: 1-4) and 22 (IQR: 13-31), respectively. Median LND was 10.6 (IQR: 6.4-17.0). Median follow-up was 27 months (Interquartile range; IQR: 16-61). Estimated five-year CSS rate was 52.5%. In univariable Cox regression models, both continously-coded (HR: 1.02, 95% CI: 1.01-1.03; $p=0.002$) and categorically-coded LND (HR: 4.63; 95% CI: 2.34-9.14; $p<0.001$) were significant predictors of CSS, where the most significant cut-off value of LND was 22. After stratification, 5-year CSS was 65.0 *vs.* 8.4% in patients with LND< *vs.* ≥22, respectively ($p<0.001$). At multivariable Cox regression models, after adjusting for several established prognostic factors, categorically-coded LND emerged as the only independent predictor of CSS (HR: 3.84; 95% CI: 1.64-8.96; $p=0.002$). *Conclusion:* Lymph node density is a powerful predictor of CSS in patients with penile cancer and pathologically-determined

lymph node metastases. Although further investigations are needed to evaluate the relationship between tumour burden and treatment intensity, LND may be of immediate use in clinical practice to better stratify the prognosis of these patients and for further therapy.

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ULTRACONSERVED REGION (UCRS) ENCODING NCRNAS INVOLVEMENT IN BLADDER CANCER TUMORIGENESIS: A NEW(P)LAYER IN THE "DARK MATTER"

Matteo Ferro[1], Vincenzo Altieri[2], Vittorino Montanaro[2], Chiara Scafuro[2], Marco De Sio[3], Michele Olivieri[4], Montano Durso[4], Jens Hansen[5], Felix K.-h Chun[5], Sisto Perdona[6], Umberto Greco[7], Daniela Terracciano[8], Amelia Cimmino[4]

[1]Urologia, Università degli Studi Federico II, Napoli;
[2]Department of Urology, University of Salerno;
[3]Department of Urology, Second University of Naples;
[4]Institute of Genetics and Biophysics, A. Buzzati Traverso" CNR, Naples;
[5]Department of Urology, University Medical Center Hamburg-Eppendorf, Germany;
[6]Department of Urology, IRCCS Fondazione G. Pascale, Napoli;
[7]Department of Urology, OO.RR. S.Giovanni di Dio E Ruggi D'Aragona, Salerno;
[8]Department of Translational Medical Sciences, University of Naples "Federico II", Italy

Introduction: Urothelial carcinoma (UCC) 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 non papillary and often invasive. In the last few years it has been clearly documented, that an important role in human cancerogenesis is also played by non-codingRNAs (ncRNAs). MicroRNAs (miRNAs) are ncRNAs of 19-25 nucleotides in length that regulate gene expression. Initially discovered as regulators of mechanisms involved in cell proliferation and development, miRNAs have been shown to be altered in several human malignancies. MiRNAs (influenced by deregulation or single nucleotide polymorphism) contribute substantially to tumor development and provide an effective biomarker for stratification of bladder tumors. Specific signatures of miRNAs are pathognomonic of specific types of cancers, and sometimes harbor prognostic implications. More recently, we have demonstrated that another class of ncRNAs, called transcribed ultraconserved regions (T-UCRs), is consistently de-regulated in several human tumors. *Background:* The role of T-UCRs in bladder cancer is completely unknown, but we hypothesize that similarly to miRNAs, T-UCRs are de-regulated in bladder cancer and this suggests the existence of an extensive regulatory network on the basis of RNA signaling associated with cancer progression. Moreover, similarly to what has been demonstrated for miRNAs, it is likely that T-UCR transcripts might be detected in the blood and urine of patients, therefore acting as tumor biomarkers, with diagnostic and prognostic implications. Finally, by studying the function of the deregulated T-UCRs in non-invasive and invasive bladder carcinoma cell lines, we will disclose the role of these ncRNAs in bladder carcinogenesis, therefore identifying new biological targets for bladder cancer treatment. *Aim:* To assess whether T-UCRs can be detected and are differentially expressed in noninvasive (RT122) and invasive (J82) bladder cell lines. *Methods:* 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 TUCR transcripts both in sense, and antisense (A) orientation (1, 2). *Results:* We obtained specific signatures of de-regulated T-UCRs. In Table I the lists of the 3 most up-regulated and the 3 most down-regulated T-UCRs in the non-invasive cell line RT112 *versus* the invasive counterpart J82 cell line.

Table I.

Down in RT112/J82	Fold change	Up in RT112/J82	Fold change
uc355A	0.009	uc.388	2.52
uc393	0.016	uc.354	2.419
uc.397	0.012	uc.263	2.393

Conclusion: Given the possible existence of signatures of de-regulated T-UCRs specific for non invasive and invasive cell lines it is possibile to hypothesize that: a) specific signatures of de-regulated T-UCRs identify sub-types of bladder carcinoma with different prognosis; b) these de-regulated T-UCRs have functional implications in bladder carcinogenesis.

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DIFFUSION-WEIGHTED MAGNETIC RESONANCE DIAGNOSIS OF LOCAL RECURRENCES OF PROSTATE CANCER AFTER RADICAL PROSTATECTOMY. PRELIMINARY EVALUATION ON TWENTY-SEVEN CASES

Salvatore Francesco Carbone[1], Luigi Pirtoli[2], Veronica Ricci[1], Tommaso Carfagno[2], Paolo Tini[2], Augusto La Penna[1], Eleonora Cacchiarelli[1], Alice Carboni[1], Luca Volterrani[1]

[1]Diagnostica per Immagini, Dipartimento di Scienze Radiologiche, Università di Siena;
[2]Radioterapia, Dipartimento di Scienze Radiologiche, Università di Siena, Italy

Objective: To assess the diagnostic performance of Diffusion-Weighted MR imaging (DWI) in patients affected by Prostatic Fossa (PF) relapse after Radical Prostatectomy (RP) for Prostatic Carcinoma (PC). *Patients and Methods:* Twenty-seven patients showing a nodular lesion in the PF at T2-weighted MRI after RP, with diagnosis of PC relapse established by biopsy or PSA determinations, were investigated by DWI. Two readers evaluated the DWI results in consensus (hyperintensity absent/present), and the Apparent Diffusion Coefficient (ADC) of the nodules separately; a mean value was obtained (ADCm). *Results:* Relapses did not significantly differ in size in respect of post-surgical alterations. The DWI qualitative evaluation showed sensitivity, specificity, accuracy, ppv, npv values respectively of 83.3%, 88.9%, 85.2%, 93.7% and 72.7% (100%, 87.5%, 95.6%, 93.7% and 100%, for nodules >6 mm). The Intraclass Correlation Coefficient (ICC) for ADC evaluation between the two readers was 0.852 (95% CI 0.661-0.935; p=0.0001). The ADCm values for relapses and benign nodules were respectively $0.98\pm0.21\times10^{-3}$ mm^2/sec and $1.24\pm0.32\times10^{-3}$ mm^2/sec (p=0.006). Sensitivity, specificity, accuracy, ppv and npv of ADCm were respectively 77.8%, 88.9%, 81.8%, 93.3%, 66.7% (93.3%, 87.5%, 85.4%, 93.3%, 87.5% for nodules >6 mm). *Conclusion:* Diffusion-weighted MR imaging is a promising tool, among MRI multi-parametric techniques, in establishing whether a hyper-intense nodule detected by T2-weighted sequences is or not a relapse of PC after RP. This might have a relevant importance in contouring radiotherapy treatment volumes.

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OUTCOME AFTER SALVAGE RADIOTHERAPY FOR PATIENTS WITH PSA RELAPSE FOLLOWING RADICAL PROSTATECTOMY (RP) FOR PROSTATIC CANCER (PC): A SINGLE-CENTER EXPERIENCE

Tommaso Carfagno[1], Paolo Tini[2], Salvatore Francesco Carbone[3], Noemi Palla[2], Veronica Ricci[3], Daniela Grassi[4], Luigi Pirtoli[2]

[1]UOC Radioterapia, Dipartimento di Scienze Radiologiche, Università di Siena;
[2]Radioterapia, Dipartimento di Scienze Radiologiche, Università di Siena;
[3]Diagnostica per Immagini, Dipartimento di Scienze Radiologiche, Università di Siena;
[4]Oncologia Territoriale, Dipartimento di Oncologia, ASL 7, Siena, Italy

Background and Aim: Local failure of PC, consisting of biochemical relapse with or without clinical and imaging evidence, occurs in 10- 53% of the patients undergoing RP within 5 years. Early post-operative radiotherapy is the best choice in presence of local recurrence (LR) risk factors, but in clinical practice many patients are treated with radiotherapy (Salvage Radiotherapy) only at the PSA relapse. The aim of this study was to investigate the prognostic factors and the efficacy of salvage radiotherapy for PSA relapse after radical prostatectomy in our Unit. *Patients and Methods:* Sixty-five relapsing patients treated with Salvage Radiotherapy from June '99 to October '09 in our Radiotherapy Unit were analyzed. Salvage Radiotherapy (SR) was undertaken at biochemical recurrence (without or with imaging evidence of local relapse) defined as 2 consecutive PSA values ≥0.2 ng/ml. Salvage radiotherapy was delivered to the prostatic bed with a conformal technique and with a total dose between 60 and 75 Gy. We analyzed: correlation between biochemical Disease-Free Survival (bDFS) after SR and age at surgery, Gleason Score, pathologic stage, status of surgical margins, pre-radiotherapy PSA level, prescribed total dose, time from RP to biochemical failure. Minimum follow-up time was 36 months after SR. *Results:* The median biochemical disease-free survival after SR was 57.5 months. The median PSA

value at the start of radiotherapy was 2.9 ng/ml (range 0.1-20.9). Multivariate analysis (Cox regression model) showed some significant prognostic factors associated with worse bDFS outcome after SR: high PSA level pre-RT (cut off value < *vs*. >2.5 ng/ml), RT total dose (< *vs*. >70 Gy), high Gleason score (≤ *vs*. >7), pathological stage (< *vs*. >T3a or N+). Among these factors, PSA level pre-RT was the strongest predictor (Hazard ratio 11,56; 95% confidence interval 2.53-33.46 p=0.004). Status of the surgical margins was correlated to pathological stage and time from RP to biochemical failure to PSA pre-RT level. *Discussion and Conclusion:* The most important prognostic factor is PSA level pre-RT in predicting outcome after SR. Patients with lower values at the beginning of RT had a better outcome in terms of local control. The biological factors related to the tumor (Gleason Score and Pathological Stage) impacted on disease relapse with a lower significance compared to the previous point. Beginning RT at early relapse of PSA seems to improve response to treatment. Increasing the number of patients, maybe through multicentric studies, could confirm the validity of these results.

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CORRELATION BETWEEN BMI AND THE PATHOLOGICAL FEATURES OF PROSTATE CANCER AT BIOPSY

Salvatore Scurria, Giovanni Caruana, Enrica Napoli, Salvatore Romeo, Francesco Sommatino, Dario Passalacqua, Carlo Pavone, Vincenzo Serretta

U.O.C. di Urologia, Dipartimento di Discipline Chirurgiche ed Oncologiche, Università degli Studi di Palermo, Italy

Introduction/Aim: Numerous clinical trials investigated the association between obesity and prostate cancer, but they yielded inconsistent results (1). Obesity has been found to be related to prostatic tumors at more advanced stages and higher Gleason grade when compared with normal population (2). An increased number of biopsy cores has been advocated by some Authors in obese and overweight men due to an increased difficulty and delay in cancer detection (3). The main aim of our research was to correlate Body Mass Index (BMI) with the pathological characteristics of prostate cancer at biopsy. *Patients and Methods:* Patients with positive prostate biopsy performed for palpable prostate nodule and/or elevated PSA levels were considered in the present study. A transrectal prostate biopsy procedure, not less than 12 cores, was performed. The number of specimens was increased in case of re-biopsy (18-24 cores or more). After informed consent, a database has been created, including clinical and pathological data: demographics, PSA, digital rectal examination, transrectal ultrasound and prostate cancer features at biopsy. Patients were divided into four categories according to their BMI as follows: 16-19,9 (underweight), 20.0-24.9 (normal weight), 25.0-29.9 (overweight) and ≥30.0 (obese). The statistical analysis was conducted with Fisher's exact test for Gleason pattern 4 (<4 or ≥4) and BMI for single weight class and the Pearson's Chisquared test with Yates' continuity correction for aggregate BMI classes. *Results:* Out of 149 patients diagnosed with prostate cancer, the Gleason score was available for 121 (81.2%), ASAP or PIN were found in 5 more patients (3.4%). Twenty-seven (21.4%) patients had a previous negative biopsy. The median age was 71 years (range 45-86). The median BMI was 26.7 kg/m^2 (range 17.5-37.4). Two patients (1.3%) were underweight, 43 (28,6%) patients had normal weight (median BMI 23), 70 (47%) were overweight (median BMI 26.8) and 34 (22.8%) were obese (median BMI 35.3). Median PSA was 9.5 ng/ml (range 0,41-1339). A prostate nodule was palpable in 45 (30.2%) patients. The median prostate volume was 44.5 cc. A Gleason pattern of 4 or more was evident in 49 (40.5%) patients, while it was not detected in the remaining 72 (59.5%) patients. The presence of Gleason pattern 4 did not result in relation to the class of BMI (p-value=0.9814), neither combining different classes: normal weight and overweight men *versus* obese ones (p-value=0.7696); normal weight *versus* overweight and obese men (p-value=0.9678). *Discussion and Conclusion:* Our study, in contrast with some evidence in literature, did not show any significant correlation between BMI and the presence of Gleason pattern 4. However, the small number of patients did not allow to include in our analysis important factors, such as biological, hormonal, environmental and life-style factors, involved in the pathogenesis of prostate cancer. A larger, prospective, multicenter investigation is on going.

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HISTOLOGICAL CHRONIC PROSTATITIS AT THE FIRST BIOPSY IS NOT ASSOCIATED WITH A LOWER RISK OF PROSTATE CANCER (PCA) AT REPEATED EXTENDED BIOPSY

Stefano De Luca, Paolo Caccia, Andrea Cavallini, Nicola Faraone, Ernesto Giargia, Massimo Pasquale, Maria Sara Squeo, Donato Franco Randone

Divisione di Urologia, Ospedale Gradenigo di Torino, Italy

Introduction: A present, up to two thirds of patients who undergo a prostate biopsy, will have a negative histology since the reason of biopsy is based on serum PSA assessment, a sensitive but unspecific test. Mild or moderate inflammation may be sufficient to alter cellular integrity and cause leakage of PSA into serum. The aim of this study was to evaluate if histological chronic prostatitis at primary biopsy is associated with a lower risk for cancer in men undergone repeated extended biopsy. *Methods:* Through a retrospective search of our prostate biopsy database from January 2009 to January 2013, 289 patients, after a negative primary biopsy (median 12 cores), underwent repeated saturation biopsy by transperineal approach (median 22 cores). 151 (52.2%) patients had a normal parenchyma and benign prostatic hyperplasia (BPH) and 72 (24.9%) had chronic prostatitis pattern (only 2 patients, 2.7%, had history of chronic prostatitis: pelvic and/or perineal pain or discomfort, dysuria, urinary frequency, ejaculatory symptoms at the time of biopsy). Median PSA and abnormal digital rectal examination were equal to 7.1 ng/ml and 1.9% for normal parenchyma/BPH *versus* 7.7 ng/ml and 2.7% for inflammatory pattern. *Results:* PCa detection rate was 21.7% (63/289 pts). of the 63 pts with PCa, 24 pts (38.1%) and 39 pts (61.9%; p=0.008) had a histological diagnosis of normal parenchyma/BPH and chronic prostatitis at the first biopsy, respectively. *Conclusion:* Along with direct trauma (*e.g.* biopsy, cystoscopy), chronic prostatitis is the most common cause (about 10% of all men suffer from the symptoms of prostatitis syndrome) of sudden, marked elevation in serum PSA levels; nevertheless an inflammatory pattern at the first biopsy is not associated with a decrease in PCa incidence at repeated extended biopsy. Accurate clinical evaluation including more parameters (*e.g.* PCA3) could hopefully select men who will really benefit from rebiopsy in the presence of a PSA rising and suspicion of cancer.

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PRELIMINARY DATA ON PSA CHANGES DURING INTRAVESICAL THERAPY FOR NON-MUSCLE INVASIVE BLADDER CANCER

Cristina Scalici Gesolfo[1], Vincenza Alonge[2], Gaetano Chiapparrone[2], Antonio Solazzo[2], Enrica Napoli[2], Francesco Sommatino[2], Marco Vella[2], Vincenzo Serretta[2]

[1]Sezione di Urologia, Dipartimento di Scienze Chirurgiche ed Oncologiche, Università degli Studi di Palermo;
[2]U.o.c. di Urologia, Dipartimento di Discipline Chirurgiche ed Oncologiche, Università degli Studi di Palermo, Italy

Introduction/Aim: Many factors can cause an increase of PSA independently from the presence of prostate cancer . The objective was to evaluate the fluctuation of the serum levels of PSA during adjuvant intravesical chemotherapy or immunotherapy. An increase of PSA due to intravesical BCG and up to 3 months later has been reported (1). *Patients and Methods:* Patients treated with intravesical chemotherapy or immunotherapy for non- muscle invasive bladder cancer (NMI-BC) were entered in the study. Serum samples were collected before starting intravesical therapy, during therapy (within 3rd and 6th instillation) and 30 days after the end of the 6-week induction regimen and during maintenance regimen when given. Patients with urinary tract infections, history of chronic prostatitis, elevated PSA before starting intravesical therapy, palpable prostate nodule or prostate cancer were not included. *Results:* Forty-five patients were studied, 34 receiving chemotherapy and 11 BCG. Thirty-three patients completed the induction regimen and in 12 more patients the research is ongoing. Out of the 33 evaluable patients, 23 received chemotherapy (mitomycin or epirubicin), while 10 immunotherapy (BCG Connaught). The pre-induction PSA mean level was 2.9 ng/ml. We observed a median PSA increase of 33,5% (p<0.0001) during therapy, in 18 (54.5%) patients.

Twelve patients (36.3%) showed a median PSA decrease of 31.4% (p=0.3638). In two patients only (6%) PSA remained unchanged. We also observed a median increase of serum PSA levels of 87.4% at one month after the end of induction regimen. No significant difference between serum PSA level fluctuations induced by chemotherapy or BCG was detected: median increases during therapy and 30 days after the end were 91.7% and 149, 7% and 91.7% and 133% respectively (p<0.001). *Discussion and Conclusion:* Our preliminary study shows a clinically relevant increase of serum PSA levels in men undergoing both adjuvant intravesical BCG or chemotherapy. We confirm the results of the few studies reporting the increase of PSA during intravesical therapy with BCG or chemotherapy (2). The above mentioned variations should be considered when selecting patients undergoing prostate biopsy.

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LEPTIN PLASMA LEVELS IN PATIENTS UNDERGOING PROSTATE BIOPSY. A PRELIMINARY STUDY IN 50 PATIENTS

Salvatore Scurria[1], Giovanni Caruana[1], Nino Dispensa[1], Carlo Pavone[1], Giuseppe Cicero[2], Stefano Caruso[2], Antonio Russo[2], Vincenzo Serretta[1]

[1]U.O.C. di Urologia,
[2]U.o. di Oncologia Medica, Dipartimento di Discipline Chirurgiche ed Oncologiche, Università degli Studi di Palermo, Italy

Introduction/Aim: To reduce the number of negative prostate biopsies and to detect clinical significant prostate tumors in patients with elevated serum PSA represent major challenges in urological oncology. Prostate tumors diagnosed in patients with elevated Body Mass Index (BMI) show higher Gleason score and more aggressive biological behavior than those diagnosed in normal population (1). Elevated plasma levels of leptin and other adipose tissue derived factors (adipokines), are evident in obese men (2). Many studies have investigated the role of leptin as a putative molecular mediator between obesity and prostate cancer with contradictory results. Also in normal or overweight (BMI <30) men, leptin might represent a marker of tumor aggressiveness (3) and a useful tool in selecting patients undergoing prostate biopsy. *Patients and Methods:* Unselected patients undergoing prostate biopsy for palpable prostate nodule and/or elevated PSA levels were entered in the study. A cut-off PSA level of 4 ng/ml was adopted. The plasma levels of leptin were measured by BioPlex immunoassay in 50 patients undergoing prostate biopsy. A 12-core transrectal biopsy was planned. The serum leptin levels were related with the results of the biopsy and the PSA levels. ROC curve analysis was exploited to test the diagnostic accuracy of leptin and PSA by AUC calculation. A potential cut-off level was computed. *Results:* Leptin was evaluated in 50 patients, 15 (30%) after a previous negative biopsy. The median PSA was 6.8 ng/ml. A prostate nodule was palpable in 18 (36%) patients. The median prostate volume was 45 cc. The median number of biopsy cores was 12. Prostate cancer was detected in 25 (50%) and ASAP and PIN in 2 (4%) more patients respectively. At a cut-off value of 2.16 ng/ml, leptin demonstrates a sensitivity of 74% and a specificity of 75%. Sixteen patients (32%) had negative leptin and negative prostate biopsy in spite of elevated PSA and/or palpable nodule. *Discussion and Conclusion:* Leptin in our preliminary experience shows promising diagnostic accuracy for the selection of patients candidate to prostate biopsy. Further and larger studies are needed to confirm our results. Adiponectin should be considered in further research.

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SOLITARY EXTRAMEDULLARY PLASMACYTOMA IN RETROPERITONEUM: A CASE REPORT AND REVIEW OF THE LITERATURE

Stefano De Luca[1], Flavia Botto Micca[2], Renato Parente[2], Paolo Caccia[1], Nicola Faraone[1], Maria Sara Squeo[1], Renato Coda[2], Donato Franco Randone[1]

[1]Divisione di Urologia, Ospedale Gradenigo di Torino;
[2]Servizio di Anatomia Patologica, Ospedale Gradenigo di Torino, Italy

Extramedullary plasmacytoma (EPM), accounting for approximately 3% of all plasma cell neoplasms with a worldwide annual incidence of 3 per 100000 populations,

results from uncontrolled plasma cell proliferation and consists of monoclonal plasmacytic infiltration without bone marrow involvement. EMP is three times more common in male and the median age is 55 years which is around ten years younger than the patients with multiple myeloma. EMP occurs most commonly in the head and neck region, followed by gastrointestinal tract, central nervous system, thyroid, breast, parotid gland, testis and lymph nodes. Solitary EMP rarely occurs in the retroperitoneum and lacks distinctive clinical manifestations. Preoperative CT scanning does not contribute to its differential diagnosis from other tumors. Serum electrophoresis can help its diagnosis by finding the M band. However, in the most of cases, the mass is considered as a common type of tumors, such as sarcoma or schwannoma, before operation. We report a 76-year-old man with a solitary asymptomatic EMP in the retroperitoneum and discuss its clinical features, diagnosis and treatment.

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BIOMARKERS OF UROTHELIAL DAMAGE IN PATIENTS TREATED BY ADJUVANT INTRAVESICAL THERAPY

Gaetano Chiapparrone[1], Vincenza Alonge[1], Stefano Caruso[2], Daniele Fanale[2], Antonio Russo[2], Rosa Maria Giaimo[1], Francesco Sommatino[1], Vincenzo Serretta[1]

[1]U.O.C. di Urologia,
[2]U.o. di Oncologia Medica, Dipartimento di Discipline Chirurgiche ed Oncologiche, Università degli Studi di Palermo, Italy

Introduction/Aim: Chemotherapy or BCG given intravesically to prevent recurrence after transurethral resection (TUR) of non-muscle invasive bladder cancer (NMI-BC) cause frequent, sometime severe, local toxicity. As a consequence, many patients do not complete the planned treatment (1). A major challenge for the urologists is to identify an early biomarker of urothelial damage to recognize and prevent local toxicity improving patient's compliance. The purpose of our research was to investigate the relation between urothelial injury by intravesical treatment and the expression of potential biomarkers in urine and/or in barbotage solution. The urinary HB-EGF expression in interstitial cystitis has been analyzed by a few studies (2, 3). As a preliminary step, the variations of Fibronectin (FN), Epidermal Growth Factor-Receptor (EGF-R) and Heparin-binding Epidermal Growth Factor-like Growth Factor (HB-EGF) during intravesical therapy and after the administration of a solution with the potential role of urothelial repairing (hyaluronic acid and chondroitin sulphate) were investigated. *Patients and Methods:* the toxicity of intravesical therapy with mitomycin, epirubicin or BCG was classified in 3 grades (absent, moderate, severe). Urine and bladder washing solution during intravesical therapy in 55 patients after NMI-BC TUR and in 10 healthy controls for a total of 200 samples were collected. Total cellular RNA was isolated from the cell pellet using miRNeasy Mini Kit (Qiagen®). FN and EGF-R gene expression by Real Time quantitative PCR were analyzed. The expression of HB-EGF was measured in urine samples by ELISA (Abcam®). *Results:* In barbotage samples the FN gene expression and the EGF-R levels in our patients were respectively increased a median of 4.7 fold and decreased of 0.9 fold compared to controls. Before intravesical therapy and in absence of local toxicity, gene expression increased 1.9 fold for FN and 1.1 fold for EGF-R. In contrast, in patients with local toxicity due to intravesical therapy, the FN gene expression levels increased to a median of 5.82 fold, while EGF-R remained unchanged. The administration of hyaluronic acid and chondroitin sulphate solution decreased the mean FN gene expression from 3 to 0.6 fold, with concomitant symptomatic relief. HB-EGF protein median urine levels were 25.7 pg/ml in 13 patients before intravesical therapy and 18.9 pg/ml in 5 healthy controls. No significant variations in relation to the local toxicity. During therapy median HB-EGF protein levels in urine varied from 21.6 pg/ml in absence of toxicity to 25.7 pg/ml in case of severe toxicity to 18.5 pg/ml after hyaluronic acid and chondroitin sulphate solution. Preliminarily, the observed variations of HB-EGF, increasing no more than 1.2 fold compared to healthy controls, do not seem possible marker of urothelial damage. *Discussion and Conclusion:* EGF-R gene and HB-EGF expressions do not seem to vary significantly in relation to local toxicity due to intravesical therapy. FN gene is overexpressed in presence of urothelial damage significantly reduced by intravesical hyaluronic acid and chondroitin sulphate solution administration, according with symptoms relief.

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CULTURAL ADAPTATION OF THE MEMORIAL ANXIETY SCALE FOR PROSTATE CANCER: PRELIMINARY RESULTS

Lara Bellardita[1], Maria Francesca Alvisi[1], Tiziana Magnani[1], Tiziana Rancati[1], Cristina Marenghi[1], Silvia Villa[1], Sergio Villa[2], Roberto Salvioni[3], Riccardo Valdagni[1,2]

[1]Programma Prostata,
[2]Radioterapia Oncologica 1,
[3]Urologia, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Purpose, Objective: The diagnosis and treatment of prostate cancer (PCa) may be associated with psychological distress. Several questionnaires that can be used to assess PCa-related quality of life are available; nonetheless, a PCa- specific anxiety evaluation tool validated for the Italian population is lacking. The Memorial Anxiety Scale for Prostate Cancer (MAX-PC) is a self-report questionnaire developed to assess PCa-related anxiety in English-speaking population (1). MAX-PC has proven to be a valid and reliable tool which can be translated and adapted for use in non-English speaking populations (2). The aim of this study was to present the procedures for cultural adaptation to the Italian population, together with the preliminary results of its psychometric properties, based on study group of patients on Active Surveillance (AS). *Patients and Methods:* Patients with localized PCa who met inclusion criteria for Prostate Cancer Research International: Active Surveillance protocol were recruited. Patients filled out MAX-PC at the time of enrolment in the AS protocol. The questionnaire consisted of 18 items divided into 3 subscales measuring general "PCa anxiety" ("I felt kind of numb when I thought about prostate cancer"), "anxiety related to prostate specific antigen (PSA)" ("I have been so anxious about my PSA test that I have thought about delaying it"), and "fear of recurrence" ("Because cancer is unpredictable, I feel I cannot plan for the future"). The translation of the original English version into Italian followed standard forward-backward procedure: it was translated into Italian by two independent researchers; the two translations were then pooled into a common version. This *interim* version underwent the backward translation by two native English-speaking independent translators. Back translations were finally discussed in a consensus meeting to obtain a definitive Italian version. Psychometric properties were assessed to obtain reliability indexes. Specifically, a) descriptive analyses were performed to detect floor/ceiling effect, b) Cronbach's alpha coefficients were calculated to estimate the internal consistency of the total MAX-PC and the three subscales, c) item to total correlation analyses were conducted to assess subscales internal consistency and identify items to be deleted. *Results:* One hundred and eighteen patients on AS completed all 18 MAX-PC items. Table I reports descriptive scores and distribution. No floor/ceiling effect (defined as more than 15% of respondents having respectively the lowest/highest score) was found except for the "PSA anxiety" subscale (floor effect, 71% of respondents). The Cronbach's alpha coefficients were high for total score (α=0.75, 0.70 is generally considered good internal consistency), as well as for "PCa anxiety" (α=0.80), "fear of recurrence" (α=0.83) and "PSA anxiety" (α=0.95) subscales. The means of item to total correlation coefficients were as follows: "PCa anxiety"=0.66 (range 0.51-0.76), "PSA anxiety"=0.75 (range 0.46-0.90), "fear of recurrence"=0.78 (range 0.75-0.80) (scores below 0.75 suggest deleting the item). *Conclusion:* Strong internal consistency and reliability were found for MAX-PC total score as well as for the specific subscales evaluating PCA, PSA and recurrence-related anxiety which means that all the items contribute to measure the facets of anxiety related to having PCa. Further analyses will include reliability of the questionnaire over time (test re-test correlations), factor analyses and test validation to discriminate PCa specific related anxiety in an Italian population. The validation of the Italian version of MAX-PC could be of interest for physicians

Table I. *MAX-PC total and subscales scores and distribution (N=118).*

	Mean	SD	Median	25th-75th percentile	Possible score range	Observed score range	% Minimum score	% Maximum score
MAX-PC total	12.9	9.1	11.5	6-20	0-54	0-41	4	0
Prostate cancer Anxiety	8.8	6.3	8	4-14	0-33	0-27	10	0
PSA anxiety	0.7	1.4	0	0-1	0-9	0-7	71	0
Fear of recurrence	3.4	2.5	3	1-5	0-12	0-11	13	0

with different background treating PCa. In particular, MAX-PC can be extremely useful in the case of AS, as it specifically measures anxiety related to PCa, to undergoing PSA test (which is repeatedly required to patients in the AS protocols) and to PCa recurrence/progression.

Acknowledgements to Foundations I. Monzino and ProADAMO Onlus.

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HEALTH RELATED QUALITY OF LIFE AND COPING IN PATIENTS ON ACTIVE SURVEILLANCE: TWO YEARS FOLLOW-UP

Lara Bellardita[1], Maria Francesca Alvisi[1], Tiziana Rancati[1], Cristina Marenghi[1], Barbara Avuzzi[2], Sara Morlino[2], Sergio Villa[2], Davide Biasoni[3], Roberto Salvioni[3], Tiziana Magnani[1], Riccardo Valdagni[1,2]

[1]Programma Prostata,
[2]Radioterapia Oncologica 1,
[3]Divisione di Urologia, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Introduction/Aim: Active Surveillance (AS) is receiving increasing consensus as a viable alternative to radical treatment for low risk prostate cancer (PCa) (1). AS aims at reducing overtreatment and the impairment in patients' quality of life (QoL), which may derive from the adverse side effects of radical therapies (commonly, erectile, urinary and bowel dysfunctions). Recent studies highlighted that men on AS reported high levels of health-related changes in QoL (HRQoL) and adjustment to cancer (2). Nonetheless, longer term follow-up is needed as the possibility of decrease in the levels of QoL was highlighted. The aim of this study was to investigate the changes in HRQoL and adjustment to cancer over the first two years on AS. *Patients and Methods:* Between November 2007 and January 2013, 208 patients were included in PRIAS-QoL study and completed questionnaires at enrolment in the AS protocol (T0). Evaluations after 10 months (T1) from diagnostic biopsy, 12 months (after the first re-biopsy- T2) and 24 months (T3) were completed by 156, 109 and 62 patients, respectively. Validated self-report questionnaires assessing QoL were administered, including: a) Functional Assessment of Cancer Therapy – Prostate Version (FACT-P), measuring HRQoL in terms of: physical wellbeing (PWB), social wellbeing (SWB), emotional wellbeing (EWB), functional wellbeing (FWB), and wellbeing related to prostate cancer symptoms (PCS); b) Mini Mental Adjustment to Cancer (Mini-MAC), evaluating the strategies of coping with cancer: fighting spirit (FS), helplessness/hopelessness (HH), fatalism (FAT), anxious preoccupation (AP) and avoidance (AV). Descriptive analyses were performed. Repeated measure analyses of variance were performed to test changes over time and Bonferroni correction was used for pair time comparisons. *Results:* The mean age of study population at T0 was 66.2 years (median 66, range 42-79). Descriptive normalized scores for FACT-P and Mini-MAC are reported in Table I.

Table I.

	T0		T2		T3	
	Mean	SD	Mean	SD	Mean	SD
PWB	3.9	0.3	3.9	0.2	3.9	0.2
SWB	2.9	0.7	2.8	0.6	2.7	0.8
EWB	3.1	0.6	3.3	0.5	3.3	0.4
FWB	2.6	0.7	2.7	0.6	2.7	0.7
PCS	3.3	0.4	3.2	0.4	3.2	0.4

Table II. *Descriptive analyses for FACT-P normalized scores (range 0-4) and Mini-MAC normalized score (range 1-4).*

FS	2.8	0.6	2.7	0.6	2.7	0.6
HH	1.4	0.5	1.3	0.4	1.4	0.4
FAT	2.4	0.7	2.3	0.7	2.2	0.6
AP	1.9	0.6	1.7	0.5	1.8	0.6
AV	2.3	0.8	2.2	0.8	2.1	0.8

Repeated measure analyses of variance showed the following significant changes over time (Figure 1): SWB decreased from T0 to T3 (p=0.001); PCS decreased between T0 and T3 (p=0.014); EWB increased between both T0 and T2 (p=0.016) as well as T0 and T3 (p=0.001). As far as Mini-MAC scores, both AP and AV significantly decreased from T0 and T2 (p=0.0001 and p=0.035, respectively). *Conclusion:* Patients on AS reported high levels of physical and psychological wellbeing throughout the first two years. QoL was not impaired by the idea of living with an untreated cancer. It is particularly interesting that anxious preoccupation, *i.e.* worry about disease progression, decreased over the first year on AS and then remained stable. The decrease in the perception of social wellbeing could be related to the fact that support from family/friends is likely to be higher in the period immediately following the diagnosis.

The increase of PCa-related symptoms is unexpected and needs to be further detailed. Our results are consistent with those of North European and North American studies, thus confirming that the acceptance of AS is highly possible in the Mediterranean culture (3).

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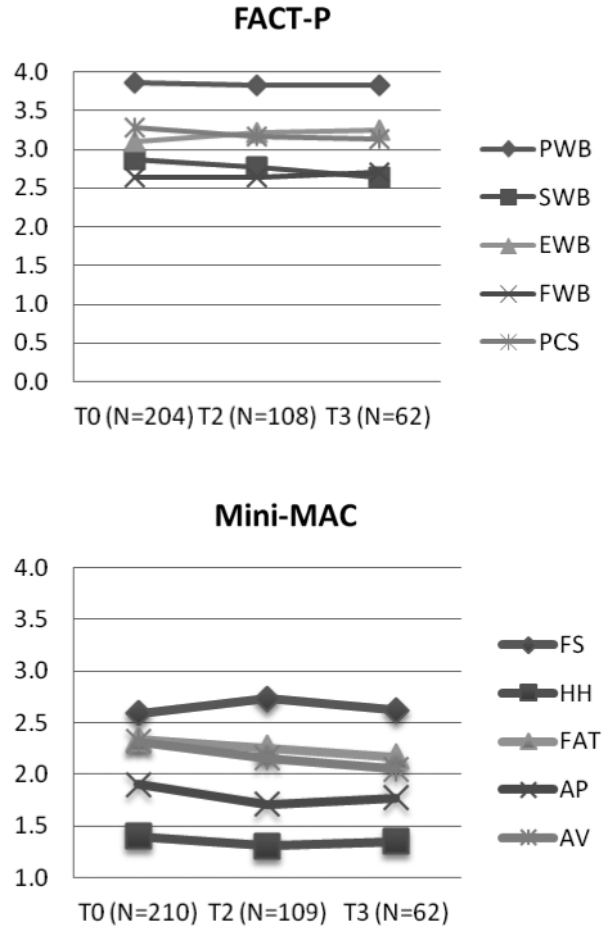

Figure 1. *Changes over the first two years on AS of FACT-P (Health-Related Quality of Life) and Mini-MAC (adjustment to cancer).*

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EFFECTIVENESS OF PROSTATE CANCER CRYOTHERAPY IN PATIENTS WITH CHARLSON COMOBIDITY INDEX AGE ADJUSTED >6: OUR EXPERIENCE

S. Ricciardulli[1], D. Del Biondo[2], A. Celia[2]

[1]Clinica Urologica G. D'Annunzio University Chieti;
[2]S.C Urologia, San Bassiano Hospital, Bassano del Grappa, Italy

Introduction: Cryotherapy has today credited as one of the true alternative therapeutic treatment of localized forms of cancer of the prostate. In 2008, the AUC released its best practices statement on cryosurgery for the treatment of localized prostate cancer. Cryotherapy may be used as a valid alternative for patients with high comorbidity index. The aim of this study is to present a preliminary experience with cryotherapy in patients with prostate cancer and high comorbity index (Charlson Score [CS] >6). *Patients and Methods:* From September 2009 to January 2011, a total of 13 patiens with mean age 76.31 years (Interquartile Range IQR 73.5-78) were treated at our Institute with cryotherapy for prostate cancer. All patients had a CHARLSON COMORBIDITY INDEX AGE ADJUSTED >6 (IQR 6-7). The median Prostate Specific Antigen (PSA) level was 7,32 ng/ml (IQR 4.05-8.75). 15 % of those patients had a pre-treatment clinical stage T1a, 15% had T1b, 8% had T1c ans 62% had T2a. Gleason score was 2+2 for 23% of patients, 3+3 for the 39%, 3+4 for the 23% and 4+3 for the 15%. All 13 patients underwent transrectal ultrasound (TRUS) to evaluate prostate volume. The median prostate volume was 32.8 cc (IQR 26.9-39.3). Cryotherapy was performed with the Galil Medicals Presice. Trans perineal approach was used for the treatment, patients under general anesthesia and in lithotomy position. From 6 to 8 cryoablation needles were inserted (type Iceseed or Icerod) with "free hands" technical TRUS guided, 3 thermal sensor and a warming catheter. Patients were evaluated at 3, 6, 9 and 12 months after the cryotherapy. *Results:* No intraoperative complications were observed. All patients were discharged 24 hours after cryotherapy with a Foley catheter. The catheter was removed 7 days post-treatment. In the early complications (in the first month after cryotherapy) we observed hematuria (1/13), urge incontinence (1/13) and edema of penis and scrotum (1/13). After 12 months 80% of patients had erectile dysfunction, but this pathology was present at the time of diagnosis due to diabetes and cardiovascular disease. After treatment, the median PSA at 3, 6, 9 and 12 months was 0.59, 0.95, 1.46 and 1.36 ng/ml (IQR 0.07-1.4, 0.3-1.8, 0.5-2.4, 0.3-3). During the follow up 1 patient had metastases. *Discussion:* Cryotherapy is a valid therapeutic alternative for treatment of prostate

cancer, specially for patients with high CS. During the follow up, PSA levels remained consistently low in line with the literature. DE is the main complication releted to cryotherapy. However, in patients with pre treatment DE, cryotherapy does not influence the quality of life and is better tolerated than other treatments. Cryotherapy can be used as a first therapeutic approach for those patients who are not suitable for surgery, get a good control of disease and a low impact on quality of life.

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A CASE REPORT OF INCIDENTAL PROSTATIC STROMAL TUMOR OF UNCERTAIN MALIGNANT POTENTIAL (STUMP) IN A YOUNG MAN

Matteo Ferro[1], Antonio D'antonio[2], Umberto Greco[3], Isabella Greco[3], Anna Rega[3], Gianmarco Silvestre[3], Angelo Colucci[3], Chiara Scafuro[3], Luigi Brindisi[3], Francesco Maiorino[3], Vittorino Montanaro[3], Vincenzo Altieri[4]

[1]Urologia, Università degli Studi Federico II, Napoli;
[2]Unit of Pathologic Anatomy and Oncology,
[3]Unit of Urology, AO San Giovanni di Dio e Ruggi D Aragona, Via S Leonardo, Salerno;
[4]Unit of Urology, University of Salerno, Italy

Introduction: Primary sarcoma tumours of the prostate are classified, according to their histology, as stromal tumours of uncertain malignant potential (STUMP) and stromal prostatic sarcoma (1). Malignant proliferations of the specific prostatic stroma are rare tumors, with about 40 documented cases (2, 3). Its clinical behavior and its histological features have been described first by Gaudin *et al*. in 1998 (2). We report a case of a 14 years old boy with a stromal prostatic sarcoma treated by a trans-uretral resection. *Patients and Methods:* A 14 year old boy, suffering from congenital intellectual deficit and hip dysplasia, came to our attention. Anamnesis revealed that the patient had been catheterized following a hip orthopedic surgery and a few days after removal of the catheter had developed dysuria. Symptoms worsened in a few weeks and patient developed urinary retention. Bladder ultrasonography revealed a protruding lesion on the inferior portion of bladder. Patient was catheterized to immediately treat urinary retention, and next day underwent a transurethral resection of the lesion. *Results:* The morphological and immunophenotypic characteristics were those of a sarcoma not rabdo of high degree and allowed diagnosis of a sarcoma of the specialized stroma of the prostate. The immunohistochemical investigations showed the following profile: Desmin, Smooth Muscle Actin, Caldesmon, CD34. Progesterone receptor: positive in 40% of the cells. *Discussion and Conclusion:* The etiology and pathogenesis of STUMP are unknown and no risk factors have been associated with this proliferation. Combination with adenocarcinoma of the prostate has been reported in just a small percentage of cases. Literature data report that 46% of patients with STUMP will develop local recurrence and 5% will progress to PSS. Since there is no definitive treatment guideline for STUMP, further research is required to provide an optimal therapy.

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INCREASING PROSTATE CANCER DETECTION BY A MODEL INCLUDING PROSTATE HEALTH INDEX (PHI) AND PROSTATE CANCER ANTIGEN 3 (PCA3)

Matteo Ferro[1], Ada Marino[2], Liberato Gargiulo[2], Vincenzo Cosimato[2], Claudia Mazzarella[2], Giuseppe Perruolo[2], Dario Bruzzese[3], Daniela Terracciano[2], Amelia Cimmino[4], Chiara Scafuro[5], Federica Mastella[5], Vittorino Montanaro[5], Vincenzo Altieri[6], Sisto Perdonà[7]

[1]Urologia, Università degli Studi Federico II, Napoli;
[2]Department of Translational Medical Sciences, University of Naples "Federico II";
[3]Department of Public Health, University of Naples "Federico II";
[4]Institute of Genetics and Biophysics, CNR, Naples, Italy;

[5]Department of Urology, AO San Giovanni di Dio e Ruggi D Aragona Via S Leonardo, Salerno, Italy;
[6]Department of Urology, University of Salerno, Italy;
[7]Department of Urology, Urology Section, Istituto Nazionale Tumori, Fondazione G. Pascale, Naples, Italy

Objectives: To evaluate the diagnostic performance of prostate health index (phi) and prostate cancer antigen 3 (PCA3) in addition to a model including currently used variables in men undergoing first prostate biopsy for suspicion of PCa. *Patients and Methods:* Two hundred and ninety male subjects were referred to a major oncologic center to undergo their first prostate biopsy. They provided informed consent and were screened to be enrolled in this prospective observational study. One hundred and sixty patients met inclusion criteria: age over 50 years, no prior prostate surgery and biopsy, no bacterial acute or chronic prostatitis, no use of 5-α reductase inhibitors in the previous six months, PSA values between 2 and 20 ng/ml, negative digital rectal examination (DRE), availability of serum and urine samples and corresponding clinical data. PSA molecular forms, phi index (Beckman coulter immunoassay), PCA3 score (Progensa PCA3 assay) and other established biomarkers (tPSA, fPSA and %fPSA) were assessed before patients underwent a 18-core prostate biopsy. The discriminating ability between PCa-negative and PCa-positive biopsies of Beckman Coulter phi [(p2PSA/fPSA)x √tPSA] and PCA3 score [(PCA3 mRNA/PSA mRNA)x 1000] and other established biomarkers were determined. *Results:* Multivariate logistic regression analysis showed that a model including patient age, tPSA, prostate volume and %fPSA along with phi index and PCA3 assays improved the discriminatory abilities of each assay in predicting PCa. Decision curve analysis (DCA) showed that the model-based diagnostic scores may offer a net benefit in the clinical management of patients. *Conclusion:* The ability of currently used variables such as patient age, tPSA, prostate volume and %fPSA to detect a PCa in men undergoing their first prostate biopsy is improved by adding phi and PCA3.

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uCyt+/ImmunoCyt™ AND CYTOLOGY IN THE DETECTION OF UROTHELIAL CARCINOMA: AN UPDATE ON 7,422 ANALYSES

Evi Comploj[1], Christine Mian[2], Andrea Ambrosini-Spaltro[2], Christopher Dechet[1,3], Salvatore Palermo[1], Emanuela Trenti[1], Michele Lodde[1], Wolfgang Horninger[4], Armin Pycha[1]

[1]Reparto di Urologia,
[2]Reparto di Istopatologia, Ospedale Centrale Bolzano; Bolzano, Italy;
[3]Division of Urology, University of Utah, Salt Lake City, Utah, USA;
[4]Reparto di Urologia, University of Innsbruck, Innsbruck, Austria

Aim: To report the results of 7,422 uCyt+/ImmunoCyt and cytology analyses, performed over 9 years at our institution for the evaluation and follow-up for patients with urothelial carcinoma. *Methods:* From January 2002 until March 2011, 2,217 patients (mean age, 69.5 years; range 15-99 years) were enrolled in this study. All patients seen in our department for the follow-up of bladder and/or upper tract urothelial cancer as well as a history suspicious for bladder cancer were recruited. In all patients, a voided urinary cytology and uCyt+/ImmunoCyt test was performed. Patients underwent routine cystoscopy as well as cystoscopy when cytology and/or uCyt+/ImmunoCyt test yielded positive results. Cystoscopically discovered lesions were biopsied and removed transurethrally. Altogether, 7,422 uCyt+/ ImmunoCyt and cytology analyses were performed. *Results:* of 7,422 uCyt+/ImmunoCyt tests and cytologies, 7,075 (95.3%) were considered adequate. A total of 578 patients (with 1,156 analyses) underwent biopsy and 728 (63%) samples had a histologically proven urothelial carcinoma. Overall sensitivity was 34.5% for cytology, 68.1% for uCyt+/ImmunoCyt and 72.8% for the two tests combined. Overall specificity was 97.9% for cytology, 72.3% for uCyt+/ImmunoCyt, and 71.9% combined. Cytology and uCyt+/ImmunoCyt test together had an overall sensitivity of 72.8%, with 59% for G1, 77% for G2, and 90% for G3 tumors. *Conclusion:* On the basis of our 9 year experience we confirm the value of the uCyt+/ImmunoCyt and cytology in the follow-up of non muscle invasive urothelial cancer. This could potentially reduce the number and cost of routine cystoscopic examinations in patients followed-up for bladder carcinoma.

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BLADDER INFLAMMATORY MYOFIBROBLASTIC TUMOR IN A YOUNG GIRL: A CASE REPORT

Matteo Ferro[1], Federica Mastella[2], Angelo Colucci[2], Francesco Maiorino[2], Chiara Scafuro[2], Luigi Brindisi[2], Anna Rega[2], Gaetano Savoia[2], Vincenzo Altieri[3], Isabella Greco[2], Umberto Greco[2]

[1]Urologia, Università degli Studi Federico II, Napoli;
[2]Department of Urology, AO San Giovanni di Dio e Ruggi D Aragona, Via S Leonardo, Salerno;
[3]Department of Urology, University of Salerno, Italy

Introduction: Inflammatory myofibroblastic tumor (IMTs) is a rare spindle tumor that appears preferentially in the visceral tissues of children and adolescents. There are not currently evidences about the malignant potential of these tumors, which appear to show a preference for local recurrence, with a lower risk of distant metastases (1). We report a case of a 19 years old girl with an IMT of the bladder treated by a bladder preserving approach. *Patients and Methods:* A 19-year-old girl presented to our hospital with painless macrohematuria and anemia. The girl executed bladder ultrasonography and abdominal and pelvis computer tomography which revealed an about 8-cm protruding sessile lesion on the front portion of superior bladder wall. The patient had a transurethral resection of the lesion. *Results:* Histopatological examination revealed inflammatory myofibroblastic tumor. Following scintigraphy was negative. Intraoperative evaluation of the malignancy extension has highlighted the possibility of a conservative approach, according to the encouraging results reported in the literature (2). Patient underwent a partial cystectomy. *Discussion and Conclusion:* Considering the short duration of follow-up available in the literature we cannot know the medium and long term prognosis. Moreover, the expression of anaplastic lymphoma kinase (ALK) seems to be a marker of malignant potential a clinic control for evaluation of local and distant recurrences was planned (2, 3).

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COMPARISON OF PROSTATE HEALTH INDEX, URINARY PCA3 ASSAY AND % FREE PSA IN PREDICTING PROSTATE CANCER AT FIRST BIOPSY

Stefano De Luca[1], Adele Parziale[2], Paolo Caccia[1], Andrea Cavallini[1], Nicola Faraone[1], Ernesto Giargia[1], Massimo Pasquale[1], Maria Sara Squeo[1], Angela Milillo[2], Donato Franco Randone[1]

[1]Divisione di Urologia,
[2]Laboratorio Analisi, Ospedale Gradenigo di Torino, Italy

Introduction: New biomarkers are required in order to avoid unnecessary prostatic biopsies. Prostate Health Index (PHI) and Prostate Cancer gene3 (PCA3) have been shown to improve the prediction of prostate cancer (PCa) in men undergoing first and/or repeat prostate biopsy (PBx). The aim of this study was to evaluate the diagnostic accuracy of PCA3, PHI and %fPSA in a cohort of patients candidates to initial PBx. *Materials and Methods:* the performance characteristics of Beckman-Coulter PHI, using the formula (p2PSA/free PSA) x √total PSA) and Progensa PCA3, calculated as PCA3 mRNA/PSA mRNA x 1000, were evaluated in a prospective cohort of 107 consecutive men undergoing first PBx between October 2011 and December 2012. Patients underwent ambulatory transperineal ultrasound guided PBx according to a standardized institutional scheme, which consisted of at least 12-16 biopsy cores taken from prostate gland. Specimens were processed and evaluated by a single experienced genitourinary pathologist. Univariable logistic regression analysis tested the ability of the three biomarkers in predicting PCa in the initial setting and their accuracy was identified using the Area Under the Curve of the Receiver Operating Characteristic analysis. *Results:* 33 of 107 biopsies (30.8%) were positive for cancer. Sensitivity, specificity, positive and negative predictive value (PPV and NPV), AUC of PHI, PCA3 and %fPSA are reported in the Table I.

Table I.

	PHI	PCA3	%fPSA
Sensitivity (%)	69.7	56.6	64
Specificity (%)	55.7	46.4	21.2
VPP (%)	77.2	36.1	30.1
VPN (%)	46	66.6	52.6
AUC	0.675	0.565	0.661

Overall, PHI accuracy in predicting PCa was significantly higher (67.5%) than PCA3% and free PSA. PHI was the only statistically significant predictor of PCa at univariate analysis (OR 2.90, p 0.020). *Conclusion:* Recent studies have shown that p2PSA and its derivatives, namely, percentage of p2PSA

to free PSA (%p2PSA) and PHI improve the accuracy of total PSA and %fPSA in predicting the presence of PCa. On the other hand, PCA3 has proven to be superior to PSA and %fPSA in the early detection of PCa. In our experience PHI seems to be the strongest parameter to predict PBx outcome in the initial PBx setting.

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ROLE OF "REPEAT SATURATION BIOPSY" IN MANAGEMENT OF HIGH-RISK PROSTATE CANCER. WHO IS THE RIGHT PATIENT?

Giandavide Cova, Francesco Beniamin, Claudio Lamon, Luigino Maccatrozzo

Divisione di Urologia, Ospedale Ca'Foncello Treviso, Italy

Introduction: The management of patients with persistent clinical suspicion of prostate cancer after repeat prostate biopsies still remains a dilemma. The purpose of this study is to evaluate data from patients who underwent a second saturation biopsy in order to find reliable predictors able to define the "right patient" suitable for a further diagnostic invasive deepening and to minimize unnecessary and uncomfortable biopsies. *Patients and Methods:* We collected retrospectively the clinical and pathological records of 119 consecutive men with persistent high degree of suspicion of prostate cancer (from DRE, PSA or suspicious pathologic findings at previous prostatic biopsies) who underwent a second saturation biopsy at our Institution from December 2005 to December 2011. Each patient underwent a 8 or 10 core initial biopsy template and a first saturation biopsy (24 cores). We performed ultrasound-guided transrectal needle biopsies with periprostatic nerve block. We considered, for each patient, the following parameters: age, familiarity, DRE, prostate volume on TRUS, PSA values, histological findings of every biopsy set and timing. According to histological findings of the last biopsy, patients were divided into two groups: presence or absence of prostatic cancer. Wilcoxon test was performed to compare variables. A logistic regression model was used for the multivariate analisys. *Results:* Prostate cancer was found in 28 patients (24%). All cancers were clinically significant according to Epstein criteria. 24 patients underwent retropubic radical prostatectomy (pathological stage was T0 in 1 patient, T2 Gleason score 7 in 16 patients and T3 Gleason score 7 in 7 patients). Univariate analysis showed that only the presence of ASAP in any set differed significantly between the prostate cancer and non-cancer groups (p=0.037). Multivariate analysis found no useful data due to limited number of patients examined; there seems to be an interesting correlation between prostate volume > 50 cc and decreased risk of presence of prostate cancer. *Discussion and Conclusion:* The management of patients at risk for prostate cancer is still controversial and the possibility of overdiagnosis and consequent overtreatment is high. At this time there is no answer to the question "who is the right patient?". Previous ASAP is an important risk factor but other studies are necessary to confirm this data. The only conclusion we could take is that a single negative sat- uration biopsy does not exclude the possibility of harbouring prostate cancer in high risk patient. The introduction in clinical practice of assay like PCA-3 test could identify patients in which repeat saturation biopsy may be useful and the use of MRI, MR/US fusion technique or multiparametric TRUS could facilitate more precise sampling of suspicious prostatic areas.

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SUBCELLULAR LOCALIZATION OF ANDROGEN RECEPTOR AND HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN K IN RESPONSE TO DIFFERENT ANTI-ANDROGENS

Paola Barboro, Luana Borzì, Cecilia Balbi

S.s. Traslazionale Urologica, IRCCS Azienda Ospedaliera, Universitaria San Martino, IST-Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy

Introduction: The androgen receptor (AR) plays a central role in development and progression of prostate cancer (PCa) and anti-androgen therapy, in combination with surgical or

medical castration, is the treatment routinely employed. Two structurally distinct anti-androgens are in common use: steroidal and non-steroidal. In both cases, initially androgen deprivation leads to remission of tumor but after a few years of treatment the majority of patients progress developing androgen independent PCa, a lethal form because there are no therapies against. Little is known about how androgens exert their effects and the mechanisms responsible for emergence of the androgen independent phenotype. AR drive gene transcription recruiting a large number of coactivator/co-repressor complexes and it has recently been demonstrated that the heterogeneous nuclear ribonucleoprotein K (hnRNP K) directly interacts with and regulates the AR translational apparatus (1, 2). Besides, an increase in the phosphorylation state of hnRNP K into the nuclear matrix (NM) is strongly associated with a worse prognosis (3). In this study we have examined the distribution into different subcellular compartments of AR and hnRNP K in the response to treatment of LNCaP cells with anti-androgens. The elucidation of the mechanisms underlying the repression of AR may provide a basis to understand the conversion of an initially androgen-dependent to androgen independent cancer. *Materials and Methods:* LNCaP cells were cultured in monolayer in the presence of 0.1 nM 5-αdihydrosterone and incubated for 48 or 72 h with steroidal anti-androgen cyproterone acetate (CPA) or non-steroidal bicalutamide (BIC). Modulation and compartmentalization of AR and hnRNP K were studied in cytoplasm, nucleus and NM by Western blot analysis. The NM localization of the two proteins was also evaluated by confocal laser scanning microscopy. Phosphate-affinity two-dimensional gel electrophoresis was employed to examine how anti-androgens modify the different phosphorylated forms of hnRNP K. *Results:* 10-6M CPA stimulated significantly ($p<0.01$) LNCaP proliferation whereas for 10-4M CPA or 10-5M BIC only the 75% of cells were vital indicating that at these concentrations the two drugs have the same antagonistic effect. After anti-androgen treatments, AR was always remarkably repressed within both the cytoplasm and the nucleus but when CPA had agonist activity (10^{-6}M) the AR associated with the NM was increased of about 2.5 times with respect to control cells. This increase was synchronous with a higher intracellular PSA expression level, indicating that the NM-associated AR may represent the active complex. After BIC treatment the expression of the hnRNP K was significantly lower within the NM (from 1.14 to 0.73, $p<0.05$) in agreement with our previous results (2), whereas no effect was detectable at 10^{-6}M CPA. In the cells treated with 10^{-4}M CPA a strong decrease of the protein expression in all cellular compartments was observed. Images obtained by confocal microscopy were in complete agreement with the Western blot results. The phosphorylation of hnRNP K is believed to play a pivotal role both in signal transduction and in PCa progression (3), therefore, its isoforms may be modulated by the different treatments. 10^{-6}M CPA determined an increase of the phosphorylation of the protein, in particular the isoforms 2 and 3 whereas after treatment with 10^{-5}M BIC a dephosphorylation of the isoforms 1 and 2 occurred. *Conclusion:* These findings demonstrate that, at least *in vitro*, whereas there is no relationship between AR content and cellular growth, there is a strong relationship between NM-associated AR and both cell vitality and PSA level indicating that AR transcriptional activity is critically dependent on its subnuclear localization. Moreover, the agonistic/antagonistic activity of antiandrogens is associated with modifications in the phosphorylation status of hnRNP K suggesting an involvement of this protein in the development of the androgen independent phenotype.

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COMPLIANCE WITH ONE YEAR MAINTENANCE INTRAVESICAL BCG IN PATIENTS AFFECTED BY T1G3 BLADDER CANCER

Gaetano Chiapparrone, Cristina Scalici Gesolfo, Antonio Solazzo, Francesco D'amato, Rosa Maria Giaimo, Giuseppe Mastrocinque, Salvatore Scurria, Vincenzo Serretta

U.O.C. di Urologia, Dipartimento di Discipline Chirurgiche ed Oncologiche, Università degli Studi di Palermo, Italy

Introduction: BCG maintenance for at least one year is the best regimen for prevention of recurrence and progression in high risk non muscle invasive bladder cancer (NMIBC), undergoing conservative approach. Noteworthy, a relevant number of patients do not complete the planned treatment interruption. Study aim was to analyze retrospectively the reasons of treatment. *Patients and Methods:* Consecutive patients affected by T1G3 BC, undergoing BCG maintenance for one year, according to the SWOG schedule (3 weekly instillations at 3, 6, 12 months) were included in this study. Connaught BCG (81 mg/50 ml) was given starting 1430 days after TUR. If toxicity occurred, treatment was postponed up to two weeks. No dose reduction was considered. The patients' compliance with the treatment was analyzed. *Results:* Out of 160 patients, 148 (92.5%) completed the induction cycle. In 10 (6.3%) more patients a recurrence was detected. In 15 (9.4%) patients induction only was planned due to personal difficulties. In 123 patients (76.8%) maintenance for one year was planned. However, 8 patients never started and

67 (54.4%) completed only one year maintenance: 6 (4.8%) interrupted for toxicity and 9 (7,3%) for recurrence. Compliance decreased from 84.5% at 3 to 57,7% at 12 months, 56 (45.6%) patients not completing one-year. In particular 109 patients (83.8%) completed the maintenance at 3 and 88 (67.2%) at 6 months. Noteworthy, mild grade I BCG toxicity, not requiring therapy on urologists' opinion, was recorded in 91 (74%) out of 123 patients in whom maintenance was planned. Main limit was the retrospective nature of the study. *Conclusion:* Maintenance interruption was due to moderate-severe toxicity in only 5% of the patients. The poor patient's compliance was probably multifactorial, partially related to grade I toxicity, not taken into appropriate account by the urologists. A correct and periodical counselling with the patients undergoing BCG maintenance regimen could ameliorate the compliance to BCG (1, 2, 3).

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SERUM LEVELS OF 17-β-ESTRADIOL ARE NOT PREDICTIVE OF PROSTATE CANCER DIAGNOSIS AND AGGRESSIVENESS

Cosimo De Nunzio[1], Riccardo Lombardo[2], Fabiana Cancrini[2], Costantino Leonardo[3], Mauro Gacci[4], Giorgio Franco[3], Fabrizio Presicce[2], Matteo Bonetto[2], Andrea Tubaro[2]

[1]U.O.C Urologia, Ospedale Sant Andrea, Roma;
[2]Department of Urology, Ospedale Sant'Andrea Roma;
[3]Department of Urology, Policlinico Umberto Primo Roma;
[4]Department of Urology, Ospedale Careggi Firenze, Italy

Introduction: The use and identification of new prostate cancer (PCa) biomarkers would help urologists in decision making and in the development of normograms with the aim of better identifying patients at risk of PCa and particularly high grade PCa, therefore overcoming the well known limitation of PSA. The aim of our study was to evaluate the relationship between serum levels of 17-beta-estradiol(17BE) and prostate cancer in a group of patients undergoing transrectal prostate biopsies in order to identify a possible relationship. *Patients and Methods:* After an Internal Review Board approval, between 2006 and 2012, a consecutive series of patients with no known history of PCa were referred to our department to undergo initial prostate biopsy because of an abnormal finding on digital rectal examination (DRE) and/or an elevation of serum levels of PSA (>4 ng/ml). Patients with uncontrolled diabetes, thyroid disease, hyperprolactinemia, hypoalbuminemia or liver disease were excluded from our cohort. Before biopsy, general data from the patient, digital rectal examination (DRE) and Body Mass Index (BMI) were recorded. Blood samples were collected before biopsy and tested for total PSA levels and 17-BE. The risk of detecting cancer and high grade cancer was assessed as a function of 17BE using crude and adjusted logistic regressions. *Results:* Overall 894 patients were prospectively enrolled, median age was 67 (IQR: 62/73) years, median BMI was 27 (IQR: 25/29.4) kg/m^2; median PSA was 6.2 (IQR: 4.4/9.3) ng/ml, median 17BE serum level was 24 (IQR: 18/31) pg/ml. Overall 216/894 (24%) patients presented a positive DRE. Overall 355/894 (39.7%) patients presented PCa on biopsy and out of them 184/355 (51%) presented high grade PCa (Gleason score≥7). Patients with PCa were significantly older (p=0.001) and presented a higher PSA (p=0.000) when compared to patients with a negative biopsy. No significant differences were observed in terms of BMI and 17BE levels. Age (OR 1.046; 95% CI 1.025-1.068 p=0.000), PSA(OR 1.069; 95% CI 1.041-1.097 p=0.000) and DRE(OR 2.811; 95% CI 1.97-3.99 p=0.000) were found to be independent predictors of prostate cancer risk. Patients with high grade disease when compared to patients with low grade disease were significantly older (p=0.001), presented a higher PSA (p=0.000) and higher BMI (p=0.010) while no difference was found in terms of 17BE levels (p=0.353). Age (OR 1.047; 95% CI 1.013-1.083 p=0.007), PSA (OR 1.075; 95% CI 1.034-1.118 p=0.000), DRE (OR 3.041; 95% CI 1.789-4.293 p=0.000) and BMI (OR 1.070; 95% CI 1.010-1.149 p=0.040) were found to be independent predictors of high grade disease. *Conclusion:* In our cohort of patients, serum levels of 17BE were not predictive of PCa or high grade disease. In patients with PCa, 17-β-estradiol should not be considered as reliable marker to predict poorly differentiated PCa in the setting of initial prostate biopsy.

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THE USE OF HORMONAL THERAPY IN LOW-RISK PROSTATE CANCER: OUR EXPERIENCE

Girolamo Spagnoletti, Maria Enfasi, Giorgia Cocco, Grazia Nardella, Vincenzo Oriolo, Angela Pia Solazzo, Ramon Gimenez De Lorenzo, Rita Marchese, Giuseppe Bove

Struttura Complessa di Radioterapia, Azienda Ospedaliero-universitaria Ospedali Riuniti Foggia, Italy;

Background: Treatment of low-risk prostate adenocarcinomas remains a challenge for both urologists and radiation oncologists.The current main modalities are radical prostatectomy, radiation therapy (RT) and active surveillance. Hormonal therapy (HT), which had mainly been indicated for treatment of patients with distant metastases, has been added to RT to improve the efficacy of treatment. However, the role of HT remains unclear in this subset of patients. Although the majority of guidelines and published studies do not suggest the use of HT in low-risk patients, several studies have shown better outcome following combined RT and HT in patients with low and intermediate risk. No randomized trial has been designed specifically for low-risk disease to compare HT plus RT with RT alone in these patients. Therefore, there are still doubts about the use of HT in the daily clinical practice. This analysis evaluates our experience in the clinical use of HT combined with RT in low-risk prostate cancer. *Patients and Methods:* We retrospectively analyzed 95 patients with low-risk prostate cancer (cT1T2a, PSA <10 ng/ml and Gleason score ≤6) treated with radical RT with or without HT from October 2006 to February 2012. Median age was 74 years (range: 54-83). All patients underwent biopsy with histologically proven prostate adenocarcinomas and they all were treated with a median dose of 76 Gy (2 Gy/die). When prescribed, HT started between one and three months before RT, continued during the entire RT course and it was interrupted between three and eighteen months after the end of RT. *Results:* Median and minimum follow-up were 47 months and 12 months, respectively. Median pretreatment PSA was 6.7 ng/mL (range: 4.2-10) and median Gleason score was 6 (range: 3-6). HT was prescribed for 67.4% of patients of whom 31 patients (48.4%) received total androgen deprivation, 25 patients (39.1%) received bicalutamide alone (150 mg/die) and 8 patients (12.5%) received LH-RH analogue alone. Most patients reported at least one of the following side effects: sexual dysfunction, gynecomastia, anemia, fatigue, muscular pain and hot flashes. *Discussion and Conclusion:* Interest has been increasing in the use of HT combined with RT in the management of localized prostate cancer. Preclinical studies have provided some rationale for the use of this combination. As regards low-risk disease, RT alone should be considered the treatment of choice. Nevertheless, there are still many inconsistencies in the daily clinical practice regarding the use, the type and the duration of HT in this subgroup of patients. In United States the number of patients with favourable low-risk disease receiving HT is growing. Our analysis confirms that many patients with low-risk prostate cancer receive HT also in Italian daily practice. Overall, low-risk patients are characterized by excellent long-term outcomes regardless of treatment option and the association of RT and HT could be an overtreatment. Side-effects should be taken into account as well. On the other hand, the combined approach could lead to a therapeutic advantage even in low-risk disease because of cytoreduction. The results of randomized trials will hopefully provide more definitive answers.

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SERUM LEVELS OF SEX-HORMONE BINDING GLOBULIN ARE NOT PREDICTIVE OF PROSTATE CANCER DIAGNOSIS AND AGGRESSIVENESS

Cosimo De Nunzio[1], Riccardo Lombardo[2], Fabiana Cancrini[2], Fabrizio Presicce[2], Mirco Leo[2], Aldo Brassetti[2], Michela Cerasini[3], Andrea Tubaro[2]

[1]U.O.C Urologia,
[2]Department of Urology,
[3]Clinica Urologica, Ospedale Sant'Andrea, Roma, Italy

Introduction: Prostate cancer diagnosis remains imperfect, limited by over detection of indolent tumors and under detection of clinically relevant cancers. The aim of our study was to explore the association between serum levels of Sex Hormone Binding Globulin and the risk of developing prostate cancer (PCa) as well as high grade disease in men undergoing prostate biopsy. *Patients and Methods:* After an Internal Review Board approval, between 2008 and 2012, a consecutive series of patients with no known history of PCa were referred to our department to undergo initial prostate biopsy because of an abnormal finding on digital rectal examination (DRE) and/or an elevation of serum levels of PSA (>4 ng/ml). Patients with uncontrolled diabetes, thyroid disease, hyperprolactinemia,

hypoalbuminemia or liver disease were excluded from our cohort. Before biopsy, general data from the patient, digital rectal examination (DRE) and BMI were recorded. Blood samples were collected before biopsy and tested for total PSA levels and SHBG. The risk of detecting cancer and high grade cancer was assessed as a function of SHBG using crude and adjusted logistic regressions. *Results:* Overall 740 patients were prospectively enrolled, median age was 70 (IQR: 64/75) years, median BMI was 27.3 (IQR:24.9/29.8) kg/m^2; median PSA was 6.2 (IQR: 4.8/12.3) ng/ml, median SHBG level was 38.6 (IQR: 29.5/49.5) pg/ml .Overall 275/740 (37.2%) presented PCa on biopsy and out of them 120/275 (44%) presented high grade PCa (Gleason score≥7). Patients with PCa were significantly older (p=0.000), presented a higher PSA (p=0.000) when compared to patients with a negative biopsy. No significant differences were observed in terms of BMI and SHBG levels. Age (OR 1.028; p=0.022), PSA(OR 1.076; p=0.000) and DRE (OR 3.321; p=0.000) were found to be independent predictors of prostate cancer risk. Patients with high grade disease were significantly older (p=0.000), presented a higher PSA (p=0.035) and higher BMI (p=0.021) while no difference was found in terms of SHBG levels. Age (OR 1.051; p=0.014), PSA(OR 1.067; p=0.000), DRE (OR 2.435; p=0.000) and BMI (OR 1.051; p=0.025) were found to be independent predictors of high grade disease. *Conclusion:* In our cohort of patients, serum levels of SHBG were not predictive of PCa or high grade disease. SHBG should not be considered as a biomarker for PCa diagnosis neither as a marker for high grade disease.

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

Cosimo De Nunzio[1], Riccardo Lombardo[2], Luca Cindolo[3], Fabiana Cancrini[2], Costantino Leonardo[4], Silvia Massimiani[4], Lorenzo Marini[4], Giovanni Giordano[4], Federica Puccini[2], Francesco Pellegrini[3], Ana Ludy Lopes Mendez[2], Andrea Tubaro[2]

[1]U.O.C Urologia,
[2]Department of Urology, Ospedale Sant'Andrea, Roma;
[3]Department of Urology, Ospedale Padre Pio da Pietralcina Vasto;
[4]Clinica Urologica, Ospedale Sant'Andrea, Roma, Italy

Introduction: 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 in a consecutive series of men undergoing prostate biopsy. *Patients and Methods:* From 2011 onwards, a consecutive series of patients 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 and trygliceridemia levels. Blood pressure was recorded. Metabolic syndrome (MetS) was defined according to the Adult Treatment panel III. PASE questionnaire was collected before the biopsy. Statistical analysis was made using the Pearson correlation coefficient and logistic regression for multivariate analysis. *Results:* 296 patients were enrolled with a median age and PSA of 67 (IQR 61/73) years and 6.9 ng/ml (IQR 5/9.6) respectively. Median BMI was 26.5 kg/m^2 (IQR: 24.7/28.7); median waist circumference was 100 cm (IQR: 100/108). Overall 60 pts (20%) presented a Metabolic syndrome. One-hundred and eight patients (36.5%) had prostate cancer on biopsy. Patients with PCa presented a higher PSA (7.6 ng/ml, IQR: 5.3/14 *vs*. 6.5 ng/ml, IQR4.8/8; p=0.001) and a lower PASE score (103, IQR: 68/165 *vs*. 131, IQR 93/201; p=0.001). No association between PCa and MetS was observed (p=0.337). PASE score inversely correlated with waist circumference (σ: –0.179; p=0.0172) and Age (σ: –0.213; p=0.001). On multivariate analysis PASE (OR: 0.996 per unit, 95%CI: 0.992-0.999; p=0.003) and PSA (1.073 per unit 95%CI: 1.023-1.123, p=0.04) were respectively an inverse and direct independent risk factor for prostate cancer diagnosis. *Conclusion:* In our single center study, an increased physical activity evaluated by the PASE questionnaire was associated with a reduced risk of prostate cancer on biopsy, however, these results should be confirmed in a larger multicenter study. Even though the molecular pathways are yet to be understood, it is assumable that a decreased physical activity and the associated metabolic abnormalities should be considered as possible factors involved in prostate cancer pathogenesis.

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MRI/TRUS FUSION AGAINST MD ANDERSON PROTOCOL AGAINST TRANSPERINEAL SECTOR PROSTATE BIOPSIES: A COMPARATIVE STUDY

Riccardo Lombardo, Andrea Cantiani, Francesco Esperto, Christof Kastner

Department of Urology, Addenbrooke S Hospital Cambridge, UK

Objectives: Biopsy detection of prostate cancer remains imperfect, limited by over-detection of indolent tumors and under-detection of clinically relevant cancers. The aim of this study was to compare differences in terms of detection rate and efficacy between TP biopsies, MDA biopsies and TRUS/FUSION biopsies in patients with previous biopsies still at risk of prostate cancer. *Patients and Methods:* A consecutive series of patients with previous negative biopsies were analysed. Patients needed rebiopsy either because of rising PSA, suspicious changes in the previous biopsy, abnormal DRE or combination of these. Patients underwent either transperineal sector biopsies, MD Anderson prostate biopsies or MRI/TRUS fusion biopsies. The MD Anderson (MDA) protocol biopsy which involves transrectal sampling of both peripheral and transitional zones, zonal transperineal template (TPT) biopsy which offers the advantage of more comprehensive access to the prostate. Patients that underwent TRUS/fusion transperineal targeted biopsies, underwent a 3T MRI prior to the biopsy, lesions on the MRI were contoured and the image was fused to a live transrectal ultrasound image in order to biopsy the lesions. In addition, standard sector biopsies were taken. Low grade disease was defined as Gleason 7 (3+4) or lower and high grade disease was defined as Gleason score 7 (4+3) or higher. Statistical analysis was made using SPSS 16 software with chi-square correlation test for univariate analysis and binary logistic regression for multivariate analysis. *Results:* 738 patients were recorded retrospectively in 2 centers. 188 patients underwent transperineal (TPT) sector biopsies, 349 underwent MDA protocol biopsies and 201 underwent MRI/TRUS fusion biopsies. Mean age was 65±7 years, mean PSA was 12.21±10.6 and mean volume was 58±29. No differences between groups were found in these terms. Detection rate of cancer in the TPT group was 79/188 (42%), in the MDA group was 106/243 (30%) and in the TRUS/FUSION group was 107/201 (53%) (p=0.000). Detection rate of high grade disease was found to be respectively 20/79 (25%) in the MDA group, 22/106 (21%) and 40/107 (37%) in the TRUS/FUSION group (p=0.031). *Conclusion:* From our experience MRI/TRUS fusion should be preferred to MDA or TPT in order to improve not only detection rate of tumours but also of high grade disease. Cost/effectiveness studies are required to validate other aspects of MRI/TRUS fusion biopsies.

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THE IMPACT OF SERUM LEPTIN AS BIOMARKER OF PROSTATE CANCER INCREASES WITH AGEING

Adriano Angelucci[1], Patrizia Sanità[1], Simona Delle Monache[1], Carlo Vicentini[2], Mauro Bologna[2]

[1]Dipartimento di Scienze Cliniche Applicate e Biotecnologiche,
[2]Dipartimento di Medicina Clinica, Sanità Pubblica, Scienze Della Vita e dell'ambiente, Università degli Studi dell'Aquila, Italy

Introduction: Obesity prevalence is growing progressively worldwide in the entire population and also in aged subjects: this phenomenon will have an ever growing impact on the future health management. Obesity and ageing are independent risk factors for chronic diseases, including cardiovascular illnesses and several types of cancer. Visceral fat accumulation and ageing have in common the deregulation of adipose tissue homeostasis, resulting in pro-inflammatory status and excessive release of adipokines. These aspects are currently investigated for their causal role in cancer progression. Epidemiologic and preclinical data suggest that leptin, an adipokine produced prevalently by adipose tissue, is associated with prostate cancer (PCa) and it can directly modulate PCa cell behavior. *Patients and Methods:* In an observational study we evaluated the role of leptin as cancer biomarker in cohorts represented by PCa patients and patients with urologic non-tumoral diseases, considering as covariables age and anthropometric measures of adiposity. *Results:* Our data confirmed the association of

leptin with PCa, and in absence of significant differences in body mass index (BMI) classification PCa patients had higher leptin values with respect to control patients. Leptin levels were correlated to BMI and waist to hip ratio (WHR) values in both cohorts and also correlated to age in PCa patients. Further analysis revealed a stronger predictive value of serum leptin in older PCa subjects, as demonstrated by a better ROC curve. These data could be explained by the fact that in elderly patients visceral obesity measured by WHR correlated with serum leptin with better respect to BMI measurements and appeared to be a more adequate indicator for obesity. The expression of leptin receptor mainly observed in invasive prostate carcinoma tissue and in aggressive prostate cancer cell lines suggests a possible molecular link between persistently high leptin levels, seen in aged obese subjects, and PCa progression. *Conclusion:* Our data may contribute to elucidating some aspects that have so far been underestimated in epidemiologic studies. Visceral adiposity appeared a more appropriate measure of obesity in elderly subjects with respect to BMI categories, and may explain the elevated leptin values seen in elderly PCa subjects with higher WHR. Further validation and description of this phenomenon may eventually indicate leptin as a new important prognostic marker of PCa in elderly patients.

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MRI TRUS/FUSION BIOPSIES: IS MRI ACCURATE IN PREDICTING HIGH GRADE PROSTATE CANCER?

Riccardo Lombardo, Andrea Cantiani, Francesco Esperto, Christof Kastner

Department of Urology, Addenbrooke S Hospital Cambridge, UK

Introduction: Biopsy detection of prostate cancer remains imperfect, limited by over detection of indolent tumors and under detection of clinically relevant cancers. The aim of our study was to determine the accuracy of MRI in detecting significant cancer in MRI/TRUS fusion prostate biopsies in patients with previous negative biopsies at increased risk of prostate cancer. *Patients and Methods:* A consecutive series of patients underwent transperineal targeted prostate biopsies using MRI/TRUS Fusion technology after previous negative biopsies. Each patient underwent pelvic 3 T MRI (T1, T2, DWI and ADC map) before biopsy and lesions on the MRI were characterized as non suspicious, suspicious or very suspicious. If lesions were present on MRI, they were contoured and fused to a live transrectal ultrasound image in order to target the suspected lesions. In addition to these targeted biopsies, additional sector biopsies were taken. If no lesions were identified, standard sector biopsies were taken. Age, PSA, DRE, prostate volume, number of cores and Gleason score on histological analysis were recorded. The prostate was divided in 12 sectors and each sector was analyzed to see correlation between MRI and Histology. Low grade disease was defined as Gleason 7 (3+4) or lower and high grade was defined as Gleason 7 (4+3) or higher. Statistical analysis was made using SPSS 16 with chi-square correlation test for univariate analysis for nominal variables, Mann-Whitney for continuous variable and binary logistic regression for multivariate analysis. *Results:* 108 patients were analyzed retrospectively in one center. At the time of biopsy, median age was 64 (IQR=58/68) years, median PSA was 9.6 (IQR=6.6/13.2)ng/ml, median prostate volume was 55 (IQR=39/82)ml and the median number of cores for each biopsy was 30 (IQR=27/33). Overall 5/108 (5%) complications were recorded, out of them 4 were acute urinary retentions and 1 bleeding that didn't require intervention. A total of 1082 sectors were analyzed and out of them 172/1082(15%) were positive on MRI. Positive sectors were: 30/172 (17%) score 3, 53/172 (31%) score 4 and 89/172 (52%) score 5 while no score 2 was given. Out of all 161/1082 (15%) had cancer and 99/161 (61%) had low grade disease while 62/161(39%) had high grade disease. In the analysis per sector, MRI reached a negative predictive value of 89%, a positive predictive value of 36% and an accuracy of 79%. On univariate analysis, age (p=0.000), PSA (p=0.000) and score (p=0.000) correlated with the presence of cancer. Moreover on univariate analysis, Age (p=0.000), PSA (p=0.000) and score (0.0020) correlated with high grade disease. On multivariate analysis Age, PSA and Score reached the level of independent predictors of cancer. Age was found to increase by 6.1% per unit the risk of having cancer, PSA increased it by 3.1% and score on MRI by 6.2%. Only PSA and Age reached the level of independent predictors for high grade disease. Risk of high grade disease was increased by 8.6% per unit of age and by 7.5% per unit of PSA. *Conclusion:* The use of MRI/TRUS fusion biopsy is a very good option for patients with previous negative biopsies and ongoing suspicion of cancer. The high negative predictive value could avoid unnecessary biopsies or decrease number of biopsies with lower morbidity rates. Moreover, MRI score could be included in normograms in order to improve detection of significant cancer. However, improving and standardization in prostate MRI reading is still necessary.

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SMOKING CESSATION AND OUTCOME OF PATIENTS AFFECTED BY NON MUSCLE INVASIVE BLADDER CANCER (NMI-BC)

Cristina Scalici Gesolfo[1], Francesco D'amato[2], Davide Castrianni[2], Giuseppe Mastrocinque[2], Dario Passalacqua[2], Marco Vella[2], Carlo Pavone[2], Vincenzo Serretta[2]

[1]U.O.C. di Urologia, Dipartimento di Discipline Chirurgiche ed Oncologiche,
[2]Department of Urology, Dipartimento di Discipline Chirurgiche ed Oncologiche, Università degli Studi di Palermo, Italy

Introduction: Does a correlation exist between smoking cessation and recurrence of non muscle invasive bladder carcinoma (NMI-BC) after TUR and adjuvant intravescical chemotherapy? Up today just few retrospective studies tried to answer this question. There is evidence that quitting decreases the risk of recurrence but nowadays it is still controversial how and how long it takes from quitting to reduce the risk (1-3). The aim of the present study is to compare the recurrence rate in smokers, non smokers and former smokers and in particular to evaluate if and how the decision of quitting at diagnosis could change the patients' outcome. *Patients and Methods:* We retrospectively analyzed the outcome in term of recurrence in patients affected by primary NMI-BC. Our population consisted of 373 patients, mean age of 66 (range 30-95) years. We considered as smokers the patients still smoking at the time of the diagnosis of primary NMI-BC, former smokers all the patients who quitted before diagnosis and never smokers all other patients. The smokers were divided into in current smokers continuing to smoke after diagnosis and ex smokers quitting only at diagnosis. The duration of smoking, the number of cigarettes per day and the clinical and pathological characteristic of the patients, were related to the recurrence rate. *Results:* Out of the 373 patients, 190 (50.9%) were smokers, 99 (26.5%) former smokers and 84 (22.5%) never smokers. Sixtyfive (17.4%) out of 190 smokers quitted at diagnosis. At 3 years 185 (49.6%) patients recurred. During follow up the recurrence rate increased from 11,3% at 3 months to 49.6% at 36 months. The recurrence rates at 3 and 6 months were higher in former smokers, 17.2% and 24.2% respectively, than in never smokers, 9.5% and 19% and smokers 9% and 21%. At one year, 75 (39.5%) smokers, 35 (35.3%) former smokers and 29 (34.5%) never smokers recurred. Among smokers at 3 months 5 (7.7%) ex smokers and 12 (9.6%) current smokers, (p=0.79) recurred; and at 6 months 13 (20%) and 27 (21.4%) recurred respectively (p=0.85). Similar results were observed at one year, with 23 (35%) ex smokers and 51 (40%) current smokers recurring (p=0.87) while at 3 years 29 (44.6%) ex smokers and 68 (54%) smokers (p=0.22) recurred. A progressive increase in recurrence rate, particularly in current smokers was observed, not reaching statistical significance due to the small numbers of our preliminary study. *Discussion and Conclusion:* In patients with non muscle invasive bladder cancer former smokers and smokers have similar recurrence rates. However to stop smoking at diagnosis reduces the risk of recurrence compared to patients continuing to smoke. The benefit however appears after 12 months only.

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ENERGY METABOLISM OF PROSTATE CANCER CAN BE SUPPORTED BY REVERSE WARBURG EFFECT

Patrizia Sanità[1], Mattia Capulli[1], Anna Teti[1], Carlo Vicentini[2], Paola Chiarugi[3], Mauro Bologna[2], Adriano Angelucci[1]

[1]Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università degli Studi dell'Aquila;
[2]Dipartimento di Medicina Clinica, Sanità Pubblica, Scienze della Vita e dell'ambiente, Università degli Studi dell'Aquila;
[3]Dipartimento di Scienze Biochimiche, Università di Firenze, Italy

Introduction: Tumors have long been known to exhibit altered metabolic profiles and increased energy requirements. High rate in cancer growth requires metabolic reprogramming sustaining the continuous proliferation of cancer cells in oxygen- and

nutrient-deprived environment. In consequence of these metabolic adaptations, tumor microenvironment may aberrantly accumulate monocarboxylic acids whose trafficking through cell membrane is regulated by monocarboxylate transporters (MCTs). MCT1 and MCT4 are the best characterized MCTs permitting, respectively, the import and the export of different monocarboxylic acids, including lactic acid. *Materials and Methods:* The mitogenic role of MCTs was investigated *in vitro* and *in vivo* using transformed prostate epithelial cells and carcinoma cell lines. Prostate tissues from carcinoma and benign hypertrophy cases were analyzed for individualizing clinical-pathological significance of MCT1 and MCT4 expression. *Results:* MCT1 and MCT4 were detected in prostate carcinoma (PCa) and transformed prostate epithelial cell lines with MCT4 expression that correlated with aerobic glycolytic metabolism. Exogenous lactate sustained cell growth in low glucose culture environment and blockade of MCT1 function performed by silencing *via* siRNA determined an appreciable antiproliferative effect when lactate was utilized as energetic fuel. MCT1 silencing determined also the reduction of tumor growth in a xenograft model with co-injection of PCa cells together with high glycolytic human fibroblasts. In non-neoplastic prostate, MCTs demonstrated a specific distribution, with MCT1 expressed in epithelial cells and MCT4 localized in stromal cells. In PCa tissue we observed a significant upregulation of MCT4 in tumoral tissue with respect to hypertrophic tissue, with a positive correlation between stromal MCT4 and tumor MCT1 staining. *Conclusion:* Our data demonstrated that PCa progression may benefit MCT1 expression in the presence of high lactate and low glucose concentration. A collaborative interaction between PCa cells and prostate stromal cells may exist based upon lactate shuttle, a phenomenon known as reverse Warburg effect. Therefore, MCTs may represent a promising therapeutic target in early phases of neoplastic transformation according to a strategy aimed at interfering with the energy metabolic adaptation of PCa cells.

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MRI TRANSPERINEAL PROSTATE BIOPSIES- ARE THERE ANY BENEFITS IN MRI/TRUS FUSION TARGETING OVER COGNITIVE DETECTION?

Riccardo Lombardo, Andrea Cantiani, Christof Kastner

Department of Urology, Addenbrooke S Hospital Cambridge, UK

Introduction: Recently the improvements in diagnostics for prostate cancer have accelerated due to a significant development in MRI technology. Existing biopsy techniques, transrectal or transperineal, may be enhanced by the support of MRI images. We compare targeting accuracy and detection rate of MRI/TRUS fusion technique over cognitive direction during transperineal prostate biopsies in patients with persistent suspicion of cancer after initial negative standard biopsy from three European centres. *Patients and Methods:* Records of patients from three centres with persistent suspicion of carrying prostate cancer after previous negative biopsy were reviewed. 407 patients having undergone MRI/TRUS fusion transperineal prostate biopsies (MTTP) or cognitive MRI directed transperineal prostate (cognTP) biopsies were selected forming two cohorts of patients. 263 patients underwent MTTP and 144 underwent cognTP. All patients had multiparametric MRI prior to biopsy. The MRI was reported and lesions were highlighted on the images. For MTTP biopsies the image was fused to a live transrectal ultrasound image for guidance of lesion biopsies. During the cognTP biopsies the surgeon had MRI images available on a separate screen in theatre. In addition sector biopsies were taken preferentially from the peripheral zone dividing the prostate into six sectors for guidance. If MRI was negative, normal TP biopsies were taken in both groups. Age, PSA, Prostate Volume, number of previous biopsies and number of cores were recorded. Correlation between lesion location on MRI and biopsy core location in the histological report was recorded only for the positive MRI patients. Low grade disease was defined as Gleason 7 (3+4) or lower and high grade disease was defined as Gleason score 7 (4+3) or higher. Statistical analysis was made using SPSS 16 software with chi-square correlation test for categorical variables and Mann-Whitney for continuous variables. *Results:* Mean age for the MTTP group was 64±7 years and for cognTP 64±7 years, respectively mean PSA was 10.9±7.5 ng/ml and 9.7±6.5; mean prostate volume was 56±27 ml and 60±31 ml; mean number of previous biopsies was 1.7±1 and 1.1±0.7 and mean number of cores was 26±5 and 28±13 cores. No differences beside for the number of cores (p=0.000) was found in these terms. Detection rate of cancer in the MTTP group was 122/263 (46%) and in the cognitive group 67/144 (46%) (p=1.000). High risk disease was found in 46/122 (38%) and 19/67 (28%) patients (p=0.203) respectively. In the MTTP group 192/263 (73%) had a lesion on MRI and 137/144 (95%) in the cognTP. Correlation of MRI lesion and positive biopsy core location was found to be 92/192(48%) in the MTTP group and 40/137 (29%) in the cognTP group with a statistically significant difference(p=0.001). *Conclusion:* Our data shows how MRI/TRUS fusion technology compared to cognitive MRI direction offers the advantage of a more precise sampling of lesions found on MRI during transperineal biopsies in patients with previous negative biopsies still at risk of prostate cancer. This leads to a higher detection rate of significant cancer with less cores needed. However, accuracy in terms of MRI reading still needs improvement.

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LEPTIN SUSTAINS PROSTATE CANCER CELL SURVIVAL IN GLUCOSE-RESTRICTED ENVIRONMENT

Patrizia Sanità, Simona Delle Monache, Adriano Angelucci

Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università degli Studi dell'Aquila, Italy

Introduction: Leptin is an adipokine produced by adipose tissue in response to food intake and its serum levels are chronically high in obese subjects. In prostate carcinoma (PCa) obesity and high serum leptin levels are risk factors for advanced tumor stage and poor prognosis. It has been proposed that adipose tissue, through the release of leptin, can regulate whole-body energy homeostasis. The detection of leptin receptor and downstream signaling in PCa tissue and cell lines has suggested to investigate the direct action of leptin in modulating energetic pathways of cancer cells. *Materials and Methods:* We investigated the involvement of leptin signaling in maintaining cell fitness through nutrient-limited culture conditions and performing coculture with cancer-conditioned fibroblasts. *Results:* Recombinant leptin stimulated cancer cell survival and proliferation in LNCaP and PC3 cells but these effects were statistically appreciable in glucose-restricted culture conditions. Exogenous leptin in conjuction with low glucose determined, with respect to untreated control cells, an increase in mitochondrial respiration and in utilization of energetic sources alternative to glucose, including acetate and lactate. The lactate import was allowed by upregulation of monocarboxylate transporter MCT1. Metabolic switch induced by leptin in PCa cells was associated with upregulation of sirtuin 3 (SIRT3) and activation of AMPK. In co-culture experiments using PCa cells and cancer-conditioned fibroblasts the addition of leptin determined a significant increment in PCa cell growth mainly in glucose-restricted conditions. *Conclusion:* Leptin through the stimulation of cancer survival in nutrient-restricted environments may explain, at least partially, the association between obesity and progression of PCa. The proposed mechanism, involving targetable intermediates of the energy metabolism, offers new opportunities in both diagnostic stratification and targeted treatment for PCa patients with high serum leptin levels. Acknowledgements: This work was supported by Italian Association for Cancer Research (AIRC, grant MFAG 6194).

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PLASMACYTOID UROTHELIAL CARCINOMA OF THE URINARY BLADDER IN A 59-YEAR-OLD WOMAN

Luca Ventura[1], Giovanni Luca Gravina[2], Claudio Festuccia[3], Luigi Zugaro[4], Cinzia Mercurio[1], Luigi di Clemente[5], Fabrizio Liberati[6]

[1]Unità Operativa di Anatomia Patologica, Ospedale San Salvatore, L'Aquila;
[2]Divisione di Radioterapia, Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università, L'Aquila;
[3]Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università, L'Aquila;
[4]Unità Operativa di Radiologia, Ospedale San Salvatore, L'Aquila;
[5]Unità Operativa di Urologia, Ospedale San Salvatore, L'Aquila;
[6]Unità Operativa di Anatomia Patologica, Ospedale San Camillo de' Lellis, Rieti, Italy

Introduction: Urothelial carcinoma is well known for its divergent differentiation and in recent years its morphologic spectrum has been expanded to include several new variants (1). Plasmacytoid variant of urothelial cacinoma is an unusual and aggressive neoplasm characterized by a poor prognosis, with male predilection and presentation at an elderly age (1-3). We report a case of plasmacytoid urothelial carcinoma of the urinary bladder observed in a 59-year-old female patient. *Patients and Methods:* A 59-year-old woman presented to our observation with gross hematuria and lower abdominal pain. Her past medical history was free of significant diseases. A computed tomography scanning showed diffuse thickening of the bladder, with adhesions to the surrounding organs. Cystoscopy revealed edema, ulcerations and a diffusely thickened bladder mucosa with a slightly stenotic left ureteral orifice. The patient underwent bladder trans-urethral resection with histological diagnosis of plasmacytoid urothelial carcinoma and was followed by radical cystectomy, hysterectomy with bilateral annessectomy and vaginal resection. *Results:* Surgical specimen consisted of the

bladder measuring 10×8 cm with a maximum parietal thickness of 1.4 cm, the uterus measuring 5×4.5×4 cm, and both adnexa. Histological examination of the formalin-fixed specimen highlighted a poorly differentiated tumor with discohesive cells in a loose stroma, showing plasma cell appearance. These features allowed the diagnosis of plasmacytoid urothelial carcinoma of the bladder, extended to perivescical tissue and infiltrating uterus, vagina, both ovaries and left salpynx, with metastasis to regional lymph nodes. Diffuse angiolymphatic invasion was observed in the bladder wall. Neoplastic cells were diffusely immunoreactive for cytokeratin 8-18, EMA, CD138, and E-cadherin; focally positive for cytokeratin 20, and cytokeratin 34βE12; negative for cytokeratin 7, CD45, CD20, kappa and lambda chains, CD79α, HMB-45, CA19-9, and β-HCG. Six months after the diagnosis the patient is alive and free of disease. *Discussion and Conclusion:* Plasmacytoid carcinoma is a rare variant of urothelial carcinoma with distinctive clinical and pathological features (1-3). Since the original description, there have been approximately 70 cases reported in literature, with a mean age at the initial diagnosis of 69 years and a male predominance (M:F=9:1) (3). Immunohistochemistry plays a pivotal role in the diagnosis. The coexpression of plasma cell and epithelial cell markers (CD138, EMA, cytokeratins) is important in the differential diagnosis from plasma cell myeloma and signet ring adenocarcinoma (1, 3). E-cadherin expression is probably associated with the discohesive phenotype and the increased cellular invasiveness of this neoplasm, which result in tumor aggressiveness and recurrence (3). The importance of this variant lies on the prognostic and therapeutic considerations resulting from such a peculiar diagnosis (1). The prognosis of this tumor is uniformly poor, with most patients discovered in an advanced stage at presentation or with metastatic disease (1, 2), and requiring aggressive treatment (3). The recognition of the distinctive clinicopathological and immunophenotypical features of this rare variant is extremely relevant, especially when chancing upon atypical patients, as in our case of a relatively young female.

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LAPAROSCOPIC POST-CHEMOTHERAPY RETROPERITONEAL LYMPH-NODE DISSECTION (L-PC-RPLND) IN RESIDUAL MASS FROM NON-SEMINOMATOUS GERM-CELL TUMOURS OF THE TESTIS (NSGCTT): EARLY EVALUATION AND COMPARISON WITH OPEN COUNTERPART

Nicola Nicolai[1], Silvia Stagni[1], Davide Biasoni[1], Mario Catanzaro[1], Tullio Torelli[1], Luigi Piva[1], Andrea Necchi[1], Patrizia Giannatempo[1], Daniele Raggi[1], Giovanni Lughezzani[2], Andrea Guttilla[3], Maurizio Colecchia[4], Roberto Salvioni[1]

[1]Urology Unit. Testis Surgery Unit., Fondazione IRCCS Istituto Nazionale dei Tumori;
[2]Department of Urology, Vita-Salute San Raffaele University;
[3]Urology Clinic, Department of Surgical, Oncological and Gastroenterological Sciences, University of Padua;
[4]Pathology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Italy

Objective: Patients with NSGCTT who had residual retroperitoneal masses following completion of chemotherapy need PC-RPLND. We report an early observation of LPC-RPLND compared with Open (O-) PC-RPLND in patients with comparable disease features at our Institution. *Methods and Results:* Eighteeen consecutive L-RPLNDs performed following first line chemotherapy (3 to 4 PEB) between Feb 2011 and Feb 2012 for residual mass from NSGCTT, were compared with 10 open post-chemotherapy RPLNDs having comparable features performed between Jun 2009 and Apr 2012 at our Institution. All patients had unilateral disease (from one side of the aorta) since the beginning, and none had undergone previous retroperitoneal surgery. Initial stage was II A to II C in both groups except a stage III in laparoscopic group. Prognostic allocation according to IGCCCG was of good prognosis in all cases except one intermediate in open group and one poor in laparoscopic group. All patients had normal markers prior to surgery. Size of residual masses was comprehended between 10 and 70 mm (p=0.18 at Mann-Withney test). Patients were evaluated for: complications, hospital stay, histology, postoperative pain control (resting and dynamic VAS), recurrence rate. Median operation time was 150 min (range 101 to 189) in O-PC-RPLND and 210 (range 131 to 278) in L-PC-RPLND (p<0.0046 at Mann Withney test). Intraoperative bleeding was negligible in all cases, but 1 L-PC-RPLND (100 cc) and 1 O-PC-RPLND (150 cc). Histology according to procedure (O Vs L) was one of mature teratoma in 6 Vs 10 patients, immature teratoma in 1 Vs 6 and fibro- necrotic tissue in 3 Vs 2 patient. One L-PC-RPLND patient underwent postoperative blood transfusion

(2 units). Postoperative lymphatic leakage lasting more than 5 days, which spontaneously resolved, occurred in 2 patients following O-PC-RPLN and in 1 following L-PC-RPLND. Dynamic VAS was inferior in L-PC-RPLND both in 1st and in 2nd postoperative days (1st day: L-PC-RPLND: 2 to 8; O-PC-RPLND: 4 to 8. 2nd day: L-PC-RPLND: 0 to 7; O-PC-RPLND 5 to 7). Median postoperative hospital stay was 8 days (6 to 14) in O-PC-RPLND Vs 3 days (2 to 6) in L-PC-RPLND ($p<0.0001$ at Mann-Withney test). Following a median follow up of 15.5 months (1-37), all the patients but one are currently alive and disease free, with one patient in L-PC-RPLND group suffering a recurrence of iliac teratoma (<1 cm), which occurred 12 months after surgery. No significant difference was recorded in terms of resting VAS at the 1st and 2nd postoperative days in both groups. *Discussion:* L-PC-RPLND is an alternative to O-PC-RPLND in selected patients with NSGCTT. This procedure needs usual longer operative times, does not differ for complication rate, was better tolerated and permits an earlier discharge. No difference in oncologic outcome was observed up to now.

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COMPLETE PATHOLOGICAL RESPONSE TO MULTIMODAL TREATMENT IN A PATIENT WITH METASTATIC RENAL CANCER

Elisa Biasco[1], Azzurra Farnesi[1], Lisa Derosa[1], Riccardo Marconcini[1], Luca Galli[1], Andrea Antonuzzo[2], Claudia Cianci[1], Sergio Ricci[2], Alfredo Falcone[1]

[1]Uo Oncologia Medica 2 Universitaria, Azienda Ospedaliera Universitaria Pisana;
[2]Uo Oncologia Medica 1, Azienda Ospedaliera Universitaria Pisana, Italy

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 (1) 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 complete pathological response of multiple metastasis (3) from a clear cell renal carcinoma after surgery, sunitinib and radiotherapy. *Case Report:* A 41-year-old female patient with no significant comorbidities presented with a 2 months history of cervicobrachialgia and weakness of the upper right limb, that led to diagnosis of pathological fracture of 6 cervical vertebra. She was hospitalized in the Department of Neurosurgery and during the hospitalization, the patient underwent a CT scan that showed a right kidney neoplasm of 6 cm and synchronous multiple metastases localized in left adrenal gland, pancreas, bladder, lymph nodes and bone. Patient was in ECOG PS 3, and she underwent corpectomy of 6 vertebra, positioning and fixing of protheses with plaque on 5th and 7 cervical vertebra. Pathological examination showed metastasis of clear cell carcinoma. In November 2010, she underwent right radical nephrosurrenalectomy and transurethral resection of bladder metastasis. Pathological examination showed clear cell carcinoma, G2, pT4NxM1(bladder and adrenal gland metastasis). In December 2010, the patient was referred to our Hospital. She was in ECOG PS 3, referring difficulties in deambulation, and motor deficit of the lower and upper right th th limbs. On January 2011, she underwent radiation therapy of the 5 and 7 cervical vertebra (TD 20Gy). At blood chemistry assay, anemia was not present; LDH and calcium were in the normal range. After cardiological assessment with ECG and echocardiography, in February 2011, she 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 3 cycles, a CT scan showed complete response of pancreatic and lymph node metastasis. The patient was in ECOG PS 0 and asymptomatic, referring mild asthenia. On May 2012, a CT scan showed bone metastases on left proximal femoral epiphysis. She underwent resection of metastasis and placement of left hip endoprothesis. Patient continued treatment with Sunitinib. On October 2012, patient referred grade 2 mucositis, mild asthenia, grade 2 Hand-Foot Syndrome, and she was placed on 50 mg sunitinib daily in a three weeks cycle according to a 2/3 schedule (2 weeks on treatment: 1 week off treatment). A CT scan performed on January 2013, showed complete pathological response. Actually, the patient is still continuing Sunitinib according to a 2/3 schedule. *Conclusion:* This case is an example of how the multimodal treatment with surgery, radiotherapy and

sunitinib can lead to a prolonged and complete pathological response with a significant improvement of quality of life.

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INVESTIGATING THE ROLE OF FDG-PET/CT FOR PREOPERATIVE LYMPH-NODE STAGING OF BLADDER CANCER: OUR PRELIMINARY EXPERIENCE

Andrea Buffardi[1], Antonella Parente[2], Paolo Destefanis[1], Marilena Bellò[2], Andrea Bosio[1], Ettore Dalmasso[1], Eugenio Alessandria[1], Paolo Gontero[1], Gianni Bisi[2], Bruno Frea[1]

[1]Clinica Urologica, Azienda Ospedaliera Città della Salute e della Scienza, Sede Molinette, Torino;
[2]S.c. Medicina Nucleare 2, Azienda Ospedaliera Città della Salute e Della Scienza, Sede Molinette, Torino, Italy

Introduction: In patients with nonmetastatic invasive bladder cancer (T2 or higher, M0) or recurrent high-risk non-muscle invasive disease (T1G3 with or without Tis, M0), locoregional lymph node metastasis is an important prognostic factor. The standard imaging modalities for staging (computed tomography [CT] or magnetic resonance imaging [MRI]) have an accuracy range of 70-90% for lymph-node staging. Fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) has been approved for imaging in many malignancies but not for bladder cancer. This study investigated the value of FDG-PET/CT for preoperative lymph-node staging of patients with MIBC. We present our preliminary results. *Patients and Methods:* Between September 2012 and February 2013, 10 patients (8 male, 2 female) with bladder cancer underwent FDG-PET/CT and a thoraco-abdominal CT scan. Four patients were found to be recurrent T1G3 at TUR-B, five T2G3 and one T2G2. Independently from the results for lymphnode status at FDG-PET/CT or at abdominal CT scan, all patients underwent radical cystectomy and lymphadenectomy. Results of FDG-PET/CT and CT for N-staging were compared to histopathology findings. Complete data are available for 8 patients. *Results:* Among the 8 patients, 3 patients had metastatically involved locoregional lymph nodes, diagnosed on histopathology. In all these patients, the lymph-nodes demonstrated increased FDG uptake on PET/CT; the same nodes were not considered as metastatic at abdominal CT scan. Five patients had lymph-nodes with a normal FDG uptake on PET/CT: these nodes were found nonmetastatic at histopathology. Only 1 patient had nodes suspected for metastases at CT scan but not at FDGPET/CT: these lymph-nodes were found nonmetastatic at histopathology. The accordance between histopathology and FDG-PET/CT findings was 100%. *Discussion and Conclusion:* Our preliminary data show that FDG-PET/CT may provide better accuracy in N-staging of bladder cancer; our study is still ongoing because a larger sample (at least 50-75 patients) is needed. According to our results and to data in the Literature, larger prospective studies are needed to elucidate the effective role of FDG-PET/CT in N-staging of bladder cancer.

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DECISION AIDS: HOW TO HELP THE PATIENTS CHOOSE THE "BEST" OPTION FOR LOCALIZED PROSTATE CANCER

Silvia Villa[1], Lara Bellardita[1], Tiziana Magnani[1], Daniela Villani[1], Silvia Stagni[2], Davide Biasoni[2], Sara Morlino[3], Sergio Villa[3], Riccardo Valdagni[4]

[1]Programma Prostata,
[2]Urologia,
[3]Radioterapia Oncologica 1,
[4]Programma Prostata, Radioterapia Oncologica 1,
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

According to international guidelines, patients diagnosed with prostate cancer (PCa) should be informed of the different but equally effective therapeutic/observational options. PCa strategies also differ in terms of risks and

benefits and adverse physical effects impacting on quality of life. To date, it is not completely clear how side-effects may affect patients' choice of the therapeutic/observational path and what the core landmarks of patients' decision-making process are. To overcome patients' uncertainty and facilitate shared decision-making, decision aids (DAs) seem helpful tools (1, 2). The aim of our study was to explore prostate cancer treatment decisional process when using a DA. *Patients and Methods:* A qualitative study was conducted between February and May 2012; 10 patients (mean age 64.8) with low or intermediate risk PCa accessing a multidisciplinary visit (MDV) at our Prostate Cancer Program were recruited. The Ottawa Personal Decision Guide (3), a structured DA grid, was administered by a psychologist after the MDV. The DA structure focused on three main areas: a) to clarify the decision; b) to identify patients' decision making needs and c) to explore those needs. A further set of questions was added in order to explore patients' emotions. Interviews were audio-recorded and verbatim transcriptions were made. Content analysis was performed by using a text analysis software (T-LAB). *Results:* Text analysis showed the following results in relation to the explored dimensions: a) all patients reported to have been properly informed of the available options; three of them were prone toward a particular treatment option and felt disoriented due to the complexity of the decision-making process; six patients wanted to reach a final decision in a short time; b) 9/10 patients had enough support and advice from their family and did not feel pressure toward a particular option; 8/10 patients did not clearly and fully understand the details of the possible strategies, the benefits and the risks of each option; all of them were aware of their personal priorities; c) patients varied in their subjective evaluation of side-effects associated with the therapeutic options; a substantial variance also emerged in their willingness to be actively involved in the decision-making process and all the patients considered physician's recommendations as a crucial factor for the choice; 8/10 patients felt the need to clarify a few doubts about unclear or contradictory medical information and to expand their knowledge as a necessary step to make a choice. As far as the emotional aspect, 7/10 patients did not report feelings of overwhelming anxiety and/or distress, but all of them mentioned specific cancer-related fear and concern about the invasiveness of medical procedures and the impact of side effects on their quality of life. *Discussion and Conclusion:* The DA was helpful to highlight the fact that PCa patients perceived the decisional process as a complicate experience involving the evaluation of medical information as well as psycho-social factors. DAs are a valid support for clinician-patient shared decision making in Pca management; further research should focus on how the use of DAs is associated to specific outcomes such as decisional regret, long-term satisfaction about therapeutic/observational treatment and quality of life. Acknowledgements to Prostate Cancer Program Multidisciplinary Clinic Team; Foundations I. Monzino and ProADAMO Onlus.

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NEED FOR MORE ACCURATE BIOPSY SAMPLING: CORRELATION BETWEEN CORES TAKEN AND INSIGNIFICANT PROSTATE CANCER AT RADICAL PROSTATECTOMY

Vincenzo Scattoni, Luca Villa, Nazareno Suardi, Umberto Capitanio, Marco Bianchi[1], Alessandro Nini, Marco Moschini, Paolo Capogrosso, Nicola Fossati, Valerio di Girolamo, Alberto Briganti, Francesco Montorsi

Urology, Vita-Salute San Raffaele University, Milan, Italy

Introduction: The role of the number of cores taken at prostate biopsy in patients suitable for active surveillance (AS) is controversial. We tested the role of the number of cores in confirming the presence of pathologically confirmed insignificant prostate cancer (pIPCa) in patients eligible for AS. *Patients and Methods:* of 3349 patients diagnosed with PCa at prostate biopsy and subsequently treated with RP at our institution between 2002 and 2012, we selected 272 patients who were eligible for AS according to PRIAS criteria (PSA ≤10 ng/mL, PSAD <0.2 ng/mL/cc, number of positive cores <2, T1c-T2 clinical stage). Patients were divided according to the number of cores taken at biopsy (≤12 *vs*. 13-18 *vs*. ≥19 cores). At pathology, pIPCa was defined according to Epstein's criteria (Gleason score ≤6, tumor volume ≤0.5 ml and organ-confined disease). We relied on Chi-square test to depict the rate of pIPCa according to the number of cores. The effect of PSA, PSA density, number of positive cores, number of cores, prostate volume and clinical stage in predicting the presence of pIPCa was addressed using univariable and multivariable logistic

regression analyses. *Results:* At pathology, 49 (18%) patients had pIPCa. The rate of pIPCa in patients submitted to ≤12 cores, 13-18 cores and ≥19 cores were 11.7% (13 of 111 pts), 25% (20 of 80 pts) and 20.6 % (16 of 81 pts), respectively (p=0.05). At unviariable logistic regression analyses, prostate volume and number of cores were the only significant predictors of pIPCa (OR=1.01, p=0.05 and OR=2.5, p=0.02). After adjusting for the effect of other available features, the number of cores taken remained the only parameter significantly associated with the presence of pIPCa. Indeed at multivariable analyses, although the probability of having pIPCa in patients with ≥19 cores is not significantly higher than patients with ≤12 cores; patients submitted to 13-18 cores had 2.4-fold higher probability of having pIPCa compared with patients submitted to ≤12 cores (p=0.03). *Discussion and Conclusion:* The number of cores taken is a major predictor of pIPCa in patients suitable for AS. In this patient group, 13-18 cores seems to be an adequate sampling to safely rely on favorable pre-operative features in addressing patients to conservative treatment. Although there are no recommendation about the sampling bioptic extent when identifying patients for AS, the number of cores taken at prostate biopsy should be carefully considered in decision making.

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NUMBER OF POSITIVE SPOTS AT PET-CT SCAN PREDICTS CANCER SPECIFIC AND OVERALL SURVIVAL IN PATIENTS TREATED WITH SALVAGE LYMPH NODE DISSECTION FOR RECURRENCE AFTER RADICAL PROSTATECTOMY

Vincenzo Scattoni[1], Manuela Tutolo[1], Nazareno Suardi[1], Nicola Fossati[1], Firas Abdollah[1], Umberto Capitanio[1], Giorgio Guazzoni[1], Maria Picchio[2], Luigi Gianolli[2], Giampiero Giovacchini[2], Cristina Messa[2], Andrea Salonia[1], Alberto Briganti[1], Francesco Montorsi[1]

[1]Urology,
[2]Nuclear Medicine, Vita-Salute San Raffaele University, Milan, Italy

Introduction: Salvage lymph node dissection (SLND) may be considered in patients with prostate cancer (PCa) and nodal recurrence at [^{11}C]Choline PET-CT scan (PET/CT) after radical prostatectomy (RP).The aim of our study was to identify clinical and pathological predictors of cancer specific (CSS) and overall survival (OS) in men treated with SLND for patients with nodal recurrence at PET/CT after RP. *Methods:* We identified 94 patients treated with SLND (pelvic and/or retroperitoneal) between January 2002 and July 2011 at a single tertiary care centre for PCa nodal recurrence after RP. Clinical nodal recurrence was defined as at least one positive spot at [^{11}C]Choline PET/CT. All patients underwent pelvic and/or retroperitoneal SLND. The Kaplan-Meier methodology was used to assess the 5-year CSS and OS rates after SLND. Univariable (UVA) and multivariable (MVA) Cox-regression analyses were used to predict CSS and OS. Covariates consisted of age and PSA at SLND, adjuvant or salvage treatment administration between RP and nodal recurrence, time from RP to BCR and number of positive spots at PET/CT (stratified according to the most informative cut-off). *Results:* Overall, 23 (24.5%) patients underwent pelvic SLND and 71 (65.5%) patients received both pelvic and retroperitoneal SLND. Mean PSA at SLND was 6.46 ng/ml (median 2.36 ng/ml). Most individuals had a single positive spot at PETCT (77; 81.4%). Overall, 8 (8.6%), and 12 (12.9%) patients experienced CSS and OS after SLND at a mean follow-up of 54 months. At 5 years, the overall CSS and OS rates were 87.8 and 86.1%, respectively. After stratification according to number of positive spots, the 5 year CSS and OS were 95.1 and 29.6 %, 88.1 and 29.6% for patients with ≤2 and 3 or more positive spots at PET/CT, respectively (all p<0.001). At MVA, number of positive spots at PET/CT emerged as the only independent predictor of CSS (HR=11.4, p<0.001) and OS (4.9, p=0.04). Specifically, after accounting for possible confounders, patients with 3 or more positive sites at PET/CT were at 11- and 5-fold higher risk of succumbing to cancer specific and overall mortality, as compared to patients with 2 or less positive spots, respectively (all p ≤0.04). *Conclusion:* The number of positive spots at PET/CT represents the only independent predictor of CSS and OS in patients treated with SLND for lymph node recurrence after RP for PCa. These results should be taken into account for the selection of the best candidate for salvage surgery.

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CHANGING AND UNCHANGING FACE OF HIGH RISK PROSTATE CANCER. RESULTS FROM A 15-YEAR, SINGLE INSTITUTION SERIES

Vincenzo Scattoni, Umberto Capitanio, Nazareno Suardi, Andrea Gallina, Nicola Fossati, Marco Bianchi, Renzo Colombo, Giorgio Guazzoni, Fabio Castiglione, Andrea Salonia, Patrizio Rigatti, Alberto Briganti, Francesco Montorsi

Urology, Vita-Salute San Raffaele University, Milan, Italy

Introduction: Several studies have shown that the outcome of high risk prostate cancer (PCa) is not invariably poor. However, such favorable outcomes might be due to a change into clinical presentation of high risk PCa towards less aggressive variants over time. The aim of this study was to

describe changes in clinical and pathological characteristics of high risk PCa patients treated with radical prostatectomy (RP) over a 15-year period. *Methods:* The study included 1154 patients with pre-operative high risk PCa (defined according to the NCCN criteria as the presence of at least one of the following adverse characteristics: PSA>20 ng/ml and/or cT3 and/or biopsy Gleason 8-10) treated with RP and extended pelvic lymph node dissection (ePLND) at a single tertiary referral center between 1997 and 2012. Preoperative data as well as post-operative pathological information (pathological stage, nodal status and Gleason sum) were available for all patients. Patients were stratified into tertiles according to the year of surgery (1997-2004 *vs*. 2004-2008 *vs*. 2008-2012). Anova and chi-square trend tests were used to report the clinical and pathological characteristics of the cohort over time. *Results:* When considering clinical characteristics, patient age (66.8 *vs*. 66.0 *vs*. 66.3 years, p=0.3) and clinical T3 cases (47.1 *vs*. 54.9 *vs*. 53.6%, p=0.2) resulted steady over the three tertiles. Mean PSA decreased (33.1 *vs*. 32.5 *vs*. 19.7 ng/ml, p=0.02) and the prevalence of biopsy Gleason sum 8-10 increased (35.1 *vs*. 46.4 *vs*. 52.3%, p<0.001) over time. Although pathological Gleason sum 8-10 rates increased (32.5 *vs*. 46.6 *vs*. 43.3%, p=0.002), all the other pathological characteristics remained stable. Specifically, extracapsular extension, seminal vesicle and lymph node invasion rates were 20 *vs*. 22.3 *vs*. 26% (p=0.2), 38.6 *vs*. 32.8 *vs*. 37.5% (p=0.2) and 30.7 *vs*. 29.4 *vs*. 37.4% (p=0.06) in the three tertiles, respectively. The prevalence of patients defined as high risk according to a single criterion (PSA>20 ng/ml or cT3 or biopsy Gleason 8-10) was 72.0 *vs*. 71.1 *vs*. 73.3% in the three tertiles, respectively (p=0.2). Similarly, the prevalence of patients defined as high risk for the simultaneous presence of two or three criteria remained stable (all p>0.2). *Conclusion:* Despite the trend towards early diagnosis, characteristics of high risk PCa patients did not change over time. Particularly, pathological characteristics and presence of more aggressive PCa variants remained virtually identical over the last 15 years. Increase of higher Gleason grade might be due to improved pathological PCa staging

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COMPARISON BETWEEN PCA3 AND PHI SPECIFICTY AND SENSITIVITY IN PREDICTING THE PRESENCE OF CANCER AT INITIAL OR REPEAT BIOPSY

Vincenzo Scattoni[1], Massimo Lazzeri[1], Giovanni Lughezzani[1], Stefano De Luca[2], Roberto Passera[2], Enrico Bollito[2], Donato Randone[2], Firas Abdollah[1], Umberto Capitanio[1], Alessandro Larcher[1], Giuliana Lista[1], Giulio Maria Gadda[1], Vittorio Bini[3], Alberto Briganti[1], Giorgio Guazzoni[1], Francesco Montorsi[1]

[1]Urology, Vita-Salute San Raffaele University, Milan;
[2]Urology, Ospedale Gradenigo di Torino;
[3]Internal Medicine, University of Perugia, Italy

Purpose: Prostate Health Index (PHI) and Prostate Cancer Antigen 3 (PCA3) have been shown to predict prostate cancer (PCa). We performed a head-to-head comparison between the two markers in the same cohort of patients. Patients and Methods: The performance characteristics of PHI and PCA3 were evaluated in a prospective cohort of 211 patients undergoing first (n=116) or repeat prostate biopsy (PBx) (n=95). Multivariable logistic regression analyses tested the accuracy (AUC) of PHI and PCA3 in predicting PCa in the overall population and in both settings . Decision curve analyses (DCA) were used to compare the clinical benefit of the different models. *Results:* In the overall population, PHI had the highest AUC values (0.70). This was significantly higher if compared to PCA3 (AUC: 0.59; p=0.043), tPSA (AUC: 0.56; p=0.002) and %fPSA (0.60; p=0.037). PHI resulted more accurate relative to PCA3 in predicting PCa both in the initial setting (AUC:0.69 *vs*. 0.57) and in the repeat setting (AUC:0.72 *vs*. 0.63), even if no statistically significant difference was found. The inclusion of PCA3 in the baseline multivariable model (BMM:PSA + %fPSA + prostate volume) did not increase the predictive accuracy in both settings. (AUC:0.79 *vs*. 0.80 and 0.75 *vs*. 0.76, respectively). Conversely, the inclusion of PHI to BMM improved the predictive accuracy of the model by a 5% extent in the initial setting (AUC:0.79 to 0.84), and by a 6% in the repeat setting (AUC:0.75 to 0.81). At DCA, the highest net-benefit was observed when PHI was added to the BMM. *Conclusion:* Both PHI and PCA3 offer a statistically significant increase in sensitivity and specificity compared to all other examined markers and may therefore be useful in guiding prostate biopsy decisions. If PHI is assessed, PCA3 does not increase the accuracy in predicting the presence of PCa.

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REPAIR OF RECTO-URETHRAL FISTULA WITH PERINEAL APPROACH AND INTERPOSITION OF GRACILIS MUSCLE

Roberto Sanseverino[1], Giorgio Napodano[2], Oliver Intilla[2], Umberto di Mauro[2], Giovanni Molisso[2], Tommaso Realfonso[2]

[1]UOC-Urologia,
[2]Divisione di Urologia, Ospedale Umberto I, Nocera Inferiore - ASL Salerno, Italy

Introduction: Recto-urinary fistula formation is a very important complication of surgery for prostatic disease. Spontaneous closure is rarely successful and reconstructive

procedures are usually performed. Although several surgical approaches have been proposed in the literature, successful repair is often difficult. We report a case of a 64 years old male with recto-urinary fistula developing after radical prostatectomy. We performed a fistula repair with a perineal approach with interposition of gracilis muscle. *Methods:* A wide rectourinary fistula was diagnosed by cystoscopy and coloscopy. A perineal approach was performed with skin incision and dissection of central tendon of perineum, mobilization of uretra. Fistula was isolated and excised. Anterior rectal wall and uretra were sutured, with skin incision on medial surface of leg was and isolation of gracilis muscle. Distal tendon was disconnected with transobturator tunnellization of gracilis flap. Injection of Tissucol® preceded positioning of Gracilis flap. *Results:* Operative time and blood loss were 150 minutes and 200 ml, respectively. No complications were registered. A 3 months postoperative cystography confirmed fistula healing. *Conclusion:* The use of perineal approach with gracilis muscle flap is an effective option to repair iatrogenic rectourethral fistula.

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PREDICTOR FACTORS OF PROSTATE CANCER ON PROSTATIC BIOPSY: OUR EXPERIENCE

Giorgio Napodano, Renato Angrisani, Salvatore Acerra, Antonio Campitelli, Tommaso Realfonso, Roberto Sanseverino

Dept of Urology, Umberto I Hospital, Nocera Inferiore (SA), Salerno, Italy

Aim: To analyze prostate biopsy outcomes and to investigate predictor factors of prostate cancer in our experience. *Patients and Methods:* Patients with suspected prostate cancer [abnormal digital rectal examination (DRE) and/or elevated PSA values and/or previous HPIN/ASAP] underwent a US guided tranrectal prostatic biopsy (PB). From 2003 to 2012, 3240 patients underwent a prostatic biopsy; prostate cancer was found in 1124 patients (35%). We analyzed data from 701 patients who underwent a first biopsy for abnormal digital rectal examination (DRE) and/or elevated PSA values. Procedure was performed using a 18G trucut needle with periprostatic anesthaesia. We evaluated predictor factors of PCa: age, BMI, indication for biopsy, DRE, PSA, prostate volume, PSA density, number of cores. RESULTS From 2010 to 2012, 701 patients underwent transrectal PB. Table I shows population characteristics. Indication for biopsy is listed in Table II. Prostate cancer was found in 292 of 688 patients (42%). At univariate analysis, predictor factors of PCa were: age, indication for biopsy, positive DRE, PSA, prostate volume, PSA density, number of cores, but not BMI ($p<0.49$). At multivariate analysis age ($p<0.003$; OR 1.1), PSA ($p<0.001$; OR 1.1), DRE ($p<0.001$; OR 3.6), prostate volume ($p<0.001$; OR 0.9) were predictor factors of PCa. *Conclusion:* In our experience, age, PSA, prostate volume and positive DRE were predictor factors of prostate cancer in patients undergone a first 12 core prostatic biopsy.

Table I. *Population.*

	Mean (DS)
Age (y)	69.8 (7.9)
PSA (ng/ml)	19.6 (81.7)
BMI	27.1 (3.5)
Prostate vol (ml)	64.6 (32.9)
PSA density	0.34 (1.6)
DRE + (%)	41
Cores (n)	12.3 (2.0)

Table II. *Indication for biopsy (%).*

PSA	80.9
PSA + ER	16
PSA + TRUS	0.4
ER	2.4
TRUS	0.3

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SIMULTANEOUS BILATERAL NEPHRECTOMY FOR RENAL CANCER: CASE REPORT

Roberto Sanseverino[1], Giorgio Napodano[2], Oliver Intilla[2], Umberto di Mauro[2], Giovanni Molisso[2], Tommaso Realfonso[2]

[1]UOC-Urologia-Umberto I Nocera Inferiore, [2]Divisione di Urologia, Ospedale Umberto I, Nocera Inferiore, ASL Salerno, Italy

Introduction: We report a case of a patient affected by bilateral synchronous renal cancer who underwent a radical left nephrectomy and partial right nephrectomy. *Methods:* The patient complained of macroscopic haematuria. TC revealed left renal neoplasm (13 cm) with vena cava invasion and a right renal neoplasm (4.7 cm). We planned an open right radical and left partial nephrectomy. Subcostal incision sec. Chevron. Radical right nephrectomy with regional lymphadenectomy was realized. Resection of left lower pole without renal vessels clamping. Renal parenchyma was repaired with Vycril suture. *Results:* Age, BMI, and ASA score were 64 years, 31 and 3, respectively. Operation time was 4 hours. Creatinine value rised to 1.9 mg/dl (day 3) and then decreased. Histological evaluation revealed renal cell carcinoma (pT3bN0G3 in left kidney and pT1bG3 in right

kidney). Surgical margins were negative. After 9 months patient was free of disease and presented normal kidney function. *Conclusion:* In selected cases, simultaneous bilateral nephrectomy (radical and partial) is a feasible and safe procedure.

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INCREASED RADIOSENSITIVITY AFTER ANDROGENIC MANIPULATION IN PROSTATE CANCER CELL MODELS

Claudio Festuccia[1], Giovanni Luca Gravina[2], Andrea Mancini[1], Francesco Marampon[2], Leda Biordi[1], Francesca Vittorini[3], Andrea Lenzi[4], Emmanuela Jannini[5]

[1]Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università degli Studi dell'Aquila;
[2]Divisione di Radioterapia, Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università degli Studi dell'Aquila;
[3]Divisione di Radioterapia, Ospedale San Salvatore L'Aquila;
[4]Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Università La Sapienza Roma;
[5]Course of Endocrinology and Medical Sexology, Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università di L'Aquila, Italy

Background: There is debate about the optimal management of intermediate and high risk localized prostate cancer. It has been demonstrated that short- and long-term hormonal manipulation improves oncological outcomes in patients with intermediate- or high risk PCa. Although hormonal manipulation in combination with RT is used to improve local tumor control in men suffering from Pca, the optimal therapy as well as the underlying mechanisms is not well understood. *Aim:* To evaluate the differential effect of castration, bicalutamide or the combination of castration and bicalutamide in terms of radiosesitizing effects. *Methods: In vitro* and *in vivo* models were used to test our study hypothesis. Pca tumor cells, the 22rv1 model, were used as preclinical models. Castrated nude mice were purchased from Charles River Laboratories and Bicalutamide was administered at the concentration of 50 mg/kg per os. Fractionated radiation therapy (5 daily fractions of 2 Gy each) was delivered by a 6 MeV linear accelerator (LINAC) *Results:* In mice bearing xenograft derived from 22rv1 RT resulted in 30.4% decrease of tumor mass (tumor weight 0.797±0.166 gr) *vs*. controls (tumor weight 1,145±0.348 gr). The treatment with bicalutamide alone reduced tumor mass by 26% (0.838±0.184 gr) *vs*. control and when associated with RT resulted in 62% decrease (tumor weight 0.433±0.161 gr) with a Combination index (CI) of 0.90 (sub-additive effect). In order to verify the effects of the total androgenic blockade, the combinational treatment of castration with bicalutamide was associated with RT. Castration slightly decreased (15% tumor weight of 0.978±0.255 gr) the tumor growth of 22rv1 tumors xenografted in nude mice *vs*. controls. When bicalutamide and castration were associated to RT a synergistic reduction (CI=0.76) of tumor mass [67.5% (0.317±0.098 gr)] was observed. *In vitro* experience demonstrated that androgen deprivation therapies reduce the levels of Akt and GSK3β activities as well as the expression levels of HIF-1α, cyclin D1, Bcl2. *Conclusion:* These data suggest that the combinational treatment of castration with bicalutamide synergistically potentiate the radioresponse of preclinical models of aggressive Pca.

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HORMONE TREATMENT PROMOTES CASTRATION-RESISTANT PHENOTYPE BY INCREASING PI3K/AKT ACTIVITY IN PROSTATE CANCER MODELS. PRECLINICAL DATA ON COMBINED PHOSPHATIDYLINOSITOL-3-KINASE/ MTOR INHIBITION WITH ENDOCRINE THERAPY FOR ANDROGEN RECEPTOR-POSITIVE PROSTATE CANCER CELLS

Festuccia Claudio[1], Giovanni Luca Gravina[2], Andrea Mancini[1], Francesco Marampon[2], Leda Biordi[1], Margherita Piccolella[3], Marcella Motta[3], David Sherris[4], Andrea Lenzi[5], Emmanuele Jannini[6]

[1]Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università Degli Studi dell'Aquila;
[2]Divisione di Radioterapia, Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università di L'Aquila;
[3]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università di Milano;
[4]Chief Executive Officer and Director, Paloma Pharmaceuticals, Inc., Jamaica Plain, Massachusetts, USA;
[5]Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Università La Sapienza, Roma, Italy;
[6]Course of Endocrinology and Medical Sexology, Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università degli Studi dell'Aquila, Italy

Background: Castration is the standard therapy for advanced prostate cancer (PC). Although this treatment is initially effective, tumors invariably relapse as incurable, castration-resistant PC (CRPC). Adaptation of androgen-dependent PC cells to an androgen-depleted environment or selection of preexisting, CRPC cells have been proposed as mechanisms of CRPC development. *Aim:* This study was carried out to

determine the mechanisms associated with loss of androgen dependency and disease progression in prostate cancer. We hypothesized that hormone therapy favors the increase of PI3K/Akt/mTOR activity. Thus we investigated the relationship between the androgen receptor (AR) and PI3K/mTOR pathways and the impact of inhibiting both pathways in androgen-dependent and castration-resistant PCa models. *Methods:* To test this hypothesis the androgen receptor (AR) inhibitor, Casodex (Bicalutamide, BCLT), was administered *in vitro* to AR positive human prostate cancer cell lines and *in vivo* to 22rv1 CRPC cells. *Results:* We demonstrated that androgen-independent cells had higher Akt activity than androgen-dependent cells and that p-Akt expression and TORC1/TORC2 activity also paralleled the development of the CR phenotype and resulted in an increased tumorigenicity of 22Rv1-BCLT-R cells. Short term androgen stimulation with 10^{-12} M DHT significantly increased Akt activity in androgen sensitive PCa cells when compared with hormone therapy. Long term androgen stimulation, however, reduced sensitively Akt activity in 22rv1 cells whereas BCLT was able to increase the activity of this enzyme. The use of the pan PI3K/mTOR inhibitor, XL-765, greatly reduced the development of the CR phenotype induced by long-term BCLT treatment and this finding correlated with reduced Akt activity. XL-765 restored bicalutamide efficacy both in BCLTR strains and in cell derivatives originated from LnCaP after androgen ablation *in vitro*. Low doses of XL-765 additively increased the anti-tumor effects of BCLT. The sole PI3K inhibition by using XL147 also amplified the response to BCLT whereas lower effects were obtained with RAD001 (TORC1 inhibitor). Dual TORC1/TORC2 inhibitor P529 possessed a similar activity as XL765 through the similar and complete mTOR-mediated signaling inhibition. BCLT additively increased the antiproliferative effects of XL-765 or P529, by reducing the IC_{50} for these agents. These super-additive effects can be explained considering that the activation of PI3K can mediate the androgen-independent AR transactivation and treatment with XL765 resulted in a reduced protein expression and activation of the AR. Conversely, inhibition of the androgen receptor resulted in increased expression of IGFR1β, pHER2, pmTOR, and pAkt. The addition of P529 to bicalutamide treatment of resistant tumours significantly reduced tumour growth rates and tumour volumes. Anti-androgen treatment also increased protein expression of multiple signal transduction pathways earlier than vehicle-treated control xenografts. Our data provide evidence that compensatory cross-talk between the androgen receptor and PI3K/Akt/mTOR pathways may account for decreased sensitivity to androgen receptor antagonists and the progression to hormone-resistant prostate cancer. *Conclusion:* This study suggests that dual inhibition of AR and mTOR in castration-resistant xenograft models can restore sensitivity of tumours to anti-androgen therapy.

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RARE CANCERS OF THE UROGENITAL TRACT IN ITALY

Annalisa Trama[1], Gemma Gatta[1], Sandra Mallone[2], Nicola Nicolai[3]

[1]Unità di Epidemiologia Valutativa, Dipartimento di Epidemiologia Preventiva e Predittiva, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[2]Centro di Epidemiologia, Istituto Superiore di Sanità;
[3]Unità Urologia, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Background/Aim: Epidemiological information on Rare Cancers of the urogenital tract is scarce. The project Surveillance of rare cancers in Italy (RITA) provides estimates of the incidence, prevalence and survival of rare cancers in Italy (1), based on a new list of these diseases defined in collaboration with the project Surveillance of Rare Cancer in Europe (RARECARE). This abstract describes the epidemiology of rare urogenital cancers in Italy, as defined by these projects (2). *Materials and Methods:* Rare cancers were defined as those with an incidence rate <6 per 100,000/year. RITA analyzed population-based cancer registry (CR) data of Italian patients diagnosed from 1988 to 2002, with vital status information available up to December 31, 2003 (latest date for which most CRs had verified data). Cancer incidence and survival rates for 1995-2002, and prevalence at January 1, 2003 were estimated. Rare urogenital cancers described in this abstract include penis, urethra, renal pelvis and the ureter and testis. Rare entities within common cancer site, such as prostate and bladder, will be also described. *Results:* The annual number of new cases of penile cancer in Italy is estimated at 380, which is equivalent to an incidence rate of 6 per million in the population. The 5-year relative survival was 71%, while squamous cell carcinoma was the predominant morphological entity. Each year around 100 persons in Italy develop cancer of the urethra and 1.100 develop cancer of the renal pelvis or ureter (RPU). The incidence rate for cancer of the urethra and RPU was 1.7 (males 2.5; females 0.9) and 17 (males 25; females 10) per million, respectively. The 5-year relative survival for cancer of the urethra and RPU was 62% and 60%, respectively. Transitional cell carcinoma was the predominant morphological entity of cancer of the urethra and RPU. Finally, 1.500 new cases of testicular cancers are expected in Italy every year which correspond to an incidence rate of 25 per million in the population. The 5-year relative survival for testicular cancers was 95%. The complete prevalence for penis, urethra/renal pelvis ureter and testis was 6, 15 and 65 per 100.000, respectively. In the prostate the squamous, the infiltrating, and the transitional cell carcinoma were the main rare histologic sub-type. All together represented the 6% of

all prostate cancers. In the bladder, there were the squamous and the adenocarcinomas which together summed up to only the 2% of all bladder cancers. Five year relative survival for rare cancers was worse than for common cancers in both, prostate and bladder. *Discussion and Conclusion:* In view of the low number of cases and of the fact that more than one third patients with penis, urethra, renal pelvis and ureter cancer die of their disease, centralisation of treatment of these rare tumours to a select number of centers of expertise should be promoted. In some countries centers of expertise and networks of these centers have been established. In Italy, the "Rete Tumori Rari" was established in 1997. In France, the National Cancer Institute launched three calls for proposals (2009-2011), aimed at organizing the provision of care for adult patients with a rare cancer combining expertise available. In the field of genitourinary cancers, national and international agencies have been promoted by pool of experts, for pursuing common strategies of care to standardise treatment and improve clinical outcome. CRs databases, such as the one established for this study, demonstrated to be a valid and unique source of data to assess frequency and outcome of rare cancers. The RITA project is undertaking patterns of care study for a selected group of rare cancers, including testicular cancers.

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SURVIVAL OF PROSTATIC CANCER PATIENTS BY PROGNOSTIC RISK AND THERAPY

Roberto Foschi[1], Riccardo Valdagni[2], Silvia Francisci[3], Giovanna Tagliabue[4], Marina Vercelli[5], Paolo Contiero[4], Nicola Nicolai[6], Alberto Quaglia[7], Gemma Gatta[2]

[1]Unità di Epidemiologia Valutativa - Dipartimento di Epidemiologia Preventiva E Predittiva, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[2]Programma Prostata, Fondazione IRCCS Istituto Nazionale dei Tumori;
[3]Cancer Epidemiology Unit, Istituto Superiore di Sanità;
[4]Registro Tumori ed Epidemiologia Ambientale, Fondazione IRCCS Istituto Nazionale dei Tumori;
[5]Epidemiologia Descrittiva: Registro Tumori, Istituto Nazionale per la Ricerca Sul Cancro - Genova;
[6]Chirurgia del Testicolo, Fondazione IRCCS Istituto Nazionale dei Tumori;
[7]Epidemiologia Descrittiva, Registro Tumori Istituto Nazionale per la Ricerca Sul Cancro, Genova, Italy

Background/Aim: For a correct choice of therapy, the knowledge of prognostic risk of patients is needed. The introduction of prostate cancer screening may lead to different kinds of bias, among which lead time bias and the diagnosis of clinically insignificant tumors. The use of cure mixture models is useful to understand if the survival increases are due to these biases or to a real improvement of survival and allow a comparison among different regions. This study shows the 10-years survival for prostatic cancer patients in two Italian provinces (Genova and Varese) by age, risk category and therapy, shows the risks of death, the proportion of cured patients and the mean survival time of fatal cases. *Patients and Methods:* Prostatic cancer cases from the period 1996-1997, resident in the Varese (602 cases) and Genova (509 cases) provinces were included. The risk category was defined as a combination of TNM and Gleason. The radical therapy (prostatectomy and radiotherapy) was applied in the first 12 months from diagnosis, patients with distant metastasis were excluded. Age was divided in two groups: 15-74 years and 75-99 years. Relative survival was estimated using the EDERER2 methods stratifying by age, registry, risk category and treatment. The relative risks of death (RER) were estimated using a Poisson regression model. The proportion of cured patients (P) and the mean survival time of fatal cases (T) were estimated using the cured mixture models. *Results:* Patients younger than 75 years were 44% for Genova and 35% for Varese. At Genova there was a stronger attitude to carry out a radical radiotherapy compared to Varese (14% *vs*. 3%); at Varese there was a stronger attitude towards radical prostatectomy (35% *vs*. 25%). The distribution by risk category was similar between the two registries. Relative survival was similar between the two registries, with values at 10-years of 70% for Genova and 73% for Varese. Survival was lower for elderly compared to young people (55% *vs*. 80%). The survivals stratified by age were similar for young people, whereas were different for the elderly (60% Genova *vs*. 50% Varese). Relative survival was 100% for prostatectomized subjects, 68% for patients with radical radiotherapy and were lower for non radical treatments. The estimates of RER was significantly higher for Varese (40%) compared to Genova. Radical prostatectomy had the lowest RER (0.1) for prostatectomy and low (0.7) for radiotherapy compared to non-radical treatments. Patients in the high risk category (any T, M1or N1 and high Gleason) had a significant RER of 19.3 compared to lower risk patients (T1T2, N0NX, M0MX and low Gleason). For the elderly the proportion of cured was significantly higher at Genova

compared to Varese, whereas the mean survival time of fatal cases was similar in the two registries. *Discussion and Conclusion:* The main prognostic factors of prostate cancer are age, risk category, therapy and the place of residence. Survival was similar between the registries for 15-74 aged patients, however the elderly survival and % of cured showed a significantly higher risk at Varese compared to Genova. The strong protective effect of prostatectomy should be considered with caution because of the selection of subjects that undertake the treatment. The use of cured models ensure that the observed survival in the two areas are not due to the cited potential biases.

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

Maria Francesca Alvisi[1], Tiziana Magnani[1], Tiziana Rancati[1], Giario Conti[2], Michele Gallucci[3], Rocco Papalia[3], Giuseppe Martorana[4], Davide Diazzi[4], Roberto Sanseverino[5], Giorgio Napodano[5], Pierpaolo Graziotti[6], Gianluigi Taverna[6], Silvia Proietti[6], Marco Tanello[7], Ezio Fregio[7], Andrea Turci[8], Giacomo Cicchetti[8], Enrico Bollito[9], Maurizio Colecchia[10], Michelangelo Fiorentino[11], Rodolfo Montironi[12], Carlo Patriarca[13], Steno Sentinelli[14], Riccardo Valdagni[15]

[1]Programma Prostata, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[2]Dipartimento di Chirurgia, Ospedale Sant'Anna, Como;
[3]Divisione di Urologia, Istituto Regina Elena, Roma;
[4]Divisione di Urologia, Policlinico Sant'Orsola Malpighi, Bologna;
[5]Divisione di Urologia, Ospedale Umberto I, Nocera Inferiore;
[6]Divisione di Urologia, Istituto Clinico Humanitas, Rozzano;
[7]Divisione di Urologia, Ospedale Civile, Desenzano;
[8]Divisione di Urologia, Ospedale M. Bufalini, Cesena;
[9]Servizio di Anatomia Patologica, Ospedale San Luigi Gonzaga, Orbassano;
[10]S. C. Anatomia Patologica, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[11]Servizio di Anatomia Patologica, Policlinico Sant'Orsola Malpighi, Bologna;
[12]Servizio di Anatomia Patologica, Ospedali Riuniti, Torrette di Ancona;
[13]Servizio di Anatomia Patologica, Ospedale Sant'Anna, Como;
[14]Servizio di Anatomia Patologica, Istituto Regina Elena, Roma;
[15]S.c. Radioterapia Oncologica 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Aim: We here report on the three year PRIAS-SIUrO-ITA experience on Active Surveillance (AS). Special focus is given on possible correlations between Active Treatment Free Survival (ATFS) and patient's characteristics at diagnosis, with the aim of investigating the ability to predict disease reclassification. *Patients and Methods:* In December 2009 the SIUrO-PRIAS-ITA project started enrolment in PRIAS (Prostate cancer Research International: Active Surveillance), the international study on observational setting for low risk prostate cancer (PC) patients, coordinated by Erasmus University Medical Center in Rotterdam. Eligibility criteria were: iPSA ≤10 ng/ml, Gleason Score ≤6 or Gleason 3+4 in over 69 year men with <10% positive cores, T1c or T2, PSA density ≤0.2 ng/ml/cc, max 2 positive cores (<10% positive cores in case of saturation biopsy), biopsy samples according to prostate volume (8 cores for 0-40 ml, 10 for 40-60 ml and 12 for >60 ml), pathologic review of diagnostic biopsy. Actuarial ATFS was assessed using Kaplan–Meier analysis. Correlation between ATFS and clinical risk factors was determined using the log rank test and Cox Proportional Hazards Model. Age, DRE at diagnosis, iPSA, PSA density, number of positive cores, number of negative cores, percentage of positive cores, maximum core length containing cancer and prostate volume were considered as factors potentially influencing ATFS. *Results:* Between December 2009 and January 2013, 310 Italian patients were enrolled in SIUrO-PRIAS-ITA. Median age at inclusion was 65 years (range 46-80 years), median iPSA was 5.4 ng/ml (range 0.15-10 ng/ml). Two hundred and forty-eight/310 patients (80%) are still on AS with a median follow-up of 42 months (range 0.13-58.8 months), median time in AS is 14 months (range 0.13-58.8 months). Forty-two patients (13.5%) dropped out from AS because of disease progression/reclassification: 3 due to PSADT, 39 due to upgrading and/or upsizing at re-biopsy (9/39 at first re-biopsy). Twenty patients dropped out due to offprotocol reasons. Patients who dropped out were addressed to active treatment on the basis of the current guidelines and patient's choice. Biopsy-driven ATFS (Figure 1) resulted to be correlated to PSA density ≤0.12 ng/ml/cc (p=0.01, ATFS at 27 months 91% *vs*. 75%), prostate volume ≤40cc (p=0.009, ATFS at 27 months 75% *vs*. 82%) and number of total cores at diagnostic biopsy ≤12 (p=0.015, ATFS at 27 months 75% *vs*. 90%). Best fit multivariable model for biopsy-driven ATFS resulted in a three-variable model (overall p=0.0023, AUC=0.70), including number of total core sampled in diagnostic biopsy ≤12 (risk factor, p=0.023, HR=2.13), prostate volume ≤40cc (risk factor, p=0.09, HR=1.79) and PSA density ≥0.12ng/ml/cc (risk factor, p=0.116, HR=1.73). Figure 2 shows survival probabilities predicted by Cox Proportional Hazard Model at 18 months from enrolment together with observed drop out events. The Hosmer and

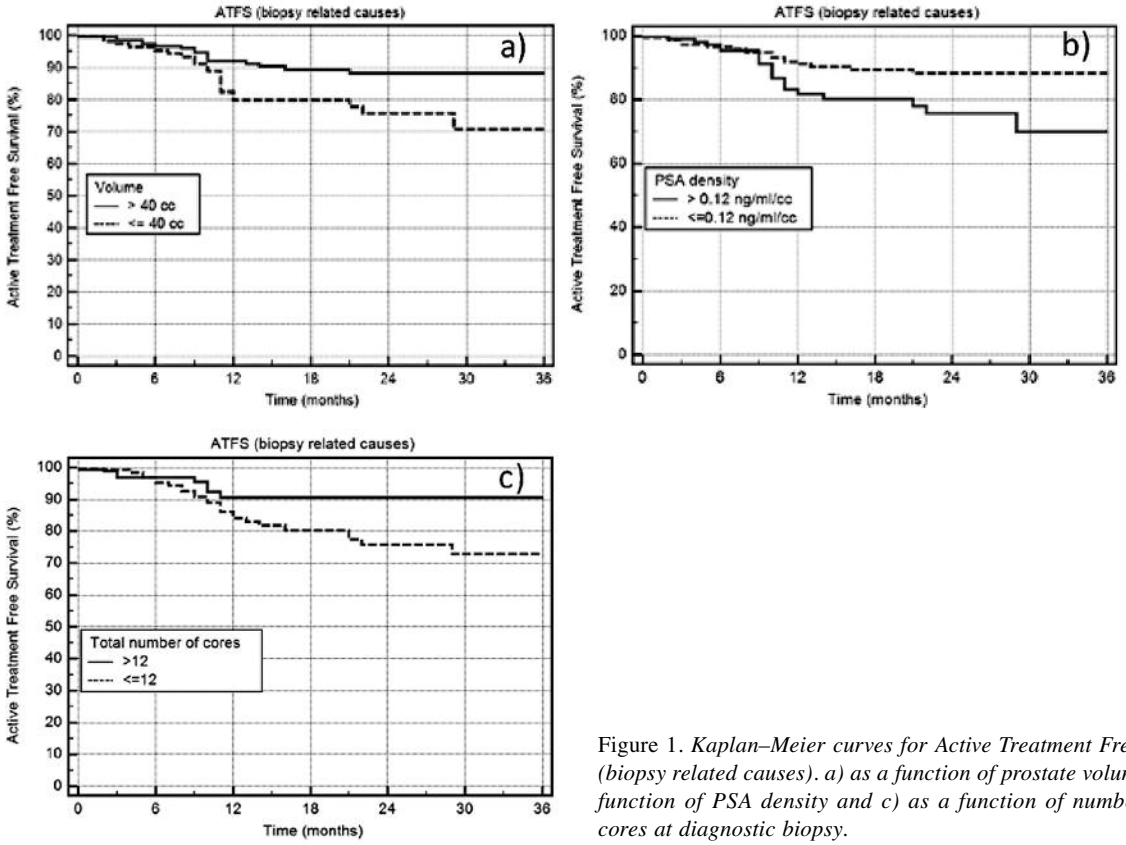

Figure 1. *Kaplan–Meier curves for Active Treatment Free Survival (biopsy related causes). a) as a function of prostate volume, b) as a function of PSA density and c) as a function of number of total cores at diagnostic biopsy.*

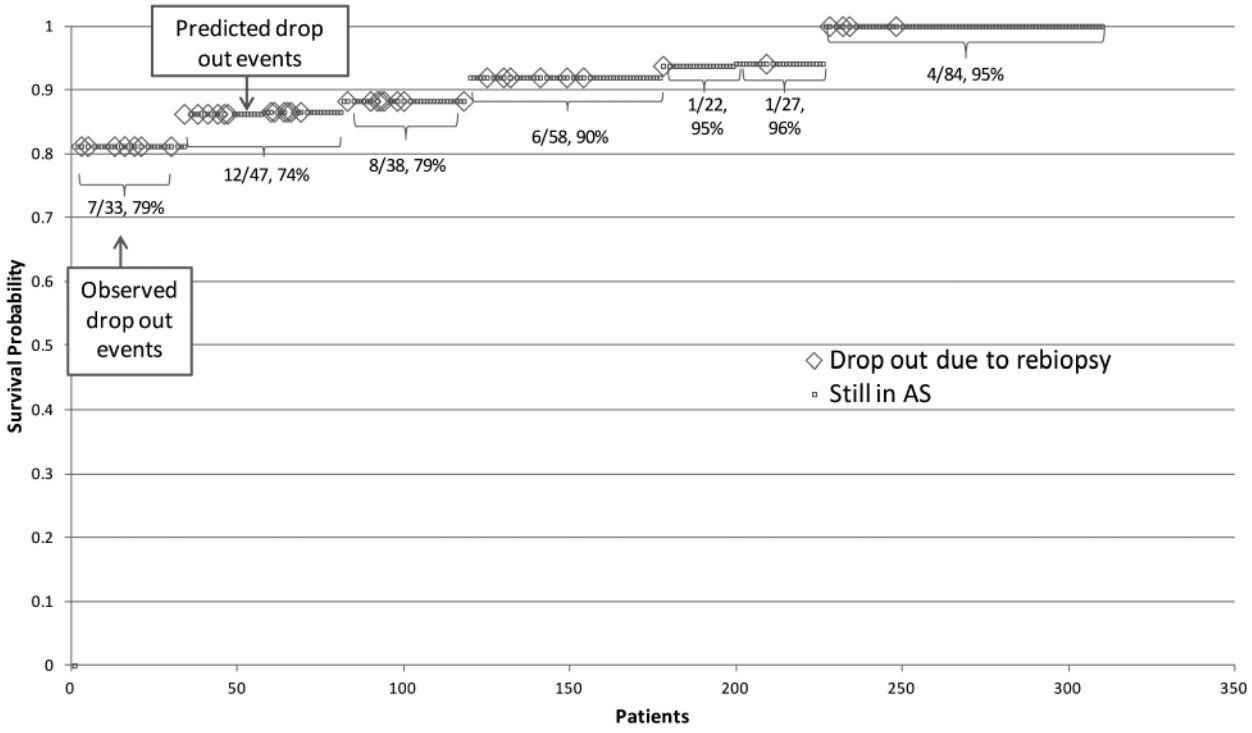

Figure 1. *Active Treatment Free Survival at 18 months form active surveillance enrollment as predicted by Cox Proportional Hazard model together with observed drop out events.*

Lameshow test confirmed good calibration of the Cox model (*i.e.* no significant differences between observed and predicted drop out events, p=0.99). Figure 1: Kaplan-Meier curves for Active Treatment Free Survival (biopsy related causes): a) as a function of prostate volume, b) as a function of PSA density and c) as a function of number of total cores at diagnostic biopsy. 1 Predicted drop out events 6/58, 90% 12/47, 74% 8/38, 79% 1/22, 95% 1/27, 96% 0.9 4/84, 95% 0.8 0.7 7/33, 79% Survival Probability 0.6 0.5 Observed drop out events 0.4 Drop out due to rebiopsy Still in AS 0.3 0.2 0.1 0 0 50 100 150 200 250 300 350 Patients Figure 2: Active Treatment Free Survival at 18 months from active surveillance enrollment as predicted by Cox Proportional Hazard model together with observed drop out event. *Conclusion:* AS is proving an acceptable alternative to radical treatment for patients with low or very low risk PC, which might harbor an indolent disease, thus sparing them overtreatment and treatment induced toxicities. Unfortunately, at present, there are no means to identify indolent PC at diagnosis and disease reclassification occurs in 20% patients after a short period on AS. In the SIUrO-PRIAS-ITA population ATFS is correlated to PSA density (risk factor related to the disease) and to prostate volume and number of bioptic cores at diagnosis, indicating an enhanced risk of disease reclassification in patients with a "suboptimal" diagnostic biopsy. Acknowledgment to Foundations Monzino for financial supports.

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DOSIMETRIC AND CLINICAL PREDICTORS OF ACUTE URINARY SYMPTOMS AFTER RADIOTHERAPY FOR PROSTATE CANCER

Cesare Cozzarini[1], Viviana Carillo[2], Tiziana Rancati[3], Sergio Villa[4], Pierfrancesco Franco[5], Claudio Degli Esposti[6], Franco Girelli[7], Vittorio Vavassori[8], Riccardo Valdagni[9], Claudio Fiorino[10]

[1]Radioterapia,
[2]Fisica Medica, Istituto Scientifico San Raffaele, Milano;
[3]Programma Prostata, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[4]Divisione di Radioterapia 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[5]Divisione di Radioterapia, Ospedale di Aosta;
[6]Divisione di Radioterapia, Ospedale di Bellaria, Bologna;
[7]Divisione di Radioterapia, Ospedale di Ivrea;
[8]Divisione di Radioterapia, Humanitas Gavazzeni, Bergamo;
[9]Divisione di Radioterapia 1 e Programma Prostata, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milano;
[10]Divisione di Fisica Medica, Istituto Scientifico San Raffaele, Milano, Italy

Background and Purpose: In April 2010 a prospective cohort study (DUE-01) was activated with the aim to develop predictive models of genito-urinary (GU) toxicity and erectile dysfunction after high dose radiotherapy (RT) for prostate cancer; patients (pts) treated with conventional (1.8-2Gy/fr, CONV) or moderate hypofractionation (2.5-2.7Gy/fr HYPO) were included. The aim of this ad-interim analysis was to find correlation between pollakiuria (POLL), dysuria (DYS) and nicturia (NICT) as measured by IPSS at RT end and clinical/dosimetric risk factors. *Materials and Methods:* IPSS questionnaire at the start and at the end of RT were prospectively collected; Planning data were recovered and analyzed with a dedicated program (Vodca, MSS GmbH, Zurich), including absolute (cc/cm^2) and % bladder dose-volume/surface (DVH/DSH) parameters referred to both the whole treatment and to the weekly delivered dose (DVHw/DSHw). Relevant clinical factors were prospectively collected including T stage, concomitant morbidities and drugs, use of hormonal therapy (HT), previous surgery, smoking, age, BMI and prostate volume. In IPSS, each item ranges from 0 to 5 with increasing score indicating increasing toxicity severity: for each question, a score≥4 at the end of the therapy was considered as the end point. Logistic uni- and backward multi-variate (MVA) analyses were performed including weekly DVHw/DSHw and clinical variables. Best DVHw/DSHw parameters were selected by statistical comparison of the differences between patients with/without the sum score of the seven questions. *Results:* At the time of this analysis (January 2013), 339 pts have been enrolled 9 Institutes. Clinical data of 212/339 pts were available (93 CONV and 119 HYPO). of 172/212 pts both baseline and end-RT IPSS were collected. For 179/212 pts also DVH/DSH were available. Questions POLL, DYS and NICT (respectively 2, 3 and 7) showed the larger increase of the fraction of pts with scores ≥4 between basal and end questionnaire; consequently, the analysis focused on these symptoms; the number of patients with scores≥4 increased from 8 to 30 for POLL, from 5 to 20 for DYS and from 12 to 34 for NICT. At MVA (overall p<0.0001), the main independent predictors of acute POLL were: smoke (OR:2.74, p=0.04) and S8.5w (OR:1.01, p=0.10); AUC=0.66. The model was confirmed also after the exclusion of pts with baseline IPSS-POLL ≥4 (AUC=0.69). Main independent predictors of acute DYS were: HT (OR:4.61, p=0.02), S8.5w (OR:1.01, p=0.16) and S12.5w (OR:1.04, p=0.08), AUC=0.74. Finally independent predictors of acute NICT were: baseline IPSSNICT (OR:13.5, p=0.001), and S12.5w (OR:1.05, p=0.012), AUC=0.69. *Conclusion:* First results of DUE01 show that bladder DSHw predicts the risk of severe acute POLL, DYS and NICT together with the baseline scores, smoke (POLL) and HT (DYS).

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THE PROGNOSTIC ROLE OF MOLECULAR TESTING IN PATIENTS WITH PROSTATE CANCER: A PRELIMINARY STUDY

Enrico Bollito[1], Matteo Manfredi[2], Eleonora Duregon[1], Massimo Freschi[3], Vincenzo Scattoni[4], Mauro Papotti[1], Francesco Porpiglia[2]

[1]Dept. of Pathology and [2]Urology, University of Turin at San Luigi Gonzaga Hospital, Orbassano, Turin; [3]Dept. of Pathology and [4]Urology, University Vita-Salute, San Raffaele Hospital, Milan, Italy

Background: The availability of new bio-markers useful to predict prostate cancer (PC) aggressiveness is a basic need in PC pathology. The distinction between indolent tumors and potentially lethal PC is currently based on serum PSA and Gleason Score evaluations. These data, especially when incorporated into nomograms have proven very useful, but often insufficient for a proper prognostic assessment. Ki67 proliferation index determination and, in special cases, the search for neuroendocrine cells gave promising results, but none of these markers permitted to obtain conclusive data. More recently, some studies aimed at identifying PC aggressiveness were focused on molecular analysis, in particular using gene-profiling methods. For this reason, different panels of genes are currently provided by companies and offered for *in vitro* analysis of tumor tissue, mainly based on RNA analysis in both diagnostic and prognostic settings. Moreover, the availability of methods that allow to use paraffin embedded material for RNA analysis is further increasing the horizon of biological parameters evaluation. *Study Design:* Among the genes studied so far, we focused our interest on a group of cell-cycle progression (CCP) related genes incorporated in a multi-gene assay named Prolaris®, developed and marketed by Myriad Genetics Laboratories (Salt Lake City, USA). With the aim to provide a more accurate risk stratification in PC affected men, 46 genes (31 cell-cycle related and 15 housekeeping genes) were selected. Total RNA was extracted and converted into cDNA before amplification with quantitative real-time PCR. To generate a CCP score, expression of the cell-cycle genes was normalized by subtracting the average of housekeeping genes. CCP score was calculated as a ratio of normal to abnormal genes. The CCP group actually assessed by Prolaris® has been previously validated retrospectively in specimens following radical prostatectomy or transurethral prostate resection (1) and, more recently, on prostate biopsy specimens (1). In these studies, the Prolaris Score™ was shown to predict the biochemical failure after radical prostatectomy and PC specific mortality. In this preliminary study, we will assess the prognostic value of the cell cycle progression (CCP) - Prolaris Score™ in an Italian case series, evaluating the distribution of the Score compared with previous cohorts and correlating it with other prognostic factors (Gleason Score, PSA, age, TNM Tumor Stage). An open-label, observational study was started at our Institutions, after receiving the ethic committee approval. Patients presenting with localized PC (T1-3, N0-x, M0-x) confirmed by biopsy, with WHO Performance Index <2, were enrolled. The Prolaris test was performed measuring the expression of 31 genes involved in CCP with quantitative RT-PCR on RNA extracted from formalin-fixed paraffin-embedded tumor samples on 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 –3.0 and +7.0 were expected by this assay. Finally we calculated CAPRA scores (3) to create a combined analysis, incorporating Prolaris and CAPRA, based on the Cox Proportional Hazards model validated previously. In the previously published paper (2), univariate analysis on 349 samples showed a hazard ratio (HR) for death from prostate cancer of 2.02 (95% CI (1.62, 2.53), $p<10^{-9}$) for one-unit increase in Prolaris Score™ . In multivariate analysis, compared to standard prognostic factors, Prolaris Score™ appeared superior (HR for one-unit increase=1.65, 95% CI (1.31, 2.09), $p=3\times10^{-5}$), when compared to Gleason score ($p=5\times10^{-4}$) and PSA ($p=0.017$), providing significant additional contributions. Based on the literature, CCP gene assay seems to be predictive of clinical outcome. Moreover, it seems to add useful information when compared to standard prognostic factors.

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STAGE I SEMINOMA: THE ROLE OF LYMPHOVASCULAR INVASION IN DECISION-MAKING BETWEEN RADIOTHERAPY AND SURVEILLANCE

Girolamo Spagnoletti, Angela Pia Solazzo, Grazia Nardella, Maria Piserchia, Raffella Rignanese, Giovanni Plotino, Anna Mazza, Anna Maria Leo, Giuseppe Bove

Struttura Complessa di Radioterapia, Azienda Ospedaliero-Universitaria Ospedali Riuniti, Foggia, Italy

Introduction: Surgery is the most important therapy for testicular cancer. For stage I seminoma, the standard adjuvant treatment options include surveillance, radiation therapy or chemotherapy with 1 or 2 cycles of carboplatin. With surgery and postoperative options, the present management of testicular seminoma can achieve excellent survival rates, in the order of 99%. A number of prospective nonrandomized studies of surveillance have been conducted. According to them, the presence/absence of risk factors could be a guide in identifying a patient-tailored strategy. Other authors discourage risk-adapted management for stage I seminoma. Our retrospective work aims at evaluating the role of lymphovascular invasion in order to identify a favourable group of patients for whom surveillance is a safe option and adjuvant therapies are unnecessary. *Patients and Methods:* Between January 2007 and December 2010, 44 patients underwent orchidectomy with a histological diagnosis of pure seminoma. Median age was 35 years (range between 25 and 55 years). Thirty-four patients presented with a tumour limited to the testis and epididymis without lymphovascular invasion (pT1); the remaining 10 patients had a vascular/lymphatic invasion (pT2). Eighteen patients with pT1 disease were treated with para-aortic lymph node irradiation. A similar group of 16 pT1 patients received no adjuvant treatment. Patients with pT2 disease were all treated with radiotherapy. Radiation therapy was administered 4-6 weeks after surgery with a median total dose of 21 Gy (range between 20 and 25.2 Gy) with 1.5, 1.8 or 2 Gy per fraction. No patient received chemotherapy. Relapse rate, metastasis rate, Disease Free Survival (DFS) and Overall Survival (OS) were calculated. *Results:* Respectively, median and minimum follow-up were 48 months and 26 months, long enough if we consider that the risk of recurrence is highest in the first 2 years and decreases after that. Follow-up for patients on surveillance included a clinical examination with serum tumour markers (AFP, betaHCG and LDH) every 3 months, an abdominal-pelvic CT every 6 months and a chest CT annually. Follow-up of patients treated with radiotherapy included a physical check with serum markers every 3 months and an abdominal-pelvic CT annually. No local relapse and no distant metastases were observed in any of the three groups. Only one patient experienced controlateral testicular cancer and he was successfully treated with surgery. DFS and OS were 100% since all patients were alive in complete remission at last control, in all of the three groups. *Discussion and Conclusion:* Some years ago standard adjuvant management was extended-field radiotherapy. During the last years alternative strategies, including surveillance, chemotherapy and para-aortic lymph node radiotherapy have been explored. With these approaches all patients affected by stage I testicular seminoma can expect to be permanently cured. Our work confirms that either radiotherapy or surveillance are effective strategies after surgery, providing excellent results in terms of local control and survival. Concerns about second cancers complicating radiotherapy are reducing its popularity; the absence of tumour markers, the need for frequent scans and evidence of poor compliance argue against surveillance. The invasion of testicular veins or lymphatics has been considered the most important predictor of recurrence. Unfortunately, recent attempts to validate this prospectively failed. Maybe surveillance could be the preferred option also for pT2 patients. However, we still recognize lymphovascular invasion as the key prognostic factor. In our experience, the absence of vascular/lymphatic invasion identifies a group of patients for whom surveillance is a valid and safe option and can be preferred to radiotherapy or chemotherapy. Finally, despite the limited numbers of patients, our retrospective analysis shows that probably, in this favourable group, surveillance does not require a more intensive follow-up than radiotherapy.

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CORRELATION BETWEEN BASAL PCA3 LEVEL AND BIOPSY-DRIVEN DISEASE RECLASSIFICATION IN ACTIVE SURVEILLANCE

Cristina Marenghi[1], Tiziana Rancati[1], Fernando Ravagnani[2], Claudia Lombardo[2], Francesca Taverna[2], Tiziana Magnani[1], Maria Francesca Alvisi[1], Maurizio Colecchia[3], Nicola Nicolai[4], Nice Bedini[5], Roberto Salvioni[4], Riccardo Valdagni[6]

[1]Programma Prostata,
[2]Oncologia Sperimentale,
[3]S. C. Anatomia Patologica,
[4]Urologia,
[5]Divisione di Radioterapia,
[6]Divisione di Radioterapia e Programma Prostata,
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Background: One of the open issues in Active Surveillance (AS) for prostate cancer (PCa) is lack of consensus on the optimal selection criteria and on triggers for drop out and

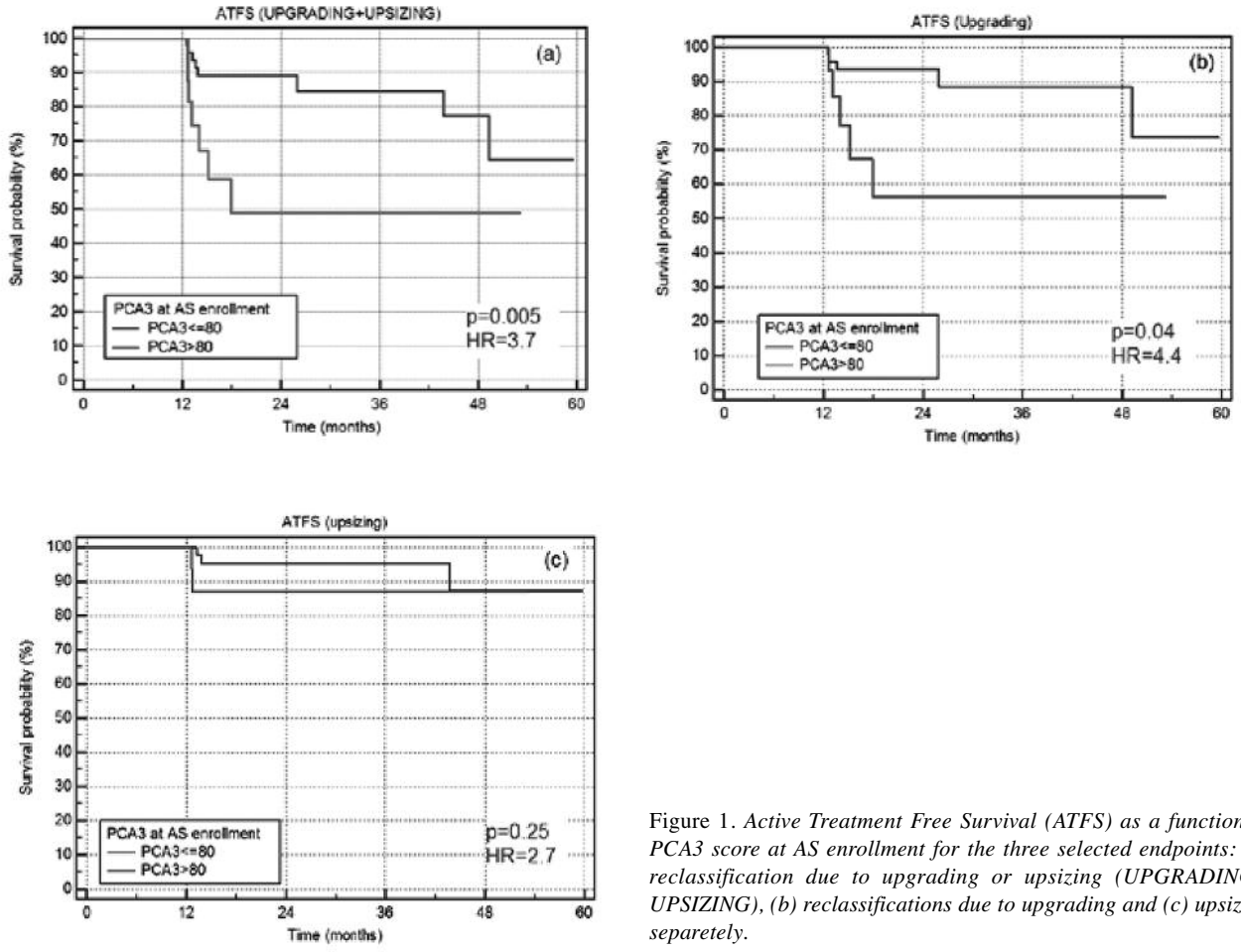

Figure 1. *Active Treatment Free Survival (ATFS) as a function of PCA3 score at AS enrollment for the three selected endpoints: (a) reclassification due to upgrading or upsizing (UPGRADING+ UPSIZING), (b) reclassifications due to upgrading and (c) upsizing separetely.*

radical intervention. The current methodologies for PCa staging are sub-optimal in distinguishing patients (pts) with indolent cancer from pts harboring aggressive disease. Ongoing research is focused on the study of new biomarkers that could more clearly discriminate PCa aggressiveness; among them PCA3, which is a prostate specific noncoding mRNA that is significantly overexpressed in PCa tissue compared to non-neoplastic prostatic cells. Urinary PCA3 level has been significantly associated with Gleason Score (GPS) and PCa volume in prostatectomy series, suggesting that this marker may be useful in the selection of pts for AS. The goal of the present study was to evaluate the relationship between PCA3 and biopsy-driven disease reclassification in an AS cohort. Preliminary results are presented. *Patients and Methods:* Starting in 2005, we are proposing AS in very low-risk Pca within an institutional protocol (SAINT). In November 2007 we activated the international PRIAS protocol. Until February 2013 a total of 454 pts were enrolled in AS (287 PRIAS + 167 SAINT). Entry criteria are: iPSA ≤10ng/ml, T≤T2a, GPS≤3+3, maximum 2 positive cores (PRIAS) and positive biopsy-cores≤20% (SAINT), max core length containing cancer≤50% (SAINT), PSA density<0.2ng/ml/cc (PRIAS). Pts are monitored through PSA kinetics and with DRE and re-biopsy. Beginning in 2008, pts were proposed to provide urine samples for PCA3 measurement at AS enrollment (no specific selection criteria were applied). Additional samples were collected before re-biopsy. PCA3 was measured using Gen-probe assay. Biopsy-driven active treatment free survival (ATFS) was assessed using Kaplan-Meier survival analysis and the log-rank test was used to assess correlation between PCA3 score at AS enrollment and ATFS. Three separate endpoints were considered: (1) reclassification due to upgrading or upsizing (UPG+UPS), (2) reclassification due to upgrading (UPG) and (3) upsizing (UPS) separately. Results Seventy-eight pts had PCA3 measured at AS enrollment (75/78 had at least one re-biopsy). Twentyone and 3 pts had a second and a third evaluation, respectively. There was no significant difference in age, PSA and PSA density between the subpopulation with PCA3 measurement and the whole AS population. A PCA3 score>80 was correlated with increased disease reclassification

rate due to UPG+UPS (log-rank test p=0.005, Hazard Ratio=3.7) and to UPG (log-rank test p=0.04, Hazard Ratio=4.4). Kaplan-Meier curves are presented in Figure 1. *Conclusion:* In this preliminary analysis, in a cohort of pts with very-low risk PCa who were selected for AS, a PCA3 score >80 was significantly associated with disease re-classification at re-biopsy. Specifically, it was correlated to enhanced rates of upgrading. Further analysis is necessary to assess the usefulness of PCA3 in AS management.

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EXTERNAL VALIDATION OF A MODEL FOR THE PREDICTION OF ACUTE GI TOXICITY IN PROSTATE CANCER PATIENTS

Tiziana Rancati[1], Barbara Avuzzi[2], Claudio Stucchi[3], Emanuele Pignoli[3], Sergio Villa[2], Claudio Fiorino[4], Viviana Carillo[4], Cesare Cozzarini[5], Riccardo Valdagni[6]

[1]Programma Prostata,
[2]Divisione di Radioterapia,
[3]Sc di Fisica Medica, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[4]Divisione di Fisica Medica,
[5]Divisione di Radioterapia, Istituto Scientifico San Raffaele, Milano;
[6]Divisione di Radioterapia e Programma Prostata, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Purpose: External independent validation of a model (nomogram, Red J 71(4) 2008) for the prediction of acute GI toxicity (tox, within 1 month after treatment end) in prostate cancer patients (pts) treated with radical radiotherapy (RT). *Materials and Methods:* Grade ≥2 acute GI tox is the endpoint of the nomogram. It includes: mean rectal dose, presence of haemorrhoids, use of anticoagulants/ antiaggregants, neoadjuvant androgen deprivation, diabetes and pelvic node irradiation. The population (POP) used to develop the model consisted of pts accrued in a multicenter prospective trial and treated in 2002-04 with 3DCRT, median dose 74Gy, 2Gy/fr. Toxicity was scored through pt assessed questionnaire. The independent POP used for external validation comprised prospective evaluated pts enrolled in 2 centers (which did not participate in the previous trial) and treated in 2010-12 with IMRT, median dose 78Gy, 2Gy/fr or moderate hypofractionation (hypo, 2.3-2.65Gy/fr). Toxicity was scored with the same questionnaire and same timing. Calibration of the model in the independent POP was judged using Hosmer-Lemeshow (HL) test, discriminating capability was assessed using AUC. Results 149 pts were enrolled, 40 (26.8%) exhibited grade ≥2 acute GI toxicity. Hypo was used in 43 (28.9%) pts. Rectal doses in the hypo subgroup were corrected using the linear-quadratic model (alpha/beta=10Gy) and total treatment time/dose recovery corrections (assumed=0.7Gy/day). Calculated toxicity probabilities in the independent POP ranged from 10% to 50%. Calibration was very good, p of HL test=0.76, *i.e.* no significant difference between expected *vs.* observed toxicity probabilities in 5 consecutive intervals: 13% *vs.* 14%, 23% *vs.* 25%, 28% *vs.* 21%, 30% *vs.* 24% and 40% *vs.* 44%. Discrimination was poor (AUC=0.61) but comparable to the one in the original POP (AUC=0.62). The model has satisfactory specificity (75%, with a cutoff=30%), but poor sensitivity (42%). *Conclusion:* The purpose of a predictive model is to provide valid outcome predictions for new pts. Validation hence is an important aspect of the process of predictive modelling. External validation of a model for acute GI toxicity was performed providing a measure of generalizability of model to POPs that are plausibly related. Validation resulted in very good calibration, despite some important differences in the POPs (year of RT, 3CDRT *vs.* IMRT, prescribed doses, hypo). The model has satisfactory capability in predicting absence of tox, while the % of false positive is quite high. The range of predicted toxicity probabilities is narrow and poor discrimination is related to this. A possible explanation might reside in important predictive variables (genetic?) which are not included in the model.

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PATIENTS' CHARACTERISTICS, DIAGNOSTIC AND PRIMARY THERAPY PROCEDURES IN PROSTATE CANCER PATIENTS ANALYZED IN THE PERIODS 1996-1999 VS 2005-2007

Laura Botta[1], Annalisa Trama[2], Roberto Foschi[2], Nicola Nicolai[3], Michele Lodde[4], Andreas Seeber[5], Michael Aigner[6], Francesco Bellù[7], Tomas Dal Cappello[8], Mario Fusco[9], Maria Francesca Vitale[10], Fabio Pannozzo[11], Maurilio Natali[11], Antonio di Croce[12], Marina Vercelli[13], Alberto Quaglia[14], Claudia Casella[14], Antonella Puppo[14], Rosario Tumino[15], Eugenia Spata[15], Lucia Mangone[16], Francesca Ferrari[17], Massimo Vicentini[17], Silvano Piffer[18], Maria Adalgisa Gentilini[18], Maddalena Cappelletti[18], Roberto Rizzello[18], Lucia Preto[19], Giovanna Tagliabue[19], Paolo Contiero[19], Riccardo Valdagni[20], Gemma Gatta[2]

[1]Unità di Epidemiologia Valutativa - Dipartimento di Epidemiologia Preventiva e Predittiva,
[2]Epidemiologia Valutativa,
[3]Clinica Urologica, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[4]Clinica Urologica, Ospedale di Bolzano, Italy;
[5]Ematologia E Oncologia, Ospedale di Merano and Medical Universtiy, Innsbruck, Austria;
[6]Clinica Urologica, Ospedale di Bressanone;
[7]Registro Tumori, Registro Tumori dell'Alto Adige;
[8]Epidemiologia: Registro Tumori, Registro Tumori

dell'Alto Adige;
[9]Registro Tumori, Registro Tumori di Popolazione della Regione Campania;
[10]Epidemiologia Descrittiva: Registro Tumori, Registro Tumori di Popolazione della Regione Campania;
[11]Registro Tumori, Registro Tumori I Popolazione della Provincia di Latina;
[12]Biologia, Istituto Nazionale Tumori Regina Elena Irccs - Ifo, Roma;
[13]Registro Tumori, Registro Tumori Regione Liguria, IRCCS A.O.Universitaria San Martino-IST Genova and Dipartimento di Scienze della Salute, Università di Genova;
[14]Registro Tumori, Registro Tumori Regione Liguria, IRCCS A.O.Universitaria San Martino-IST Genova;
[15]Registro Tumori, Registro Tumori della Provincia di Ragusa;
[16]Statistica, Qualità e Studi Clinici, ASMN-IRCCS, Reggio Emilia;
[17]Struttura Operativa Registro Tumori Reggio Emilia_epi, Registro Tumori Reggiano, Reggio Emilia;
[18]Epidemiologia Clinica e Valutativa, Registro Tumori della Provincia di Trento;
[19]Registro Tumori, Registro Tumori della Provincia di Varese;
[20]Divisione di Radioterapia e Programma Prostata, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano, Italy

Introduction/Background/Aim: In Italy, prostate cancer is the first cancer among the most frequently diagnosed in men. The incidence rates vary considerably across Italy (109.5 cases per year over 100,000 in Northern Italy, 85.3 over 100,000 in the Central regions, and 61.4 over 100,000 in the South). 5yr relative survival being 88% with geographic variation that may depend on the different use of PSA testing (North-West regions: 90% *versus* 78% in the South). The main goal of the present report is to describe patients' characteristics at diagnosis and to analyze diagnostic and therapeutic procedures for prostate cancer in the different Italian regions in two different periods (1996-1999 and 2005-2007). *Methods:* 8 different Cancer Registries (CRs) form North to South participated in the study. Each CR contributed with a maximum of 600 incidence cases, 300 from 1996-1999 (first period) and 300 from 2005-2007 (second period). Cases were randomly selected from the EUROCARE (European Cancer Registry based study on survival and care of cancer patients) database. Information were collected on diagnostic procedures, stage at diagnosis, treatment (radical prostatectomy, radical radiotherapy, hormonal therapy, chemotherapy, no treatment and unknown treatment), clinical follow-up and life status. Clinical Stage (cTNM) was grouped in five categories: 1. T1/T2, N0/NX, M0/MX 2. T3/T4, N0/NX, M0/MX 3. Any T, N1, M0/MX 4. Any T, any N, M1 5. Unknown primary treatment was identified as the treatment delivered within one year after the diagnosis. *Results:* 4577 cases were analyzed, 2140 in 1996-1999 and 2438 in 2005-2007. Regarding the clinical staging, T1/T2, N0/NX, M0/MX increased in 2005-2007 (42% *vs*. 73%) while all other categories decreased as follows: T3/T4, N0/NX, M0/MX (10% *vs*. 5%), any T, N1,M1 (17% *vs*. 8%), cTNM unknown (31% *vs*. 14%). The variability among registries was high; specifically in the first period, those who had T1/T2, N0/NX, M0/MX varied from 67% in Varese, to 15% in Latina. T3/T4, N0/NX, M0/MX from 19% in Varese, to 2% in Reggio Emilia and metastatic disease from 24% in Naples to 9% in Alto Adige. In the second period, those with T1/T2, N0/NX, M0/MX varied from 88% in Genoa, to 44% in Naples. T3/T4, N0/NX, M0/MX were 10% in Trento *vs*. 0.8% in Ragusa. Metastatic disease varied from 11% in Naples to 3% in Genoa. Radical radiotherapy and prostatectomy doubled in 2005-2007 (21% *vs*. 40% and 7% *vs*. 12%, respectively), hormonal therapy decreased (36% *vs*. 22%); cases with unknown treatment halved (25% *vs*. 14%), with variability across registries. Mean age at diagnosis decreased in 2005-2007 (73yr to 70yr). On the other hand, the percentage of PSA value at diagnosis <10 ng/ml increased in this period (30.3% to 54%). Analyses on the risk class are in progress. *Discussion and Conclusion:* This study shows heterogeneities of patients' features at diagnosis and of primary treatments in different periods and geographic areas with more significant differences in registries in the first period of analysis when compared to the second (2005-2007). This study highlights, also in our country, the recent, well known phenomenon of stage migration and the consequent changes in primary treatments over time. These findings are mostly due to the extensive use of PSA testing, which also explains the widely recognized problem of over diagnosis. This study was carried out thanks to the funding received from AIRC (Associazione Italiana per la Ricerca sul Cancro), Amgen Dompé and "Fondazione Trentina per la Ricerca sui Tumori".

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IMMUNOHISTOCHEMICAL INVESTIGATION OF β HEMOGLOBIN (HBB) EXPRESSION IN PROSTATE CARCINOMA

Luca Ventura[1], Mattia Capulli[2], Cinzia Mercurio[1], Adriano Angelucci[2], Anna Teti[2], Nadia Rucci[2]

[1]Unità Operativa di Anatomia Patologica, Ospedale San Salvatore, L'Aquila;
[2]Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università, L'Aquila, Italy

Background: The first demonstration of hemoglobin expression in breast cancer revealed a pattern increasing with disease progression (1). Subsequently, we hypothesized

a role of β hemoglobin (HBB) in breast cancer progression (2), demonstrating a positive correlation between HBB expression and tumor cell aggressiveness (3). This is conceivable if we consider the well known anti-oxidant role of HBB, which act as a free radical scavenger that cancer cells may use to survive. Based on these observations and given the similarities between breast and prostate cancer, the same rationale was shifted to prostate carcinoma. The aim of this study was to investigate HBB immunoreactivity in prostate carcinoma, other lesions and normal tissues. *Materials and Methods:* After routine diagnostic examination and reporting, paraffin blocks from 22 selected patients, who underwent trans-urethral resection (3 cases), and radical prostatectomy (19 cases), were cut to obtain slides immunostained with a mouse monoclonal antibody against HBB. Red blood cells were used as internal positive control and negative controls were performed by omitting primary antibody in each case. The selected cases included normal tissues and prostatic diseases, such as adenocarcinoma, prostatic intraepithelial neoplasia, prostatitis, adenosis, hyperplasia and glandular atrophy, as well as two nodal metastases. HBB expression was recorded as the percentage of positively stained cells. Known prognostic factors (Gleason grading, percentage of cancer, perineural infiltration, lymphovascular invasion, pT category, and margin status) were available for each case. Results Weak and focal (1%) cytoplasmic positivity was noted in one out of 22 adenocarcinomas. This particular case did not show peculiar clinicopathological features. The neoplastic cells in the remaining 21 primary tumors and nodal metastases were constantly negative. A weak positive signal was focally detected in normal (1 case out of 22) and hyperplastic luminal cells (3 out of 22 cases). Prostatic basal cells were negative. Moderate and focal positivity was observed in atrophic glands in a single case. Multifocal immunostaining of extracellular space was present in one case. Urothelial cells in normal urethra and urothelial metaplasia were positive in 3 cases. Seminal vesicle epithelium showed moderate positivity with a patchy pattern of expression in 1 case. *Discussion and Conclusion:* No significant expression of HBB was found in prostate carcinoma cells, in contrast with the results obtained in breast carcinoma. This allows to speculate that prostate carcinoma may not be able to take advantage of HBB free radicals scavenging systems, giving a reason for its relatively indolent course in the majority of patients. Therefore, the lack of HBB expression in prostate cancer may explain its peculiar behaviour and the features of its progression and metastatic spread. Despite focal positivity in occasional cases, benign lesions and normal tissues were negative. The positive staining of extracellular space, urothelial and seminal cells may be related to the diffusion of normal hemoglobin.

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USE OF STAT IN PROSTATE CANCER: CORRELATION WITH RISK FACTORS AND IDENTIFICATION OF RESIDUAL COHORT

Sara Morlino[1], Tiziana Rancati[2], Claudio Fiorino[3], Viviana Carillo[3], Cesare Cozzarini[4], Gianni Fellin[5], Vittorio Vavassori[6], Riccardo Valdagni[7]

[1]Divisione di Radioterapia 1,
[2]Programma Prostata, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[3]Divisione di Fisica Medica,
[4]Divisione di Radioterapia, Istituto Scientifico San Raffaele, Milano;
[5]Divisione di Radioterapia, Ospedale Santa Chiara, Trento;
[6]Divisione di Radioterapia, Humanitas - Gavazzeni, Bergamo;
[7]Divisione di Radioterapia 1 e Programma Prostata, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Purpose: Standardized Total Average Toxicity (STAT) score was proposed by Barnett (IJROBP11) as a global score which may be used to (a) facilitate the analysis of overall radiation (RT) toxicity (tox), (b) pool data from multiple trials (in order to increase statistical power) and (c) select patients (pts) to be included in studies of possible genetic determinants of RT tox. In the same paper application of STAT to 2 cohorts of breast cancer pts was presented. We here evaluate application of STAT to 2 prostate cancer populations (A and B), with the aim of verifying that STAT keeps all known correlations of single tox endpoints with clinical/dosimetric risk factors and to select possible radiosensitive pts. *Patients and Methods:*

Population A (646 pts, doses 70-80Gy, 1.8-2Gy/fr) was included in a prospective trial on rectal tox (recorded by questionnaires). Population B (179 pts, doses 60-80Gy, 1.8-2.65Gy/fr) was included in a prospective trial on genitourinary tox (measured by IPSS). STAT calculation was made following definition by Barnett. Key point is that STAT defines whether a pt's global tox is high or low relative to the distribution of the global tox of other pts. STAT measures the distance between the single pt and the average of all considered pts in terms of standard deviations. For population A, 2 STATs were considered: baseline STAT (BSTAT) and late (3yrs follow-up) STAT (STATGI). For population B, only acute tox was available and acute STAT (STATGU) was calculated. We considered pts with STATGI/STATGU>0.8 as exhibiting high tox with respect to the whole cohort and clinical/dosimetric predictors of STATGI/STATGU>0.8 were determined through multivariable logistic analysis. Analysis of residuals was used to individuate the radiosensitive cohorts. *Results:* STATGI>0.8 (43/646pts) was predicted by: BSTAT (continuous variable (cv), OR=2, p=0.04), previous diseases of the colon (OR=3, p=0.02), the % volume of rectum receiving more than 40Gy (V40Gy, cv, OR=1.02, p=0.08) and V75Gy (cv, OR=1.05, p=0.03). Overall p=0.0006, AUC 0.74. STATGU>0.8 (39/179pts) was predicted by: pre-RT IPSS (cv, OR=1.14, p=0.0008), Body Max Index (cv, OR=0.94, p=0.2), clinical T3 stage (OR=2, p=0.1), absolute bladder surface receiving≥8.5 Gy/week (S8.5w, cv, OR=1.014, p=0.03) and absolute bladder surface receiving≥12.5 Gy/week (S12.5w, cv, OR=1.035, p=0.06) Overall p<0.0001, AUC 0.81. From analysis of residuals, 14 and 11 pts emerged as possible radiosensitive pts (with high STAT which is not predicted from model) for STATGI and STATGU, respectively. *Conclusion:* Correlation between high STATGI/STATGU and clinical/dosimetric risk factors confirmed previous results found in the 2 populations for the single tox endpoints. This global approach allows objective identification of pts whose tox are not explained by the global model and who may be included in studies of possible genetic determinants of RT tox.

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BIOCHEMICAL CONTROL AFTER RADIATION THERAPY FOR PROSTATE CANCER: HYPOFRACTIONATION *VERSUS* CONVENTIONAL FRACTIONATION

Girolamo Spagnoletti, Raffaella Rignanese, Giorgia Cocco[2], Vincenzo Oriolo, Maria Piserchia, Maria Enfasi, Valentina Verile, Antonio di Fiore, Giuseppe Bove

Struttura Complessa di Radioterapia, Azienda Ospedaliero-Universitaria Ospedali Riuniti Foggia;

Background: Many hypofractionated protocols are being tested in radiotherapy for prostate cancer. Since the alpha/beta ratio estimates for this tumour are much lower than the typical values for many other cancers, we performed a small randomized trial to compare a hypofractionated *versus* a conventional schedule for radiation therapy in localized prostate carcinoma. We have already reported about acute and late toxicities in our experience. Now our aim is to evaluate early biochemical control in the two arms of treatment. *Patients and Methods:* From September 2008 to July 2009, 40 patients with cT1-T2N0M0 prostate cancer were randomized to receive either a conventional or a hypofractionated radiation therapy with curative intent. Patients were stratified according to stage, Gleason score and presenting prostate-specific antigen level; 9 patients were at low risk and 31 patients were at intermediate risk according to Partin classification. The latter received neoadjuvant hormonal therapy that started 2 months before the radiotherapy onset and continued during radiotherapy. Treatments were delivered using four to six coplanar 10-18 MV photon beams at a dose of 72- 78 Gy in 36-39 fractions within 7-8 weeks or 64.8-70.2 Gy in 24-26 fractions within 5 weeks. Relapse rate, metastasis rate, Progression-Free Survival (PFS) and Overall Survival (OS) were calculated. *Results:* All patients completed the whole course of radiotherapy without interruptions. Median follow-up was 50 months. Minimum follow-up was three and a half years. Efficacy of radiotherapy, based on clinical, radiologic and prostate-specific antigen data, was evaluated every 3 months for 2 years and every 6 months subsequently. No biochemical relapse was observed since no patient had a rise in PSA by 2 ng/ml or more above the nadir PSA, according to the Phoenix definition which is the current standard for biochemical failure after radiotherapy. No distant metastasis was observed in the two groups: bone scans were obtained only when clinically indicated and always resulted negative. PFS and OS were 100% since all patients were alive and free from PSA failure at last control, in both groups. *Discussion and Conclusion:* No difference was already noted in the acute and chronic complications between hypofractionated and conventionally fractionated radiotherapy. As regards biochemical control, we are aware that our follow-up is still too short. Nevertheless, it is not insufficient if we consider that, without androgen deprivation, nearly a half of recurrences are experienced in the first 2 years. Our study confirms that both hypofractionated and conventionally fractionated radiotherapy are effective strategies, providing similar results in terms of local control and survival, and that hypofractionation is a promising regimen for prostate cancer radiotherapy. Longer follow-up is mandatory to evaluate the effectiveness of the two regimens. Regarding tumour control, assuming a low alpha/beta ratio for prostate carcinoma, we expect an interesting therapeutic gain.

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CLINICAL, RADIOLOGIC AND PROGNOSTIC FEATURES OF RENAL ANGIOMYOADENOMATOUS TUMOR: DESCRIPTION OF A NEW ENTITY

Alessandro Antonelli[1], Regina Tardanico[2], Fabio Franco[3], Giacomo Galvagni[1], Claudio Simeone[1]

[1]Clinica Urologica, Università degli Studi di Brescia;
[2]Servizio di Anatomia Patologica, Spedali Civili di Brescia;
[3]1° Servizio di Radiologia, Spedali Civili di Brescia, Italy

Introduction and Objectives: Renal angiomyoadenomatous tumor (RAT) is a rare subtype of renal tumor with only 7 cases reported to date in the literature. Its pathological and immunohistochemical features have been well described and do not fit with any entity actually encompassed into the WHO classification of renal tumors. Besides a complete pathological definition of this entity, very little information is available on its clinical, radiological and prognostic characteristics. The aim of the present study is to review a single-centre series of 12 patients with RAT focusing on its clinical, radiological and prognostic features. *Methods:* An expert uro-pathologist reviewed the specimens of more than 1000 patients undergone surgery for a renal tumor between 2002 and 2012 and made a diagnosis of RAT on the basis of morphology (well capsulated nodules with an admixture of epithelial, smooth muscle and vascular components) and immunohistochemistry (stromal component desmin +; epithelial component CK7+, 34betaE12 +, focal Cd10+, racemase –). The clinical, surgical and follow up data of the patients with a diagnosis of RAT were then retrieved from an institutional database dedicated to the patients submitted to surgery for renal tumor at our institution. An expert uro-radiologist, aware of the diagnosis, critically reviewed the available radiological examinations. *Results:* 12 cases with morphological and immunohistochemical features fully consistent with the diagnosis of RAT were found (6 F, 6 M, mean age 63.1 yrs, 42.5-76.8), all previously diagnosed as unclassifiable renal tumors. Clinical presentation was asymptomatic in 11/12 patients. Radiological examinations were available for 8/12 patients: for all of them ultrasonography revealed a solid hyperechoic cortical nodule and CT a nodule with sovraliquid density at basal scan, highly vascularized during arterial phase and with a non homogeneous wash out during the parenchymal phase, giving to the mass a mosaic pattern aspect. 10/12 patients underwent a partial nephrectomy, 2/12 a radical nephrectomy; the mean pathological diameter was 2.4 cm (1.5-4 cm). At a mean follow up time of 6 yrs (range 1-10 yrs) there were no recurrences. *Conclusion:* RAT has a typical radiological aspect (well capsulated small hyperechoic nodule, enhancing with a mosaic pattern at CT) and a benign biological behaviour. When a renal mass with these radiological features is found, a conservative management should be recommended.

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THE PERCENTAGE OF CORE INVOLVED BY CANCER IS THE STRONGEST PREDICTOR OF INSIGNIFICANT PROSTATE CANCER, ACCORDING TO AN UPDATED DEFINITION (TUMOR VOLUME UP TO 2.5 CC): ANALYSIS OF A COHORT OF 210 CONSECUTIVE PATIENTS WITH LOW RISK DISEASE

Alessandro Antonelli[1], Regina Tardanico[1], Andrea Vismara Fugini[2], Luca Giovanessi[2], Tiziano Zambolin[2], Claudio Simeone[1]

[1]Clinica Urologica, Università degli Studi di Brescia;
[2]Servizio di Anatomia Patologica, Spedali Civili di Brescia, Italy

Objectives: The insignificant prostate cancer (ins-PCa) is generally defined as an organ-confined neoplasm with Gleason score ≤6, having a volume lower than 0.5 cc. A recent study moved the limit value used to define the ins-PCa up to 1.3 cc, 2.5 cc considering the whole tumor volume. This study aimed at researching the predictive factors linked with the updated ins-PCa diagnosis (overall tumor volume up to 2.5 cc; final Gleason score ≤6; organ-confined disease) Methods: Retrospective analysis of 210 patients undergoing radical prostatectomy for a cT1c prostate neoplasm with bioptic Gleason score ≤6. A logistic regression model in order to assess the differences in the distribution of some possibly predictive factors between the ins-PCa cases, according to the updated definition, and the remaining cases *Results:* By applying an updated definition of ins-PCa, the prevalence of this condition increased from 13.3% to 49.5% (104/210 patients). The univariate analysis showed a statistically different distribution of the following factors: PSA density, prostate volume, number of cores involved by cancer, maximum percentage of core involvement by cancer. At the univariate analysis, the maximum percentage of involvement of the core retained its relevance (27.0% in ins-PCa cases, 43.8% in the remaining cases; p=0.046, HR 0.972), and a 20% cut-off

could be detected. *Conclusion:* In a cohort of PCa cT1c/bioptic Gleason score ≤6, cases the ins-PCa rate, according to the updated definition, is close to 50% and the percentage of cancer involvement of the core was the single factor that best predicted this diagnosis.

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WIDESPREAD PIN CAN PREDICT THE DIAGNOSIS OF PROSTATE CANCER AFTER A FIRST NEGATIVE RE-BIOPSY

Alessandro Antonelli[1], Luca Giovanessi[1], Regina Tardanico[2], Tiziano Zambolin[1], Claudio Simeone[1]

[1]Clinica Urologica, Università Degli Studi di Brescia; [2]Servizio di Anatomia Patologica, Spedali Civili di Brescia, Italy

Introduction and Objectives: Actually no recommendations exist on the management of patients with a negative re-biopsy after the diagnosis of prostatic intraepithelial neoplasia (PIN) and little is known on the risk of prostate cancer (pCa) in this setting. The aim of the present study was to find out which factors could predict the diagnosis of PCa after the diagnosis of PIN and a further negative re-biopsy. *Patients and Methods:* At our institute prostatic biopsy follows standard indications; usually an extended sampling (10-12 cores) is performed *via* a transperineal approach with local anaesthesia. According to an internal protocol, after the diagnosis of PIN, three further re-biopsies at a 6-months interval are recommended. Since 2001 the data of these patients have been perspectively stored in a dedicated database that currently includes 725 cases. Among them, the cases with a second biopsy negative for PCa have been reviewed to evaluate which of the clinical or bioptic characteristic available at the time of the first biopsy or the second biopsy, could predict the later diagnosis of PCa. A linear binary logistic regression was performed. *Results:* 232 patients were selected (age 64 years, range 49-87) with a median number of 3 biopsies/patient (range 3-6) and followed for a mean period of 18 months (interquartile range 13-25 months). A diagnosis of PCa occurred in 45/232 patients (19.4%). The results of statistical analysis are summarized in the table (bx – biopsy, DRE – digital rectal examination, US - ultrasonography). *Conclusion:* The real need of further re-biopsies after the diagnosis of PIN is a controversial issue. In a systematic protocol of re-biopsies the risk of PCa in patients with PIN and a negative rebiopsy is equal to 19.4% and is significantly related to the "amount" of PIN at the first biopsy, expressed as a higher PIN density or the presence of more than 4 cores positive for PIN (so called "widespread PIN" according to Epstein and Netto [2]).

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TRANSPERINEAL PROSTATIC BIOPSY WITHOUT PROSTATIC ANESTHESIA: OUR EXPERIENCE

Piergustavo De Francesco, Stefano Ricciardulli, Lucia Mastroserio, Pietro Castellan, Rossella Manco, Manuela Ingrosso, Michele Nicolai, Raffaele Tenaglia

Clinica Urologica Università G. D'Annunzio Chieti, Italy

Aim: Prostatic biopsy is one of the most important examinations in Urology. Transperineal method presents some benefits in terms of withdrawal quality and amount. In

Table I (Abstract No 92).

Feature	no CaP	CaP	*p*	RR (CI 95%)
Age (yrs) 1st bx	64.1±6.4	65.7±6.6	0.142	1.039 (0.987-1.094)
Previous negative bx	9.1% (17/187 pz)	13.3% (6/45 pz)	0.395	1.538 (0.570-4.155)
Positive DRE 1st bx	20.3% (36/187 pz)	15.9% (7/44 pz)	0.508	0.741 (0.305-1.799)
Positive US 1st bx	42.6% (75/186 pz)	41.9% (18/43 pz)	0.929	0.970 (0.493-1.905)
PSA value (ng/ml) 1st bx	7.1±5.5	7.5±3.8	0.627	1.014 (0.958-1.074)
Delta PSA (1st bx - 2nd bx) (ng/ml)	0.19±3.38	0.58±2.12	0.540	1.036 (0.925-1.160)
Number of cores 1st bx	11 (8-13)	10 (8-13)	0.459	0.969 (0.891-1.054)
Number of cores with PIN 1st bx	2 (1-3)	3 (1-4)	0.146	1.107 (0.965-1.269)
Number of cores with PIN ≥4 1st bx	20.3% (38/187 pz)	35.6% (16/45 pz)	0.032	2.163 (1.067-4.386)
PIN density 1st bx	0.27±0.20	0.34±0.27	0.053	3.857 (0.981-15.164)
2nd bx with normal hystology	20.9% (39/187 pz)	20.0% (9/45 pz)	0.889	0.985 (0.340-1.205)
2nd bx positive for PIN	78.6% (147/187 pz)	80.0% (36/45 pz)	0.933	0.982 (0.450-1.540)

fact it allows to have more peripheric tissue, but it is less used in comparison to the transrectal method, because of its increased invasiveness. A lot of anesthetic techniques have been described in licterature in order to increase its tolerability: prostatic block, pudendal block, intraprostatic anesthesia, used alone or in combination with each other. In this study we evaluated the effectiveness in terms of pain during and after biopsy, using only the anesthetic infiltration in perineal undercutaneous tissues. *Patients and Methods:* From January 2011 to January 2012 we performed 90 transperineal echoguided biopsies with 7 Mhz biplanar transrectal probe. Each patient received antibiotic prophylaxis with Levofloxacina 500 mg, from the day before to three days after biopsy. The perineal zone was disinfected with povidoneiodine solution. Under ecoguide mepivacaine 1% 5ml was injected with 22G needle. After 5 minutes from anesthesia a 16G CVP was located as a guide. Subsequently a transperineal ecoguided biopsy of 10 samples was performed, following the Presti scheme, with 18G needle. We evaluated pain using visual scale VAS, during anesthesia, biopsy and 1 hour after the treatment. *Results:* 90 patients with mean age of 68.5±5.2 were subjected to transperineal ecoguided prostatic biopsy, from January 2011 to January 2012. Average PSA was 8.52 ng/ml (range 1.6-44 ng/ml). The treatment length, evaluated from the beginning of anesthesia to 10 samples end-time, was 15.62±3.11 minutes. Pain was evaluated using VSA scale. Patients presented mean average score of 3.15±1.52 during probe introduction, 3.62±1.71 during anesthesia, 1.52±0.70 during bioptic samples and 0.72±0.70 1 hour after the treatment. No patients needed an extra anesthetic dose. 1 patient needed hospitalization for severe hematuria. No patients presented rectal hemorrhage, sepsis or allergic reactions. *Conclusion:* The anesthetic infiltration of perineal undercutaneous tissues with mepivacaine 1% in ecoguided transperineal prostate biopsy, allowed to use less anesthetic quantity, with none collateral effect. This facilitated the receipt of 10 peripheric prostatic tissue samples, following the Presti scheme, with a very good tolerability. Periprostatic anesthesia during ecoguided prostatic biopsy was not necessary.

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AGE IS THE MAIN PREDICTOR OF COMPLICATIONS AFTER SURGERY FOR RENAL TUMOR: SYSTEMATIC EVALUATION OF 1800 PATIENTS IN A SINGLE-CENTRE COHORT

Alessandro Antonelli, Giacomo Galvagni, Stefano Legramanti, Mario Sodano, Serena Corti, Alberto Cozzoli, Claudio Simeone

Clinica Urologica, Università degli Studi di Brescia, Italy

Introduction and Aim: Age at diagnosis in patients with renal cell carcinoma is increasing and so the risk of surgery in older and comorbid patients is a raising issue. The aim of this study was to evaluate which factors play a role in determining post-surgical complications. *Methods:* retrospective evaluation of an Institutional database prospectively compiled to store the data of all the patients undergone surgery for renal tumour at our institution. Complications were registered up to 90 days after the operation and classified according to the Clavien-Dindo system. For this study the events of grade 2-3-4-5 were considered as "major complications". The correlation of some parameters with a major grade complication was evaluated by a logistic regression model. *Results:* 1798 patients (age 62.1±12.1 years) submitted to radical (1245 patients) or partial nephrectomy (553) were evaluated. No complications occurred in 1352 patients (75.2%), a single event of complication in 358 cases (19.9%), 2 events in 80 (4.4%) and 3 in 7 (0.4%). The worse complication recorded was grade 1 in 142 cases (31.5% of patients with at least one event of complication), grade 2 in 215 (47.7%), grade 3a in 32 (7.1%), grade 3b in 28 (6.2%), grade 4 in 25 (5.5%) and grade 5 in 9 (2.0%). Overall, 1489 patients had no complications or only a grade 1 complication (82.8%), whereas 309 experienced a major complication (17.2%). The Table I summarises the statistical analysis. There was a significant difference in the mean age of patients without or with major complication considering separately the cases with Charlson score 0 (58.9 *vs*. 64.0 yrs, $p<0.0001$), 1-2 (64.8 *vs*. 67.8 yrs, $p=0.014$), but not ≥3 (68.1 *vs*. 69.2, $p=0.539$). *Conclusion:* In the present analysis the risk of developing a major complication after surgery for renal tumor was not related to the extent of the disease (symptoms, histology, diameter and staging) or the type of surgery (radical or partial nephrectomy), but to the age and, only in univariate analysis, to comorbidities. At subanalysis, age was not a determinant only for patients with a higher comorbidity index (Charlson score ≥3). The options of active surveillance or ablative therapies could be reasonable for older and more comorbid patients due to the higher risk of severe complications after surgery.

Table I (Abstract No 94).

	No or minor complication	Major complication	p univariate	p multivariate	HR (95% CI)
Age (yrs)	61.2±12.8	66.7±20.6	<0.001	<0.001	1.031 (1.019-1.043)
Gender					
male	82.9% (908 pts)	17.1% (187 pts)	0.910	-	
female	82.7% (581 pts)	17.3% (121 pts)			
Charlson score					
0	85.3% (967 pts)	14.7% (166 pts)	0.001	0.130	
1-2	79.0% (373 pts)	21.0% (99 pts)			
≥3	77.2% (149 pts)	22.8% (44 pts)			
Symptoms					
none	82.4% (845 pts)	17.6% (180 pts)	0.462	-	
local	84.3% (494 pts)	15.7% (92 pts)			
systemic	80.7% (138 pts)	19.3% (33 pts)			
Pathological diameter (cm)		5.5±3.4	6.0±3.8	0.101	-
Histology					
benign	86.2% (125 pts)	13.8% (20 pts)	0.302	-	
malignant	82.5% (1364 pts)	17.5% (289 pts)			
pTNM stage					
1-2	83.6% (912 pts)	13.8% (179 pts)	0.116	-	
3-4	80-4% (451 pts)	19.6% (110 pts)			
Surgery					
radical nephrectomy	83.3% (1037 pts)	16.7% (208 pts)	0.417		
partial nephrectomy	81.7% (452 pts)	18.3% (101 pts)			

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RETROPERITONEAL CELLULAR SCHWANNOMA INCIDENTALLY FOUND IN A 21-YEAR-OLD MARTIAL ARTS MALE PRACTITIONER

Luca Ventura[1], Guido Ranieri[2], Giovanni Luca Gravina[3], Claudio Festuccia[4], Antonella Dal Mas[1], Luigi di Clemente[2], Fabrizio Liberati[5]

[1]Unità Operativa di Anatomia Patologica, Ospedale San Salvatore, L'Aquila;
[2]Unità Operativa di Urologia, Ospedale San Salvatore, L'Aquila;
[3]Divisione di Radioterapia, Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università Degli Studi de L'Aquila;
[4]Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università degli Studi de L'Aquila;
[5]Unità Operativa di Anatomia Patologica, Ospedale San Camillo De' Lellis, Rieti, Italy

Introduction: Schwannoma is a benign peripheral nerve sheath tumor, presenting as a slowly growing mass that may cause vague local symptoms, but usually diagnosed only incidentally (1). Retroperitoneal location is fairly uncommon and its presence in perirenal region may generate confusion with a primary kidney neoplasm. We report a case of retroperitoneal schwannoma of the psoas muscle, incidentally discovered in a 21-year-old male patient. *Patients and Methods:* A 21-year-old man presented to our observation for a scheduled medical check-up, complaining of a mild right flank pain. He was a long-time martial arts practitioner and recently had become world champion of korean karate (hwal moo do). For this reason he had suffered repeated trauma in the abdominal region, but his past medical history was free of significant diseases. Abdominal ultrasonography showed a well-encapsulated hypoechoic mass adjacent to the psoas muscle and the right lower renal pole. Magnetic resonance imaging (MRI) displayed a 58×50×55 mm, well-circumscribed, round mass, close to the right psoas muscle, and displacing the homolateral kidney. The slight enhancement observed after gadolinium injection allowed to better display the cystic spaces within the mass and the clearcut margins that separated it from the renal pole. The patient underwent surgical excision with the suspect diagnosis of an hematoma or a vascular neoplasm. Results Surgical specimen consisted of a roundish, encapsulated mass, measuring 6 cm in largest diameter with an external grey surface covered by fat and yellow tan cut surfaces presenting multiple pseudocystic spaces. Microscopic examination revealed cellular fascicles of spindle cells with focal evidence of nuclear palisading, multiple cystic and pseudoglandular spaces, multifocal

foamy cells and sclerotic areas. Numerous thickened and hyalinized blood vessels were evident throughout the tumor tissue. No mitotic figure was observed. Neoplastic cells were diffusely immunoreactive for S100 protein, focally positive for GFAP, and negative for α-smooth muscle actin, desmin, CD34, CD117 and AE1/AE3 cytokeratins. Ki-67 proliferation index was 3%. Histological diagnosis was of cellular schwannoma. *Discussion and Conclusion:* Schwannomas are benign soft tissue tumors that originate from the peripheral nerve sheath. Their most common sites are head and neck region and extremities, whereas the retroperitoneal location is rare, accounting for 0.3 to 3.2% of all schwannomas (2). MRI with gadolinium enhancement has been advocated as superior to computed tomography in highlighting cystic degeneration, defining margins and identifying the point of origin from the nerve (1). Retrospective evaluation of MRI in our case allowed to confirm this assessment and to identify the possible origin of the lesion from the genitofemoral nerve. Definitive diagnosis can only be made by histopathological examination with immunohistochemical confirmation (1), but preoperative fine needle aspiration diagnosis may be performed (2). According to a recent report, retroperitoneal schwannoma often occurs in middle-aged women, exhibits cellular subtype features and extensively expresses GFAP (3). Except for the classification in the cellular subtype, our case does not confirm such observation, showing only limited areas of GFAP positivity and occurring in a young adult male patient.

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TESTING THE AGILE DATABASE FOR AN EXTERNAL VALIDATION OF A NOMOGRAM TO PREDICT MALIGNANCY OR AGGRESSIVENESS OF RENAL MASSES, BASED ON R.E.N.A.L. SCORE

Alessandro Antonelli[1], Andrea Minervini[2], Luca Cindolo[3], Angelo Porreca[4], Simone Crivellaro[5], Paolo Parma[6], Stefano Zaramella[7], Bernardo Rocco[8], Pierluigi Bove[9], Vincenzo Pagliarulo[10], Antonio Celia[11], Carlo Ceruti[12], Mario Falsaperla[13], Roberto Nuciotti[14]

[1]Clinica Urologica Università degli studi di Brescia;
[2]Clinica Urologica, Università di Firenze;
[3]Unità Operativa di Urologia, Ospedale di Chieti-vasto;
[4]Unità Operativa di Urologia, Ospedale di Abano Terme;
[5]Clinica Urologica, Università di Udine;
[6]Unità Operativa di Urologia, Ospedale di Mantova;
[7]Unità Operativa di Urologia, Ospedale di Novara;
[8]Clinica Urologica, Università di Milano;
[9]Clinica Urologica, Università La Sapienza di Roma;
[10]Clinica Urologica, Università di Bari;
[11]Unità Operativa di Urologia, Ospedale di Bassano del Grappa;
[12]Unità Operativa di Urologia, Università di Torino;
[13]Università Operativa di Urologia, Ospedale di Catania;
[14]Unità Operativa di Urologia, Ospedale di Grosseto, Italy

Introduction and Aim: Actually only a few preoperative systems are available to predict malignancy or aggresiveness of a renal mass, and all of them suffer from a low predictive accuracy. Recentely, Kutikov *et al*. (1) generated a nomogram based on R.E.N.A.L. score, that showed a predictive accuracy higher than 70%. The aim of this study was to perform an external validation of this predictive tool on a cohort of patients submitted to partial nephrectomy. *Methods:* Agile is a collaborative group of Italian young (<40 yrs) urologists with a specific interest in mini-invasive surgery. Since 2011 the group perspectively shared and compiled a database to collect the data of all the patients undergoing open, laparoscopic or robotic partial nephrectomy. Among the data, also R.E.N.A.L. score has been calculated in its attributes by an urologist blinded of the final pathology. After the centralization of database, the nomogram proposed by Kutikov has been applied to each case, using the online calculator available at www.cancernomograms.com, to calculate the predicted probability of malignancy and aggressiveness. A logistic regression model has been used to estimate the correlation of each of the parameters included into the nomogram and the final pathology. *Results:* The data of 294 patients have been collected (185 male, 109 female, age 63±12 yrs), submitted to open (197 patients), laparoscopic (28) or robotic (69) partial nephrectomy. Histology was benign in 60 cases (21.6%), malignant in 234 (79.4%); among malignant cases, was aggressive - high grade - in 34 (17.9%), not aggressive in 144 (82.1%). Mean total R.E.N.A.L. score was 5.8±1.6. The Tables present the results of statistical analysis that estimate the correlation of the parameters included into the nomogram with malignancy (Table I) or aggressiveness (Table II) at final pathology (in bold correlation with statistical significance).

Table I. *Statistical correlation between characteristics and malignant histology.*

	p	RR (95% CI)
Age (yrs)	0.364	1.011 (0.988-1.034)
Male gender	0.010	2.138 (1.203-3.798)
Nephrometry sum	0.217	1.129 (0.931-1.368)
R attribute	0.303	
1	referent	
2	0.544	1.252 (0.606-2.588)
3	0.175	0.347 (0.075-1.603)
E attribute	0.376	
1	referent	
2	0.326	1.371 (0.731-2.572)
3	0.265	2.360 (0.521-10.689)
N attribute	0.322	
1	referent	
2	0.685	1.262 (0.410-3.889)
3	0.141	2.524 (0.737-8.644)
L attribute	0.049	
1	referent	
2	0.021	2.471 (1.145-5.332)
3	0.924	0.968 (0.498-1.881)
involvement of renal sinus		
no	referent	
yes	0.347	0.59 (0.201-1.758)

Table II. *Statistical correlation between characteristics and high grade RCC.*

	p	RR (95% CI)
Age (yrs)	0.364	1.011 (0.988-1.034)
Male gender	0.010	2.138 (1.203-3.798)
Nephrometry sum	0.217	1.129 (0.931-1.368)
R attribute	0.303	
1	referent	
2	0.544	1.252 (0.606-2.588)
3	0.175	0.347 (0.075-1.603)
E attribute	0.376	
1	referent	
2	0.326	1.371 (0.731-2.572)
3	0.265	2.360 (0.521-10.689)
N attribute	0.322	
1	referent	
2	0.685	1.262 (0.410-3.889)
3	0.141	2.524 (0.737-8.644)
L attribute	0.049	
1	referent	
2	0.021	2.471 (1.145-5.332)
3	0.924	0.968 (0.498-1.881)
Involvement of renal sinus		
no	referent	
yes	0.347	0.59 (0.201-1.758)

The malignancy rate predicted by the nomogram for benign and malignant tumors was 79.2% and 80.3%, respectively (AUC 0.541, p=0.326); the predicted aggressiveness rate for non aggressive and aggressive renal cancer was 30.9% and 38.6%, respectively (AUC 0.660, p=0.004). *Conclusion:* Conversely to the cohort in which the nomogram has been generated – that included also advanced or metastatic tumors – the present study aims at validating the nomogram on a cohort of cases submitted to partial nephrectomy, in which the prediction of malignancy or aggressiveness could be more clinically important because these masses could be amenable of ablation or observation. The nomogram showed a poor predictive ability for malignancy, whereas a discrete accuracy for aggressiveness, mainly due to a strong relationship with the diameter of the tumor. Since the external validation failed, the nomogram should be re-calibrated on a cohort of small renal masses.

1 Kutikov A, Smaldone MC, Egleston BL *et al*: Anatomic features of enhancing renal masses predict malignant and high-grade pathology: a preoperative nomogram using the RENAL Nephrometry score. Eur Urol *60(2)*: 241-248, 2011.

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COMPLICATION RATE AFTER TURP AND HIFU

Roberto Sanseverino[1], Oliver Intilla[2], Giovanni Molisso[2], Tommaso Realfonso[2], Umberto di Mauro[2], Giorgio Napodano[2]

[1]UOC-Urologia-Umberto I Nocera Inferiore, UOC-Urologia-Umberto I Nocera Inferiore;
[2]Divisione di Urologia, Ospedale Umberto I, Nocera Inferiore, ASL Salerno, Italy

Introduction: To evaluate whether splitting TURP and Hifu in two sessions can reduce complication rate in patients with localized prostate cancer. *Patients and Methods:* From November 2004 to November 2012, 118 patients affected by localized prostate cancer underwent HIFU following TURP. In 39 patients both procedures were performed in the same session (Group A); in 79 patients HIFU was delayed (Group B). Follow up included serial PSA measurements and prostate biopsies 6 months after the treatment in all patients. Biochemical recurrence was defined as PSA nadir + 2 ng/ml (ASTRO 2005 criteria). We have evaluated complication rate in the Group A and B. *Results:* The mean age, PSA and prostate volume were 78.9 years, 8.7 ng/ml and 31 cc, respectively. Mean procedure time was 127 minutes and mean hospitalization was 3.8 days. Complication rate was not associated with clinical stage (T1 *vs*. T2) (p<0.6), Gleason score (p<0.5), age (p<0.2), prostate volume (p<0.06), PSA (p<0.9). Complications rate was lower when

HIFU has been delayed after TURP (Group B). Complications occurred in 31% (12/39) of Group A patients and in 12% (10/79) of Group B patients ($p<0.02$). Prostatic biopsy was positive in 17 patients. Overall and cancer specific survival was 93%. *Conclusion:* Splitting TURP and HIFU in two different sessions seems to reduce postoperative complications and improve patient tolerance of the procedure. Longer follow up and a larger patient population are needed to obtain more robust evidence.

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INTRAVESICAL BAOBAB OIL IN THE MANAGEMENT OF BCG-INDUCED LOWER URINARY TRACT SYMPTOMS

Cristian Verri[1], Emanuele Liberati[2], Francesco De Carlo[3], Savino Mauro di Stasi[3]

[1]Dipartimento di Scienze Chirurgiche/Urologia, Università Tor Vergata;
[2]Urologia Oncologica, Policlinico Casilino;
[3]Divisione di Urologia, Universita Tor Vergata, Roma, Italy

Objectives: Baobab oil is often used in traditional medicine as antipyretic, antioxidant, anti-inflammatory, analgesic and antimicrobial. It also regenerates the epithelial tissue in a short time improving tone and elasticity. We evaluated the effects of intravesical Baobab oil in patients with BCG-induced lower urinary tract symptoms. *Methods:* From September 2012 to January 2013, 40 patients on induction course of intravesical BCG with lower urinary tract symptoms BCG-induced and unresponsive to standard therapies were enrolled. The symptoms were assessed using a detailed grid of classification for BCG lower urinary tract related side effects. Patients were treated with an intravesical instillation of 50 ml sterile Baobab natural oil (Baotrophic, Physion Srl, Mirandola, Italy). After draining of the bladder, the suspension was infused intravesically through a Foley catheter. The solution was retained in the bladder for 60 min, followed by emptying of the bladder and removal of the catheter. Outcome measures were cystitis, diurnal frequent micturition, nocturnal frequent micturition, stress incontinence, hematuria, pelvic pain that were analyzed before and one week after treatment. All patients were assessed for safety. *Results:* At baseline and one week after an intravesical instillation of Baobab oil, cystitis was recorded in 40/40 patients (100%) and 21/40 (52.5%, [$p=0.0001$]), diurnal frequent micturition in 40/40 (100%) and 20/40 (50%, [$p=0.00001$]), nocturnal frequent micturition in 40/40 (100%) and 20/40 (50%, [$p=0.0001$]), stress incontinence in 17/40 (42.5%) and 6/40 (15%, [$p=0.0023$]), hematuria in 22/40 (55%) and 6/40 (15%, [$p=0.0047$]), and pelvic pain in 7/40 (17.5%) and 2/40 (5%, [$p=0.0001$]), respectively. There were no adverse events with intravesical Baobab oil instillation. *Conclusion:* Intravesical natural Baobab oil is feasible, safe and confers therapeutic benefits *via* localized direct action within the bladder wall. Compliance with induction and maintenance intravesical BCG may be improved by adjuvant intravesical Baobab oil. However, randomized studies must be done to confirm these initial findings.

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VERUMONTANUM: AN ANATOMICAL LANDMARK DURING RADICAL PROSTATECTOMY FOR THE COMPLETE SAVING OF STRIATED SPHINCTER

Federico Lanzi, Nicola Tosi, Filippo Cecconi, Filippo Gentile1, Gerardo Pizzirusso, Giovanni De Rubertis, Gabriele Barbanti

UOC di Urologia, AOU Senese, Siena, Italy

Aim: To investigate functionally and oncologically the role of verumontanum as a landmark for the complete saving of striated sphincter in patients undergone radical prostatectomy. *Materials and Methods:* Verumontanum can be considered as an anatomical landmark in saving the maximal length of urethra and, consequently, the maximum of striated sphincter. Either by retrograde or antegrade approach to the radical prostatectomy it is afoundamental anatomical preparation of urethral sphincter with an excellent visualization of the apex. 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*. From January 2008 to December 2011 we prospectively collected the data of 123 patients undergone radical retropubic prostatectomy (RRP) for clinically localized prostate cancer. We determined two cohorts: Group A (59 patients) undergone RRP without the saving of verumontanum, and Group B (64 patients) undergone RRP with the saving of verumontanum. Both, Groups 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 and 12. *Results:* Mean follow-up was (range) 23.7 (13-45) months for Group A and 22.4 (13-47) months for Group B. In 5/59 (8.4%) cases of Group A and in 6/64 (9.3%) of Group B it was found a positive apical surgical margin ($p=0.3219$): of these patients, 2 in Group A and 3 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 12 months; continence was obtained within the first month in 38 (71.7%) patients of Group A Vs 50 (78.1%) of Group B, 43 (81.1%) Vs 56 (87.5%) within the

third month, 47 (90.5%) Vs 60 (93.7%) within the sixth month and in 50 (94.3%) Vs 61 (95.3%) respectively. The saving of verumontanum didn't result significantly in overall continence (p=0.09) but resulted influential in early recovery of continence (p<0.0001). *Discussion:* Verumontanum can be considered an anatomical landmark in saving the maximum of striated sphincter. 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 a large, randomized trials to define the role of verumontanum in overall and early continence recovery.

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MINIMIZING COSTS OF ROBOTIC UROLOGIC SURGERY: A COST-EFFECTIVENESS ANALYSIS

Federico Lanzi, Nicola Tosi, Filippo Gentile, Filippo Cecconi, Gerardo Pizzirusso, Giovanni De Rubertis, Gabriele Barbanti

UOC di Urologia, AOU Senese, Siena, Italy

Objectives: The aim of this study was 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 money-saving procedures. *Methods:* From April 2011 to January 2013 87 patients underwent robotic surgery for prostate (52 patients) and renal cancer (35 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 of the first set of patients to the latest one. Technical features of prostatic and renal surgery are summarized in Tables I and II respectively. *Results:* Instrumentation costs of both radical prostatectomy and tumoral enucleation resulted 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 226.2 (165-270) minutes Vs 172.5 (150-180) minutes of Group B (p=0.0041). Both groups of robotic radical prostatectomies resulted similar

Table I.

ROBOTIC RADICAL PROSTATECTOMY

First cases

Item	n°	Unitary cost (€)	Total cost (€)
Sterile drape for arms	3	100	300
Sterile drape for camera	1	100	100
Cadiere Forceps	1	471	471
Hot Shears (Monopolar Curved Scissors)	1	753	753
Meryland Bipolar Forceps	1	636	636
Permanent Cautery Hook	1	470	470
ProGrasp Forceps	1	500	500
Large Needle Driver	2	516	1032
Robotic trocar	3	0	0
Sterile robotic trocar mount	3	37	111
5" laparoscopic trocar	1	92	92
12" laparoscopic trocar	2	92	194
Single-use suction irrigator	1	105	105
Tip for suction irrigator	1	21	21
Laparoscopic needle driver	1	0	0
Laparoscopic scissors	1	70	70
Johan grasping forceps	1	0	0
Hem-o-lok Clips (5-pieces blister)	2	12	24
Endo Catch	1	70	70
Monocryl 2/0 UR6/SH	2	6	12
			4961

Last cases

Item	n°	Unitary cost (€)	Total cost (€)
Sterile drape for arms	2	100	200
Sterile drape for camera	1	100	100
Cadiere Forceps	1	471	471
Hot Shears (Monopolar Curved Scissors)	1	753	753
Large Needle Driver	1	516	516
Robotic trocar	3	0	0
Sterile robotic trocar mount	3	37	111
12" laparoscopic trocar	2	92	194
Single-use suction irrigator	1	105	105
Tip for suction irrigator	1	21	21
Laparoscopic needle driver	1	0	0
Johan grasping forceps	1	0	0
Hem-o-lok Clips (5-pieces blister)	2	12	24
Endo Catch	1	70	70
Monocryl 2/0 UR6/SH	2	6	12
			2577

Mean saving: 48%

Table II. **ROBOTIC TUMORAL ENUCLEATION**

First cases

Item	n°	Unitary cost (€)	Total cost (€)
Sterile drape for arms	2	100	200
Sterile drape for camera	1	100	100
Cadiere Forceps	1	471	471
Hot Shears (Monopolar Curved Scissors)	1	753	753
Meryland Bipolar Forceps	1	636	636
Permanent Cautery Hook	1	470	470
ProGrasp Forceps	1	500	500
Large Needle Driver	2	516	1032
Robotic trocar	2	0	0
Sterile robotic trocar mount	3	37	74
5" laparoscopic trocar	1	92	92
12" laparoscopic trocar	2	92	194
Single-use suction irrigator	1	105	105
Tip for suction irrigator	1	21	21
Laparoscopic needle driver	1	0	0
Laparoscopic scissors	1	70	70
Johan grasping forceps	1	0	0
Hem-o-lok Clips (5-pieces blister)	2	12	24
Endo Catch	1	70	70
Monocryl 0 MH1	3	6	18
Monocryl 2/0 UR6/SH	1	6	6
			4836

Last cases

Item	n°	Unitary cost (€)	Total cost (€)
Sterile drape for arms	2	100	200
Sterile drape for camera	1	100	100
Cadiere Forceps	1	471	471
Hot Shears (Monopolar Curved Scissors)	1	753	753
Large Needle Driver	1	516	516
Robotic trocar	3	0	0
Sterile robotic trocar mount	3	37	111
12" laparoscopic trocar	2	92	194
Sterilizable suction irrigator	1	0	0
Laparoscopic needle driver	1	0	0
Johan grasping forceps	1	0	0
Hem-o-lok Clips (5-pieces blister)	2	12	24
Endo Catch	1	70	70
Monocryl 0 MH1	3	6	18
			2457

Mean saving: 49.2%

in intraoperative blood loss (p=0.482), histopatologically-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 115.8 (75-170) minutes Vs 104.1 (85-150) 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 positive surgical margins were not found, while in Group B a peritumoral pseudocapsule incision. *Conclusion:* In literature it is widely demonstrated that the feasibility and safeness of robotic surgery allows minimally invasive procedures and oncologic and functional results comparable to standard open procedures with fewer major complications and shorter length of hospital stay. On the other hand, the DaVinci System determines higher costs of each single procedure than the relative open and laparoscopic surgery. This study should be considered a step in driving down costs of robotic surgery. Technical difficulties in using less tools are usually limited to the very first procedures. Our instrumentation expedients, compared with conventional robotic radical prostatectomy and renal robotic tumoral enucleation, determined a saving up to 49.2% for each single procedure with intra- and postoperative result comparable to the standard procedures.

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DIAGNOSTIC VALIDATION OF URINARY TYR-PHOSPHORYLATED PROTEINS AS BLADDER CANCER MARKER

Antonino Battaglia[1], Marco Allasia[1], Andrea Gonella[1], Amina Khadjavi[2], Agata Notarpietro[2], Francesca Mannu[3], Giuliana Giribaldi[2], Franco Turrini[2], Dario Fontana[1], Paolo Destefanis[1], Bruno Frea[1]

[1]Clinica Urologica,
[2]Dipartimento di Scienze Biochimiche, Azienda Ospedaliera Città della Salute e della Scienza, Sede Molinette, Torino;
[3]Dipartimento di Scienze Biochimiche, Nurex Srl, Sassari, Italy

Background and Aim: Different urinary markers of transitional cell carcinoma (TCC) have been proposed. None of them, however, is approved by the international guidelines or used with scientific safety by urologists in their clinical practice. Cystoscopy continues to represent the gold standard method of diagnosis, and is highly accurate, sensitive and specific. The urine cytology is instead non-invasive but has a high rate of false negative, especially in low-grade TCC. We try to give a

significant answer of these open questions using a proteomic approach, that is widely used in molecular oncology. Using proteomic approaches, we previously demonstrated (1) that the levels of Tyr-phosphorylated proteins (TPPs) are highly increased in bladder cancer tissues and that soluble TPPs can be also detected in patient urine samples. Now, we have evaluated their diagnostic performances measuring urinary TPP levels in 230 urine samples from bladder cancer patients and healthy subjects. *Patients and Methods:* Patients with suspected bladder cancer were enrolled in this study before undergoing transurethral resection of the bladder or radical cystectomy. Patients with a histological diagnosis different from bladder cancer or with a previous bladder cancer history were excluded. Urines for the control group were collected from healthy blood donors, after an interview, to exclude urological problems. Only volunteers more than 50 years old were enrolled. The urinary levels of TPPs were analyzed using an experimental diagnostic test (pYtest, provided by Nurex srl). The area under the ROC curve (AUC), sensitivity, specificity, positive and negative predictive values (PPV and PNV) were calculated using Bayes' theorem (MedCalc 11.3.3). *Results:* Urinary TPP levels from 87 bladder cancer patients (7 Tx, 47 Ta, 17 T1, 12 T2/3, 4 CIS) and from 143 healthy subjects were measured. The AUC was 0.875 with a 95% confidence interval of 0.8260.915. For the best cut-off value (261.26 standard units), a sensitivity of 80.46% and a specificity of 79.72 % were obtained. PPV and PNV were 70.1% and 87.7%, respectively. *Conclusion:* The proteomic approach is shown to be helpful uro-oncology too, not only toward understanding the molecular pathways of carcinogenesis, but also toward detection of possible markers in the urine samples. Preliminary evaluation confirms the excellent diagnostic performances of TPPs as bladder cancer marker. To confirm and validate the proteomic approach through the individualisation of TPPs with the pYtest we need to increase the enrolled patients within a multicenter study. Next aim is to recruit more patients to confirm stastically the results and validate definitely the pYtest as a bladder cancer marker.

1 Khadjavi A, Barbero G, Destefanis P *et al*: Evidence of abnomal tyrosine phosphorylated proteins in bladder cancer patient urine: the road toward a new diagnostic tool?; J Urol *185(5)*: 1922-1929, 2011.

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THE STABILITY AND ELECTROMOTIVE ADMINISTRATION OF RESINIFERATOXIN INTO THE PIG BLADDER WALL

Savino di Stasi[1], Emanuele Liberati[2], Cristian Verri[1], Renato Massoud[3], Pierluigi Navarra[4], Antonella Giannantoni[5]

[1]Department of Surgery/Urology, Università di Roma Tor Vergata;
[2]Operative Unit of Urologic Oncology, Università di Roma Tor Vergata;
[3]Department of Chemical Sciences and Technologies, Università di Roma Tor Vergata;
[4]Institute of Farmacology, Università Cattolica di Roma;
[5]Department of Urology and Andrology, University of Perugia, Italy

Introduction & Objectives: Intravesical vanilloids such as Capsaicin and Resiniferatoxin (RTX), which are still under investigation for the treatment of detrusor overactivity, seem to have a role also in the management of urothelial cancer. We investigated the stability of RTX stock solutions under different experimental conditions, and bladder wall tissue concentrations of drug following passive diffusion (PD) and electromotive drug administration (EMDA). *Materials and Methods:* For stability studies, RTX 1 mg was dissolved in 1 ml of absolute ethanol and diluted (10 fold) in ethanol/water (50/50), so that we had RTX 1 mg in 10 ml of equal parts ethanol/water solvent as our stock solutions. Aliquots of 250 ml were then stored in glass containers or high grade polypropylene (plastic) containers and subjected to different temperatures (room temperature, +4˚C and –20˚C) and light/dark conditions over times ranging from 0-144 hours. 10 ml of samples were loaded for HPLC analysis. Results were normalized by taking the value at time 0 as 100%. For comparative bladder wall tissue content studies, full thickness sections of viable pig bladder wall were placed in two chamber cells with urothelium exposed to donor compartments containing RTX 100 nM concentration in 100 ml 0.9% NaCl solution and with serosa-facing receptor compartments containing 100 ml 0.9% NaCl solution. An anode and a cathode were placed in the donor and receptor compartments, and 10 paired experiments – current 23 mA (EMDA)/no current (PD) – were conducted over a 30-min. RTX tissue content was assessed by HPLC. Tissue viability and morphology were assessed by trypan blue exclusion test and histological and mass spectrometry analyses. *Results:* Both, room temperature and light exposure affect RTX stability and the combined effect of these factors is additive. RTX degradation, if present, falls to a nadir at 48 hours. At low temperatures (+4˚C or –20˚C), in the dark, plastic storage affords better stability than glass. Mean RTX tissue concentrations were 0.894±0.22 mg/ml in samples exposed to EMDA and 0.212±0.05 mg/ml in samples exposed to PD (p=0.0076). After EMDA tissues were viable, undamaged histologically and no RTX structural modification was observed. *Conclusion:* RTX stock solutions should be stored at temperature 4˚C in the dark; the material comprising the container for RTX is of secondary importance. EMDA enhances administration of RTX into viable bladder wall tissue compared to PD. These results could allow more appropriate treatment' modalities with better results for the use of RTX in clinical practice.

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

Federico Lanzi, Filippo Gentile, Nicola Tosi, Gerardo Pizzirusso, Filippo Cecconi, Giovanni De Rubertis, Gabriele Barbanti

UOC di Urologia, AOU Senese, Siena, Italy

Objectives: The aim of this study was 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. *Methods:* From April 2011 to January 2013, 35 consecutive patients underwent robotic surgery for clinically localized renal cancer. Overall 31/35 patients presented no major contraindications to hypotensive anesthesia; mean age (range) was 68 (45-77) years. RTE was usually performed through a transperitoneal approach without renal hylum isolation. Tumoral enucleation was performed by blunt dissection using the natural cleavage plan between the pseudocapsule and renal parenchyma. 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 68 mmHg (ranging between 65 and 95 mmHg) and hypotension was prolonged meanly for 12.4 (range: 9.3-19.5) minutes. Mean (range) operative time was 115.8 (75-170) minutes with mean blood loss of 150 ml (55-480 ml). No patients required intraoperative blood transfusions. Mean (range) tumor size was 27 (10-54) mm and mean postoperative hospital stay was 3.4 (2-10) days. Overall 3 patients developed postoperative complications: 2 anemization treated by blood transfusions and 1 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 postoperative serum creatinine was 1.0 (0.7-2.3) and 1.2 (0.7-2.7) mg/dl respectively (p=0.487); mean estimated pre and postoperative glomerular filtration rate were 85.9 and 75.2 ml/minute/1.73m^2. At histopathological evaluation no positive surgical margins were found; in only one case a peritumoral pseudocapsule incision was discovered. *Conclusion:* In literature, the need of minimizing ischemia during nephron sparing surgery for renal tumors has been widely demonstrated. 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; moreover, in our series avoiding hilar clamping did not increase the complication rate and provided excellent functional outcomes. Available data are not adequately mature to determine long-term functional outcomes and further experience and follow-up is mandatory.

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A RANDOMIZED PROSPECTIVE STUDY: HYALURONIC ACID VERSUS STANDARD THERAPY IN BLADDER CANCER LOCAL COMPLICATIONS

Andrea Gonella, Antonino Battaglia, Marco Allasia, Andrea Bosio, Alessandro Bisconti, Carlo Negro, Andrea Buffardi, Maria Teresa Carchedi, Paolo Destefanis, Bruno Frea

Clinica Urologica, Azienda Ospedaliera Città della Salute e della Scienza, Sede Molinette, Torino, Italy

Background: Hyaluronic acid is a glycosaminoglycan of the extracellular matrix. Scientific literature suggests a correlation between bladder inflammation and glycosaminoglycan layer absence. Many studies point out that hyaluronic acid intravesical somministration can reduce disabling symptoms, *i.e.* interstitial cystitis. It is possible to emphasize a satisfactory reduction of lower urinary tract symptoms due to intravesical immune or chemotherapy for bladder cancer. A preliminary Italian study underlines an improvement of quality of life recorded on patients who underwent intravesical hyaluronic acid instillations after the development of local toxicity after immuno or chemotherapy. *Objectives:* The primary end-point of this study is the evaluation of the effectiveness of therapy with hyaluronic acid, measured as reduction of voiding symptoms, compared to standard therapy (interruption of BCG/Immunotherapy instillations + antibiotic and antispasmodic therapy). The second end-points are: the reduction of inflammation at histopathology findings, the evaluation of the toxicity of the therapy and the possible improvement of cancer intravesical treatment. *Patients and Methods:* Patients with previous bladder cancer, suitable for immune-chemotherapy and who experienced a local toxicity (WHO grade II or III) were included in the study. During the visit, patients were invited to fill an international questionnaires like: VAS; IPSS; CPSE-NIH; ICQ-MLUTS; OAB-q SF and BCG symptoms questionnaire. Furthermore, we also collected: urinalysis; urine culture; renal-bladder ultrasound; cystoscopy and urine cytology. In the second step we randomized the patients in two main groups: Group A, therapy with intravescical hyaluronic acid according to the scheme:1 instillation (40 mg hyaluronic acid) to maintain inside the bladder for at least 30 minutes + 1 instillation/week for 6 weeks + 1 instillation/month for 3 months + 1 instillation/every 3

months as maintenance; Group B, standard therapy: oxybutynin hydrochloride 5 mg (2.5 mg × 3 times/die until the disappearance of the symptomatology) + ofloxacin 200 mg (1 co/12 hours for 10 days). The evaluation of efficacy of two therapies was performed after: 6 weeks; 3 months, 6 months and after one year by a new filling of the questionnaires: VAS, IPSS, CPSE-NIH, ICQ-MLUTS, OAB-q SF, BCG symptoms; and a new collection of exams: urinalysis, urine culture, renal-bladder ultrasound, cystoscopy and urine cytology. *Results:* We recruited 14 patients (8 Group A and 6 Group B). Group A-patients did not present at the moment side-effects after hyaluronic acid instillations and reported a subjective decrease in voiding symptoms. Two of them (2/8) dropped out of the study after tumor recurrence and subsequent radical cystectomy. Some patients of Group B (2/6) were forced to exit the protocol due to the development of intolerance to oxybutynin (severe urinary retention); others (3/6) presented mild side-effects (dry mouth); 1/6 finished the protocol with full benefit. *Conclusion:* In order to have a general view of the effectiveness of hyaluronic acid we plain toenrol more patients in this study. The analysis of the first results and the satisfaction of the patients are positive points to encourage the continuation of the use of intravesical hyaluronic acid.

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DIFFERENTIAL EXPRESSED PROTEINS IN URINE SAMPLES FROM VON HIPPEL-LINDAU DISEASE AND RENAL CELL CARCINOMA PATIENTS *VERSUS* HEALTHY PEOPLE

Marco Allasia[1], Antonino Battaglia[1], Andrea Gonella[1], Barbara Lucatello[2], Agata Notarpietro[3], Giorgia Mandili[3], Amina Khadjavi[4], Andrea Bosio[1], Beatrice Lillaz[1], Giuliana Giribaldi[3], Mauro Maccario[2], Paolo Destefanis[1], Bruno Frea[1]

[1]Clinica Urologica,
[2]Endocrinologia,
[3]Dipartimento di Scienze Biochimiche,
[4]Biochimica,
Azienda Ospedaliera Città della Salute e della Scienza, Sede Molinette, Torino, Italy

Background: Von Hippel-Lindau (VHL) disease is an autosomal dominant, inherited syndrome occurring in 1 out of 35,000 births. VHL is characterized by the development of retinal and CNS haemangioblastomas, phaeochromocytomas, pancreatic neuroendocrine tumours, clear-cell renal cancers (RCC) and renal cysts. In particular, RCC occurs in about 40% of patients affected by VHL disease and is often bilateral and multifocal. Actually the only method to identify abdominal lesion is the yearly radiological imaging. There are no reliable methods and markers to classify the VHL patients based on the risk of developing renal cancer (RCC). In order to identify differentially expressed proteins, that could be useful as predictors of the VHL related RCC, we performed 2DE analysis on urine samples from healthy subjects, patients with sporadic RCC and VHL syndrome patients. The latter were collected during the annual follow-up in our clinical care VHL-centre. *Materials and Methods:* Urine samples were collected from 9 healthy subjects, 10 patients affected by VHL syndrome and 9 patients with RCC. Proteins were obtained through Acetone Precipitation and solubilised in Lysis Buffer (9M Urea, 4% CHAPS, 1mM Na_3VO_4, 80 mM DTT, protease inhibitors). Following protein quantification, 200 µg of each sample were loaded on IPG strip gels (7 cm IPG strips, pH 3-10 NL) after dialysis. For second dimension 10% poly-acrylamide gels were run. Colloidal Comassie-stained gels were analysed by PD Quest 2D analysis software and statistical analysis was performed (T test). The study was approved by the internal institution ethical committee. *Results:* From January 2012 to January 2013 we collected urine samples (100 ml) from 10 VHL patients, 9 sporadic RCC and 9 healthy people and we compared the protein expression profile among them. Mean age of the VHL group was 34.33 years (range 24-58), 6 male and 3 female, 3 patients had positive history of renal cancer. Mean age of sporadic RCC patients was 65 years (range 43-78), 4 male and 5 female, all with histological diagnosis of clear cell RCC. The healthy urine samples were collected from 9 blood donors, with mean age of 42 years (range 25-58) 4 male and 5 female. Image analysis of the 2DE maps showed 35 statistically significant ($p<0.05$) differentially expressed spots among the three groups. *Conclusion:* Through PD Quest 2D analysis software of the 2DE urine maps we demonstrated the presence of 35 statistically significant ($p<0.05$) differentially expressed proteins in VHL patients *versus* RCC and healthy people. These preliminary evidence could suggest the possibility to develop a risk assessment tool for RCC in VHL patients.

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POLYTETRAFLUOROETHYLENE PLEDGETS DURING NEPHRON-SPARING SURGERY FOR RENAL TUMORS: INTRAOPERATIVE AND LONG-TERM RESULTS

Nicola Tosi, Federico Lanzi, Filippo Gentile, Gerardo Pizzirusso, Filippo Cecconi, Giovanni De Rubertis, Gabriele Barbanti

UOC di Urologia, AOU Senese, Siena, Italy

Objectives: The aim of this study was to evaluate the feasibility and safety of hemostasis performed through polytetrafluoro-ethylene pledgets placement during open nephron-sparing surgery for renal tumors. *Methods:* From 2008 to December

2012, 84 consecutive patients underwent open nephron-sparing surgery (NSS) for clinically localized renal cancer. NSS was performed as tumoral enucleation technique, usually by a lateral retroperitoneal approach, and always by blunt dissection on the natural cleavage plane between the tumor and normal parenchyma. Smaller exophytic lesions were approached avoiding the clamp of renal pedicle. Incidental opening of the calyces were ligated using a running suture with 4/0 monofilament. In 54/84 cases, we adopted Polytetrafluoroethylene pledgets to firm a significant parenchymal defect. Polytetrafluoroethylene pledgets are fashioned into 10×5 mm strips and used to dissipate the high tensile strenght of mattress suture with 2/0 adsorbable polyfilament. Polytetrafluoroethylene is fully chemically inert and insoluble in organic solvents; moreover its peculiar fluency with very low friction rates helps its placing. We adopted Polytetrafluoroethylene pledgets in 54/84 cases. *Results:* Mean (range) operative time was 97.6 (55-189) minutes with mean blood loss of 250 ml (55-680 ml). Renal pedicle was clamped in 16/54 (29.6%) cases and mean warm ischemia was 13.5 (range: 10-21) minutes. Mean tumor size was 31 (range: 10-72) mm. Overall, 11 perioperative complications occurred (7/54=12.9%); of these, 6 were medical and 1 surgical. Medical complications included fever, blood loss requiring transfusions, while surgical complication was prolonged blood loss from drainage treated by a second invasive procedure. Mean (range) pre and postoperative serum creatinine was 1.1 (0.7-3.6) and 1.26 (0.7-5.9) mg/dl respectively. At histopathological evaluation, a focal positive surgical margin was found in 4/54 (9.2%) of cases: 3 of these resulted endophitic in more than 50% of their volume. Mean (range) follow-up was 29.6 (2-48) months; none of the patients developed allergenic reactions to Polytetrafluoroethylene pledgets. *Conclusion:* Nephron-sparing surgery with polytetrafluoroethylene hemostasis was found to be a safe procedure without other additional hemostatic agents, irrespective of tumor size, because the tensile strength was sufficient to keep the repaired parenchyma firm and to allow an excellent control of enucleation bed bleeding. In our experience the procedure is low-price, easy to perform and time-saving. In our series the procedure did not affect renal function.

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THE MAXIMUM SAVING OF FUNCTIONAL URETHRA DURING RADICAL CYSTECTOMY AND ILEAL ORTHOTOPIC NEOBLADDER IDENTIFYING VERUMONTANUM

Federico Lanzi, Gerardo Pizzirusso, Filippo Gentile, Nicola Tosi, Filippo Cecconi, Giovanni De Rubertis, Gabriele Barbanti

UOC di Urologia, AOU Senese, Siena, Italy

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 selfcorporeal image. The aim of this study was 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 2011, we prospectively collected the data of 42 patients undergone radical retropubic cystoprostatectomy plus ileal orthotopic bladder substitution for clinically localized bladder cancer. We compared the intraoperative identification and saving of verumontanum and follow-up data determined through urodynamic evaluation. Clinical, surgical and complete follow-up data were available for 37/42 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 uretrocystoscopy to confirm the presence or absence of verumontanum. Continence was evaluated with ICIQ-SF questionnaire at months 1, 3, 6 and 12. *Results:* Mean follow-up was (range) 21.5 (12-41) months. In 4/37 (10.8%) cases transitional cancer was found in the bladder trigone and in 2 of them an unespected presence of tumor was found in the prostatic urethra. In one case a pT2b prostatic carcinoma Gleason 3+3 was discovered. None of the cases showed a positive apical surgical margin. Overall, 30/37 (81.1%) patients completely fulfilled our continence criteria (≤1 pad/die and ICIQ-SF≤2/2/2) in daytime and 24/37 (64.8%) on nighttime at a minimum follow-up of 12 months. In 15/37 (40.5%) patients with verumontanum (Group A) continence was obtained within the first month in 2/15 (13.3%) cases Vs 0/22 in patients without the saving of verumontanum (Group B), 5/15 (33.3%) Vs 5/22 (22.7%) within the third month, 10/15 (66.7%) Vs 13/22 (59%) within the sixth month and in 13/15 (86.7%) Vs 16/22 (72.7%) at a 12-months follow-up in Group A and B respectively. The saving of verumontanum resulted 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 14/15 patients of Group A demonstrated a Valsalva leak point pressure ≥40cmH_2O Vs 13/22 of Group B. *Discussion:* Verumontanum can be considered an anathomical landmark in saving the maximum of striated sphincter and consequently, the maximum of striated sphincter. 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 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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URETERAL STENTING WITH URO-RADIOLOGICAL COMBINED MANEUVER IN IATROGENIC URETERAL INJURIES

Nicola Tosi[1], Federico Lanzi[1], Marco Cini[2], Claudio Ceccherini[2], Filippo Gentile[1], Gerardo Pizzirusso[1], Filippo Cecconi[1], Carmelo Ricci[2], Gabriele Barbanti[1]

[1]UOC di Urologia,
[2]Uo di Radiologia Interventistica, AOU Senese, Siena, Italy

Objectives: The aim of the present study was to present our JJ stenting technique in ureteral iatrogenic injuries in patients non suitable to reconstructive surgery. *Patients and Methods:* From 2009 to 2012 three patients undergone adjuvant radiotherapy plus radical hysteroannessiectomy for endometrial cancer were evaluated for anuria (2/3 patients) or sepsis (1/3). CT-urography demonstrated an avulsion in the ureters. In urgency, a nephrostomic catether was placed in the involved kidney. All patients were non suitable for an open ureterocystoneostomy or ureteral repair due to very low performance status. After general clinical stabilization a combined uro-radiological maneuver was performed to place a JJ stent. Cystoscopically, the distal ureteral segment was cannulated and a guidewire was advanced into the urinoma. An angiographic catheter was then advanced over the guidewire to the site of rupture. A guidewire was then placed through the indwelling nephrostomy tube and an Amplatz gooseneck snare was placed antegrade into the urinoma cavity. The guidewire was grasped from below by the snare and pulled through the percutaneous access site. A 6F double J ureteral stent was then placed. Nephrostomy was removed on postoperative day 10. *Results:* Mean operative time (range) was 8.4 (5-12) minutes. At a mean (range) follow-up of 12.3 (8-16) months all the three patients demonstrated a conserved renal function. Due to very low performance status and local tumoral progression, it was indicated to maintain ureteral stents which were substituted every 6 months. A retrograde pielography performed during substitutions demontrated the absence of ureteral defects in 2/3 patients. *Conclusion:* Double J stenting with uro-radiological combined maneuver is an effective and safe approach to ureteral iatrogenic injuries. The minimally invasive aspect of this procedure may be considered whenever a patients presents critical clinical and surgical conditions that contraindicate ureterocystoneostomy.

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ACTIVE SURVEILLANCE IN PROSTATE CANCER: 8 YEAR EXPERIENCE

Riccardo Valdagni[1], Cristina Marenghi[2], Tiziana Rancati[2], Maria Francesca Alvisi[2], Tiziana Magnani[2], Nice Bedini[3], Lara Bellardita[2], Nicola Nicolai[4], Maurizio Colecchia[5], Roberto Salvioni[4]

[1]Programma Prostata - SC Radioterapia Oncologica 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;
[2]Programma Prostata,
[3]Sc Radioterapia Oncologica 1,
[4]Sc Chirurgia Urologia,
[5]Anatomia Patologica, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

Aim: In March 2005 we started proposing active surveillance (AS) as an alternative option to radical treatments for very-low risk prostate cancer in a multidisciplinary setting. Patients and methods: Two AS protocols are open to recruitment: the international PRIAS study and the mono-institutional SAINT protocol. Inclusion criteria for both protocols are: initial PSA≤10 ng/ml, DRE≤T2 and GPS≤3+3. Differences in protocols are: PSA density<0.2 ng/ml/cc required by PRIAS and number of positive cores which are no more than 2 in PRIAS, no more than 25% and no more than 50% in each core in SAINT. Follow-up is monitored with PSA, DRE, re-biopsy at definite intervals. Extra biopsies are recommended when PSA doubling time (DT) is between 3 and 10 yrs. Whenever during follow-up the PSADT turns under 3yrs, clinical stage becomes >T2, re-biopsies show more than 2 (or 25%) positive cores or GPS>3+3, patients are switched to active treatment. Active treatment free survival (ATFS) was assessed using Kaplan-Meier survival analysis and correlation between pts' characteristics and protocol-advised drop out was analysed through log-rank test and Cox analysis. *Results:* 454 pts were enrolled in AS (February 2013): 167 in SAINT and 287 in PRIAS. 266/454 (58.6%) pts are still on AS (median f-up of 37.2 mos, range 2.3-107.7; median time in AS 21.4 mos, range 2.4-107.7). 136/454 (29.9%) pts dropped out: 22 due to PSADT, 114 to upgrading and/or upsizing at re-biopsy (64/114 at first re-biopsy). 10 pts dropped out due to comorbidities, 7 due to personal choice (anxiety-related), 34 due to off-protocol reasons and 1 due non-PCa death. Actuarial ATFS was 76% and 58% at 18 (after the first re-biopsy) and 36 months, respectively. To date, no unfavorable outcome has been observed. Biopsy-related ATFS correlates with age <66 yrs (p=0.06, Hazard Ratio (HR)=1.6, ATFS at 36 mos 62% *vs*. 77%), with PSA density<0.12 ng/ml/cc (p=0.03, HR=1.8, ATFS at 36 mos 80% *vs*. 60%) and prostate volume <52cc (p=0.004, HR=2.2, ATFS at 36 mos 85% *vs*. 65%). ATFS results are shown in Figure 1.

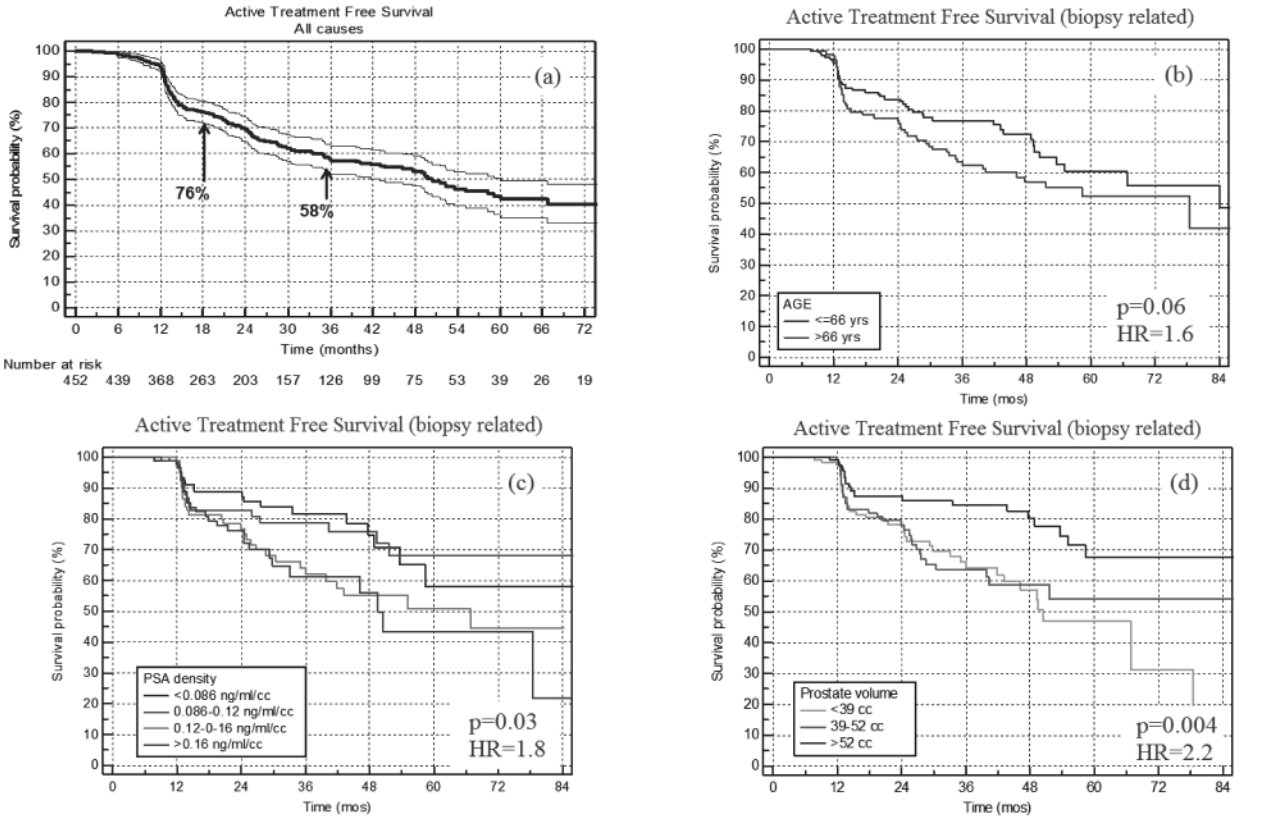

Figure 1. *(a) Active Treatment Free Survival (ATFS), whole Active Surveillance population, all causes; (b) biopsy-related ATFS as a function og age; (c) biopsy-related ATFS as a function of PSA density.*

Conclusion: AS is feasible in selected men with early PCa. Most of pts dropped out at1yr re-biopsy which should probably be considered as a confirmatory biopsy. Age>66yrs, PSA density>0.12 ng/ml/cc and prostate volume >52cc correlate with biopsy-related ATFS as risk factors for reclassification. Better multivariable models are obtained when more specific endpoints are considered and PCA3 is added as prognosticator. Detailed results will be available in a dedicated analysis. The research was partly supported by Fond Monzino.

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TARGET THERAPIES (TT) FOR METASTATIC RENAL CELL CARCINOMA (MRCC) IN THE REAL WORLD. RESULTS OF AN ITALIAN SURVEY

Anna Paola Fraccon[1], Carmen Barile[2], Felice Pasini[2], Cosimo Sacco[3], Teodoro Sava[4], Francesco Valduga[5], Umberto Basso[6], Emanuela Vattemi[7], Giovanni Rosti[8], Emilia Durante[9], Maurizio Nicodemo[10], Giovanni Lo Re[11], Rita Cengarle[12], Paola Bertocchi[13], Daniele Bernardi[14], Donata Sartori[15], Donatella Donati[16], Cristina Pegoraro[17], Franco Bassan[18], Fable Zustovich[6], Fernando Gaion[19], Luigi Salvagno[20], Francesco Massari[4], Ignazio Martellucci[21], Caterina Modonesi[22], Mauro Giusto[23], Alessandra Bearz[24], Romana Segati[25]

[1]Oncologia, Casa di Cura Dott. Pederzoli;
[2]U.O. di Oncologia Medica, Ospedale Santa Maria Della Misericordia, Rovigo;
[3]U.O. di Oncologia Medica, Ospedale Universitario ,Udine;
[4]U.O. di Oncologia Medica, Azienda Ospedaliera Universitaria Integrata, Verona;
[5]U.O. di Oncologia Medica, Ospedale Santa Chiara, Trento;
[6]U.O. di Oncologia Medica, Istituto Oncologico Veneto, Padova;
[7]U.O. di Oncologia Medica, Ospedale Centrale Regionale, Bolzano;
[8]U.O. di Oncologia Medica, Ospedale Ca'foncello, Treviso;
[9]U.O. di Oncologia Medica, Ospedale Mater Salutis, Legnago;
[10]U.O. di Oncologia Medica, Ospedale Sacro Cuore-Don Calabria, Negrar;

[11]U.O. di Oncologia Medica, Ospedale Santa Maria degli Angeli, Pordenone;
[12]U.O. di Oncologia Medica, Ospedale Carlo Poma, Mantova;
[13]U.O. di Oncologia Medica, Fondazione Poliambulanza, Brescia;
[14]U.O. di Oncologia Medica, Assl10 Veneto Orientale, San Dona' di Piave;
[15]U.O. di Oncologia Medica, Azienda Ulss13, Mirano;
[16]U.O. di Oncologia Medica, Ospedale, Ferrara;
[17]U.O. di Oncologia Medica, Ospedale, Montecchio Maggiore;
[18]U.O. di Oncologia Medica, Ulss4, Thiene;
[19]U.O. di Oncologia Medica, Ulss15, Camposampiero;
[20]U.O. di Oncologia Medica, Ospedale, Vittorio Veneto;
[21]U.O. di Oncologia Medica, Ospedale, Siena;
[22]U.O. di Oncologia Medica, Ospedale, Este;
[23]U.O. di Oncologia Medica, Ospedale, Belluno;
[24]U.O. di Oncologia Medica, Centro Riferimento Oncologico, Aviano;
[25]U.O. di Oncologia Medica, Ospedale, Feltre, Italy

Background: This Italian multicentric survey aimed at assessing the role of some prognostic factors already described in literature and to verify the outcome of mRCC pts treated with TT in the community setting outside clinical trials. *Methods:* Individual data from the clinical records of 902 mRCC pts treated with TT from 2007 to December 2012 were obtained from 28 Italian Institutions, through a questionnaire sent to each participating center and approved by local ethical committee. *Results:* Median age was 60 (range 25-89), 75% pts were males. Median overall survival (mOS) was 24 mo (range 1-85), without statistical difference among the centres. Histology was clear cell (CC), CC with sarcomatoid component, papillary, NOS, not available in 82%, 6%, 4%, 4% and 4%, respectively. mOS was 28 and 12.5 mo for CC and non-CC histology, respectively ($p<0.001$). Nephrectomy was performed in 88% of the cases. mOS of these pts was 28 mo *vs*. 6.5 of those not receiving surgery ($p<0.001$). The number of metastatic sites was ≥3 in 43% of the pts; mOS of this group was 18 mo *vs*. 31 mo of pts with ≤2 metastatic sites ($p=0.0001$). MSKCC risk score (542 evaluable pts) was poor in 15%, intermediate in 53% and good in 32% of the pts; mOS was 6.4, 24 and 49 mo for poor, intermediate and good risk pts, respectively ($p<0.001$). ECOG PS was 0-1 in 90% of the pts; mOS of pts with PS ≥2 was 6 mo ($p=0.0001$). First line treatment was: sunitinib 693 pts (76.6%), sorafenib124 (13.7%), temsirolimus 35 (4%), bevacizumab 26 (3%), pazopanib 19 (1.5%) and other therapies 5 pts. Median 1st line PFS (mPFS1) was 11 months for sunitinib and 7 months for sorafenib. Overall response rate was 33.5% (CR 3.5% + PR 30%), 30% SD, not evaluable 3.5%. Dose reduction of sunitinib and sorafenib was required in 49% and 39% of the cycles administered, respectively; 137 pts (15%) received only 1 cycle of sunitinib mostly for rapid progression and/or deterioration. Second line therapy was performed in 46% of the pts: sorafenib 143 (16%), everolimus 121 (13%), sunitinib 100 (11%), temsirolimus 25 (3%), chemo-immunotherapy 26 (3%), others (1%). mPFS2 was 6 mo with sunitinib and about 4 mo with the other therapies ($p=0.001$). 155 pts (17%) received 3 treatment lines, with different sequences and the 3rd line PFS was 6 months. OS was slightly better for the TKI-TKI-mTOR sequence than for the TKI-mTORTKI (48 *vs*. 37 months, $p=0.06$). At multivariate analysis, CC histology, prior nephrectomy, number of metastatic sites, PS, MSKCC risk, platelets and neutrophils count were independent prognostic factors. *Conclusion:* This survey confirms the results of prospective clinical trials in terms of outcome. Many patients achieved long term OS after subsequent lines of therapy, but, on the other hand, a similar percentage of pts experienced rapid progression. Further studies are needed to better identify the subset of pts who may benefit the most from TT. Moreover, our study showed that clear cell histology, prior nephrectomy, number of metastatic sites, PS, MSKCC risk, platelets and neutrophils count maintain their prognostic value also in mRCC pts treated with TT in the everyday clinical practice.

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IS MULTIPARAMETRIC MRI RELIABLE IN SELECTING PATIENTS WITH PROSTATE CANCER FOR ACTIVE SURVEILLANCE?

Francesco Porpiglia[1], Cristian Fiori[2], Fabrizio Mele[2], Matteo Manfredi[2], Susanna Grande[2], Massimiliano Poggio[2], Diletta Garrou[2], Enrico Bollito[3], Mauro Papotti[3], Filippo Russo[4], Daniele Regge[4]

[1]SCDU Urologia, AOU San Luigi Gonzaga;
[2]Scdu Urologia, Ospedale San Luigi Gonzaga, Orbassano;
[3]Scdu Anatomia Patologica, Ospedale San Luigi Gonzaga, Orbassano;
[4]Sc Radiologia, IRCC Candiolo, Italy

Introduction: In case of low risk incidental prostate cancer (PCa), the question arises whether to treat or follow a program of active surveillance (AS) (1). These programs, based on clinical and pathological features, can sometimes mistakenly select patients (2). Multiparametric MRI (mp-MRI) has shown promise in localizing and characterize PCa (3). The aim of this study was to evaluate the role of mp-MRI in improving the selection of patients eligible for AS programs. *Methods:* We reviewed our prospectively maintained PCa database and extracted the data about consecutive patients treated with radical prostatectomy (RP)

Table I (Abstract No 111).

TV (cc)	mp-MRI		PB		TOT	*p*-Value
	Identified	Not identified	Identified	Not identified		
≤0.5 (insignificant)	79 (53.0%)	70	32 (21.5%)	117	149	<0.0001
>0.5 (significant)	238 (96.4%)	9	208 (84.2%)	39	247	<0.0001
TOT	317 (80.1%)	79	240 (60.6%)	156	396	<0.0001

previously undergone mp-MRI. We compared data of patients who fulfilled the AS criteria with data of mp-MRI and the pathological analysis. Clinical AS criteria were those of PRIAS (Prostate Cancer Research International: Active Surveillance) protocol: PSA<10 ng/ml and density<0.2 ng/ml; <2 positive cores at prostate biopsy and GS<6; clinical stage T1c-T2. Radiological criteria of inclusion of AS on mp-MRI were major tumor diameter <10 mm, organ-confined PCa, ADC <0.8/1. Pathological criteria using Epstein definition of insignificant disease were: organ-confined PCa, no evidence of Gleason 4 or 5; tumor volume <0.5 cc. The same surgeon, the same uro-pathologist and the same uro-radiologist performed all the procedures. Sensitivity, specificity, positive and negative predictive value (PPV and NPV) of PRIAS criteria, mp-MRI and PRIAS + mp-MRI were calculated based on 2x2 tables, using pathological results as gold standard. *Results:* On pathological examination, 19/180 (10.6%) patients would have been properly selected for AS. Using PRIAS criteria to select patients for AS, sensitivity, specificity, PPV and NPV were 15.8%, 75.8%, 7.1% and 88.4%, respectively. Using only mp-MRI criteria to select patients for AS, sensitivity, specificity, PPV and NPV were 100%, 87.9%, 50% and 100%, respectively. Using PRIAS + mp-MRI criteria, sensitivity, specificity, PPV and NPV were 15.8%, 98.8%, 60% and 90.9%, respectively. Only 2 patients selected for AS with PRIAS and MRI criteria had a non-low risk PCa (GS 7). PRIAS criteria fulfilled, PRIAS criteria not fulfilled, TOT mp-MRI criteria fulfilled, mp-MRI criteria not fulfilled TOT PRIAS + mp-MRI criteria fulfilled, PRIAS + mp-MRI criteria not fulfilled, TOT Epstein criteria fulfilled 3 16 19 Epstein criteria fulfilled, 19 0 19 Epstein criteria fulfilled 3 16 19 Epstein criteria not fulfilled, 39 122 161 Epstein criteria not fulfilled 19 138 161 Epstein criteria not fulfilled 2 159 161 TOT 42 138 180 TOT 38 138 180 TOT 5 175 180. *Conclusion:* The results of our study suggested that actual inclusion criteria are inadequate to candidate patients with PCa for AS. In our cohort, mp-MRI seems to improve selection of patients for AS when used in combination with clinical criteria such as PRIAS.

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DETECTION OF CLINICALLY SIGNIFICANT PROSTATE CANCER: A COMPARISON OF MULTIPARAMETRIC MRI AND PROSTATE BIOPSY

Francesco Porpiglia[1], Cristian Fiori[2], Fabrizio Mele[2], Matteo Manfredi[2], Susanna Grande[2], Marco Cossu[2], Giovanni Cattaneo[2], Enrico Bollito[3], Mauro Papotti[3], Filippo Russo[4], Daniele Regge[4]

[1]SCDU Urologia, AOU San Luigi Gonzaga;
[2]SCDU Urologia, Ospedale San Luigi Gonzaga, Orbassano;
[3]SCDU Anatomia Patologica, Ospedale San Luigi Gonzaga, Orbassano;
[4]Sc Radiologia, IRCC Candiolo, Italy

Introduction: Since the introduction of PSA in clinical practice, we have seen a rise in incidental prostate cancer (PCa), with an increase in low-risk disease (1). The current definition of clinically significant disease is a PCa with a tumor volume (TV) >0.5 cc (2). Recently, with the introduction of prostate multiparametric MRI (mp-MRI), we can benefit of anatomical, morphological and functional information for the most suitable therapeutic approach for

PCa (3). The aim of this prospective study was to analyse the ability of prostate biopsy (PB) and preoperative mp-MRI to correctly identify clinically significant PCa foci in patients undergoing radical prostatectomy (RP) for PCa. *Patients and Methods:* We extracted data from our prospectively maintained database of 180 consecutive patients with PCa. All of them underwent mp-MRI prior to laparoscopic or robot-assisted RP. MRI was performed with a conventional study with T1-w, T2-w and diffusion sequences. After precontrast acquisitions, patients were intravenously given gadobutrol. RP specimens were evaluated according to a validated international protocol. The same surgeon, the same uro-pathologist and the same uro-radiologist performed all the procedures. We defined significant disease based on the current cut off of TV (0.5cc) measured on RP specimen, considered our gold standard. We then compared transrectal PB (with at least 12 samples) and mp-MRI in terms of detection rate of significant PCa. Statistical analyses were performed using Chi-square test. All analyses were performed by using Statistic 7 software (Statsoft, Tulsa, Oklahoma) (*p*-values<0.05 were considered as statistically significant). *Results:* On histological examination, 396 neoplastic lesions were identified (Table I). Compared to PB, mp-MRI demonstrated a high sensitivity in detecting PCa. Although mp-MRI had also values of sensibility higher than biopsy, both had low sensitivity in detecting small lesions. mp-MRI missed 79 lesions, of which 9 were significant: 7 with a TV > 0.5cc and 2 with both a TV >0.5 cc and a pGS 7. 6 tumors with GS 7 and volume <0.5cc were lost. PB missed 156 lesions, of which 39 neoplastic lesions with a TV >0.5cc (1 had a GS >8, 26 had a GS 7 and 12 had a GS <6). 28 tumors with GS 7 and volume <0.5cc were lost. *Conclusion:* In our study, mp-MRI was able to correctly identify almost all clinically significant PCa. This technique seems to be a reliable tool in order to select the best treatment tailored for each patient.

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TRANSPERITONEAL EXTENDED LYMPH NODE DISSECTION WITH ROBOTIC APPROACH: 50 PATIENTS TREATED DURING ROBOT-ASSISTED RADICAL PROSTATECTOMY

Francesco Porpiglia, Ivano Morra, Fabrizio Mele, Riccardo Bertolo, Daniele Amparore, Andrea di Stasio, Cristian Fiori

SCDU Urologia, Ospedale San Luigi Gonzaga, Orbassano, Italy

Introduction: Lymph node dissection (LND) is a basic diagnostic step in selected patients with prostate cancer. When dissection is limited to the obturator fossa, about 50% of lymph node metastases will be missed; for this reason extended LND has been recommended by EAU guidelines. Some Authors proposed the use of da Vinci system to perform the procedure and literature results are encouraging. The aim of this study was to present our experience with robotic extended "modified" LND (emLND). *Patients and Methods:* From August 2011 to September 2012, 50 patients were treated with transperitoneal emLND with robotic approach at our Institution. *Surgical technique:* The dissection begins with the incision of peritoneum, laterally to the umbilical ligament until the ureter, external iliac vessels are identified and exposed. The ureter is identified, dissected, suspended by using a vessel loup and then displaced. Hypogastric artery is identified and dissected close to common iliac artery. The external iliac lymph nodes are progressively dissected. This dissection is limited to the medial portion of the vessels, whilst the tissue that covers the lateral portion is left in place to prevent lymphedema. An Hem o lok clip is placed just cranially to the Cloquet lymph node, which is preserved to prevent lymphocele and lymphedema. Then the obturator fossa is reached and the lymph nodes are progressively dissected until complete exposition of obturator nerve is achieved. The presacral lymphnodes are then identified and dissected. The same technique is used at the left side. At the end of radical prostatectomy, the peritoneum is sutured by using a running 3/0 "barbed" suture. At the end of the suture the peritoneal cavity and retropubic space do not communicate thanks to prevesical fascia. Perioperative and pathological data were recorded, complications were recorded and classified according to Clavien system. *Results:* Mean operative time was 34 minutes; right and left LND were equally time-consuming. No intraoperative complication occurred, in particular no vessel injuries were recorded. Post operative complications occurred in two cases (4%): a prolonged ileus (grade II) and ureteral fistula treated with JJ stent placement (grade III). In this last case no further complications were

recorded after the stent removal (2 months after surgery). Notably, no symptomatic lymphoceles or lymphedema were recoded. Mean of removed lymph nodes was 24.6, pN1 rate was 10% while mean of positive LN was 2. *Conclusion:* It is our experience that robotic system allows a safe and effective LND and our details of technique tend to further reduce complications. It is our subjective feeling that robotic technology, with the increased freedom of movement significantly facilitates LND.

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A COMPARISON OF MULTIPARAMETRIC MRI AND PROSTATE BIOPSY IN PATIENTS WITH PROSTATE CANCER WITH PSA <10 NG/ML AND NEGATIVE DRE UNDERGOING RADICAL PROSTATECTOMY

Francesco Porpiglia[1], Cristian Fiori[1], Fabrizio Mele[1], Matteo Manfredi[1], Giovanni Cattaneo[1], Nicoletta Serra[1], Francesca Ragni[1], Enrico Bollito[2], Mauro Papotti[2], Filippo Russo[3], Daniele Regge[3]

[1]SCDU Urologia, Ospedale San Luigi Gonzaga, Orbassano; [2]SCDU Anatomia Patologica, Ospedale San Luigi Gonzaga, Orbassano;
[3]Sc Radiologia, IRCC Candiolo, Italy

Aim: To analyse the ability of prostate biopsy and multiparametric (mp) MRI to correctly identify tumour foci in patients undergoing radical prostatectomy (RP) for PCa with a PSA <10 ng/ml and a negative DRE and to compare these results dividing our population in terms of diagnosis at first or second PB. *Patients and Methods:* 157 patients with clinically localised PCa with a PSA <10 ng/ml and a negative DRE diagnosed on the first or second prostate biopsy were enrolled. First biopsies consisted of twelve samples (Group A) while second biopsies consisted of 18 samples (Group B). All patients underwent mp-MRI with T2-weighted images, diffusion-weighted imaging (DWI), dynamic contrast enhanced (DCE)-MRI prior to RP at our institution. A map of comparison describing each positive biopsy sample was created for each patient, with each tumour focus shown on the MRI and each lesion present on the definitive histological examination in order to compare tumour detection and location. *Results:* Compared to prostate biopsy, mp-MRI demonstrated a higher detection rate, reaching statistical significance ($p<0.05$) in most of stratifications (tumour volume, tumour location and pathological Gleason Score) except for tumour location in Group B, GS <6 in Group B, GS 7b in Groups A and B, GS >8 in overall and subdivided population. Overall sensitivity of prostate biopsy and mp-MRI in identifying tumour lesions were 59.4% and 78.9%, respectively ($p<0.0001$). PB missed 144/355 lesions, 59 of which (16.6%) were significant: 11 with a TV >0.5 ml, 25 with a pGS=7 and 23 with both a TV >0.5 ml and a pGS=7. No statistically significant differences in the number of missed significant lesions were recorded between Groups A and B. mp-MRI missed 75/355 lesions, 12 of which (3.4%) were significant: 4 with a TV >0.5 ml, 6 with a pGS=7 and 2 with both a TV >0.5 ml and a pGS=7. Positive predictive value of prostate biopsy and mp-MRI to detect the prevalence of Gleason pattern 4 (GS >7b) are 96.3% and 99.6%, respectively. Pearson's correlation coefficients were 0.6067 and 0.9207 for PB and mp-MRI, respectively. *Conclusion:* mp-MRI identifies more tumour lesions than first and second prostate biopsies. Furthermore, mp-MRI provides more information concerning tumour anatomy (tumour volume and location) and aggressiveness (prevalence of Gleason pattern 4). In patients with clinically localized PCa, mp-MRI is a useful tool for better therapeutic planning.

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MARGINS, ISCHAEMIA AND COMPLICATIONS (MIC) RATE FOLLOWING LAPAROSCOPIC PARTIAL NEPHRECTOMY: EVALUATION OF IMPACT OF LEARNING CURVE AND TUMOUR COMPLEXITY

Francesco Porpiglia, Riccardo Bertolo, Ivano Morra, Daniele Amparore, Andrea di Stasio, Cristian Fiori

SCDU Urologia, Ospedale San Luigi Gonzaga, Orbassano, Italy

Introduction and Aim: Standardising the reports of Partial Nephrectomy (PN) outcomes, not only in terms of oncology but also in terms of functional results and complications, is critical to compare different techniques. Combining surgical margins status, complications according to the Clavien system and the duration of ischaemia, some authors recently proposed the novel "margin, ischaemia, and complications" (MIC) binary system, with the aim of standardising the reporting of PN results Primary aim of the study was to present our laparoscopic PN (LPN) results according to the MIC system; the secondary aim was to assess the role of learning curve and tumour complexity on the outcomes by using MIC system. *Patients and Methods:* Data were obtained from our prospectively-maintained LPN database, including only patients who underwent LPN performed with vascular clamping. According to MIC system definition, the goal of LPN was reached when surgical margins were negative, warm ischaemia time (WIT) was<20 min and no major complications occurred. Patients

were stratified by quartiles of distribution (named "LPN-eras" 1-4): MIC rates in different LPN-eras were compared evaluating the impact of learning curve and tumour complexity (as assessed by the PADUA score) on the outcomes. Chi-square, Kruskall-Wallis, one-way- and factorial-ANOVA tests were used for statistical analysis (p-values <0.05 were considered as statistically significant). *Results:* Studied population consisted of 206 patients. Overall MIC rate was 63.1%: it progressively increased along the learning curve, reaching 84.9% in LPN-era 4 (p<0.0001). PADUA score risk-group categories were inversely correlated with MIC score (p=0.0014). When simultaneously considering the effects of both LPN-eras and PADUA score risk-group categories, a trend towards a higher MIC rate was found in latest series regardless of tumour complexity. When MIC score components were separately analysed, WIT was significantly decreased from LPN-era 1 to 4 (p<0.001) and PADUA score risk-group categories 3 to 1 (p=0.001). A trend towards a decrease in the complications rate along the learning curve was observed (p=0.251), while LPN-era and PADUA score together significantly influenced the complications rate (p<0.001). Positive surgical margins rate was stable throughout the case study. *Conclusion:* MIC rate increased with surgeon's experience and decreased when complex lesions were treated. In our opinion MIC system was an easy, useful and reproducible tool to evaluate LPN data series.

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FLUORESCENCE CYSTOSCOPY WITH HEXAMINOLEVULINATE IN DIAGNOSIS AND FOLLOW UP OF BLADDER CANCER: FIVE-YEARS EXPERIENCE

Francesco Porpiglia, Massimiliano Poggio, Marco Cossu, Nicoletta Serra, Riccardo Bertolo, Giovanni Cattaneo, Diletta Garrou, Cristian Fiori

SCDU Urologia, Ospedale San Luigi Gonzaga, Orbassano, Italy

Introduction and Aim: Fluorescence cystoscopy (FC) with hexaminolevulinate (HAL) compared to standard white light cystoscopy (WLC) can improve detection of transitional cell carcinoma (TCC) of the bladder and carcinoma *in situ*.We present our experience using combined WC and HAL-FC for diagnosis and follow up of bladder TCC. *Patients and Methods:* We retrospectively reviewed our prospectively maintained TCC database (1/2007-9/2012) and we extracted the data of 80 patients (70 males and 10 females, mean age 69.7 years) with history of high risk TCC undergone WLC and HAL-FC. One hour before the procedure HAL 85 mg diluted in saline 50 ml was administered intravesically. In all patients traditional WLC followed by a FC with blue light was performed. In case of negative WLC and HAL-FC, no biopsies were performed; in case lesions suspicious to be TCC, a cold biopsy and/or transurethral resection were performed. Patent TCC were not considered in this study. *Results:* Overall, we performed bioptic resection of all suspect lesions (154 biopsies) detected in white and/or blue light. In 12 cases simple FC without biopsies was carried out (negative WLC/HALFC). WLC detected 98 suspect lesions, being negative in 44 cases. FC detected 140 suspect lesions, being negative in 76 cases. WLC found 54 cancer/dysplasia, while FC 64 cancer/dysplasia. In particular, FC detected a higher number of carcinoma *in situ* than WLC. Among the 98 WLC+(FC+/FC-) lesions, 36 were neoplastic, 18 CIS and 44 flogistic; the 140 FC+ (WLC+/WLC-) lesions, 38 were neoplastic, 26 Cis and 76 flogistic. FC+/WLC- lesions were 44: 10 were positive cancer/dysplasia (6 CIS). The 2 WLC+/FC- lesions were all negative for cancer, as well as the 12 WLC-/FC- lesions. False positives were similar in both groups (FC 45% *vs*. WLC 44.8%), but the FC diagnostic gain was higher (22.7%) than WLC, especially regarding the diagnosis of carcinoma *in situ*. *Conclusion:* FC with HAL is a safe and effective procedure, and is a useful adjunct to WLC, improving its diagnostic gain toward carcinoma *in situ*. In our opinion, considering cost and effectiveness, this procedure should be reserved to patients affected by high risk superficial bladder carcinoma as optimal therapeutic choice.

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THE VALUE OF HISTOLOGICAL REVISION OF BIOPSY CORES IN PATIENTS SUITABLE FOR ACTIVE SURVEILLANCE: COMPARISON WITH SURGICAL SPECIMENS AFTER RADICAL PROSTATECTOMY AND CLINICAL FOLLOW-UP

R. Schiavina[1], M. Fiorentino[2], E. Brunocilla[1], A. Bertaccini[1], F. Manferrari[1], S. Rossi[1], S. Rizzi[1], D. Romagnoli[1], M. Cevenini, L. Bianchi[1], M. Borghesi[1], D. Diazzi[1], H. Dababneh[1], G. Passaretti[1], G. Martorana[1]

[1]University of Bologna, Dept. of Urology, Bologna; [2]S. Orsola-Malpighi Hospital, Institute of Oncology and Pathology, Bologna, Italy

Objectives: The aim of this study was to evaluate the value of histological revision of biopsy cores and pathological specimens after radical prostatectomy (RP) in patients with low-risk prostate cancer (PCa) potentially suitable for active surveillance (AS). *Patients and Methods:* Among 1344 patients treated with RP between 2004 and 2011, we identified 134 men (10%) who fulfilled the inclusion criteria

for the AS of P.R.I.A.S. study (PSA≤10; PSA density 0.2 ng/ml. Pathological indolent PCa was defined as organ-confined PCa and Gleason ≤6 of any volume. The main end points were: a) quantify the difference between biopsy and pathological Gs and stage before and after revision; b) quantify the real amount of "true" biopsy Gs 3+3 after revision and assess the pathological and oncological outcomes of patients with "true" biopsy Gs 3+3 (GROUP 1) *versus* patients with biopsy Gs >3+3 (GROUP 2); c) assess the accuracy of the revision of biopsy Gs in the prediction of pathological indolent PCa. T-student, Mann-Whitney and Pearson chi-square tests and ROC analysis were used. *Results:* The mean (IQR) age, PSA and number of cores taken were 69.5±5.3 (61-70) yrs, 5.9±1.8 (4.6-7.4) ng/ml and 13.2±3.1 (11-15 cores taken) respectively. With mean follow-up 40.8±21.2 mo (10-93), cancer-specific survival was 100% at 7 yrs and 2 patients died for unrelated disease. After revision, median Gs of biopsy cores and pathological specimen increased by 1 point (from 6 to 7) and the amount of patients with pathological stage T3a-b increased from 6 (4.4%) to 11 (8.2%) (all P3+3 (GROUP 2). In GROUP 1, 19 (43.2%) had pathological indolent disease, while in 90 patients of GROUP 2 only 11 (12%) had pathological indolent disease ($p<0.001$). Two patients underwent adjuvant radiotherapy (ART) in GROUP 1, while 4 patients underwent ART and 2 had BCR in GROUP 2 ($p=0.619$). After revision, the AUC of biopsy Gs revision in the prediction pathological indolent disease (GROUP 1 *vs*. GROUP 2) was 0.696. *Conclusion:* After revision of biopsy cores performed by a single experienced uropathologist, 2/3 of patients would rather have been excluded from AS. The wide study period can partially explain these significant divergence in Gs before and after revision. The histological revision is essential to enhance the likelihood of revealing indolent PCa.

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ACCURACY OF [^{11}C] CHOLINE POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY IN PREOPERATIVE STAGING IN PATIENTS WITH BLADDER CANCER REFERRED TO RADICAL CYSTECTOMY: COMPARISON WITH CONVENTIONAL COMPUTED TOMOGRAPHY

R. Schiavina[1], G. Passaretti[1], D. Romagnoli[1], A. Bertaccini[1], E. Brunocilla[1], F. Manferrari[1], M. Garofalo[1], V. Vagnoni[1], G.C. Rocca[1], L. Bianchi[1], F. Chessa[1], L. Bianchi[1], M. Borghesi[1], M. Fiorentino[2], G. Martorana[1]

[1]University of Bologna, Dept. of Urology, Bologna; [2]S. Orsola-Malpighi Hospital, Institute of Oncology and Pathology, Bologna, Italy

The preoperative detection of lymph node (LN) involvement in patients with Bladder Cancer (BCa) is of the utmost importance for the medical and surgical management. Computed Tomography (CT) is so far the standard staging modality, but it affords only morphological information. ^{11}C-choline PET/CT value in prostatic cancer detection has been already confirmed nevertheless few and conflicting data are reported about the diagnostic value of ^{11}C-choline PET/CT in the preoperative staging of bladder cancer.The aim of this study was to evaluate the efficacy of the ^{11}C-choline Positron Emission Tomography with CT (PET/CT) and contrast enhanced CT for LNs staging in BCa. Twenty male patients with BCa were studied with ^{11}C-choline PET/CT and diagnostic CT before radical cystectomy (RC) with extended pelvic lymph nodes dissection (ePLND). Lymph nodes histological findings were compared with ^{11}C-choline PET/CT and CT. Patient, lymph node and zonal-based analyses were obtained. Pelvic zonal dissection template included 3 fields: para-aortal, interaortocaval, para-caval and presacral LNs(A); right pelvic LNs(B); left pelvic LNs(C). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were evaluated. A total of 655 LNs were removed; LN metastases were found in 4 of 20 patients (20%). In patient based analysis ^{11}C-choline PET/CT and CT sensitivity, specificity, PPV, NPV and accuracy were 75% 81% 50% 93% 80%; and respectively 25%,94%,50%,83%,80%. In LN-based analysis, sensitivity, specificity, PPV, NPV and accuracy were respectively 10% 70% 50% 96% 94% for ^{11}C-choline PET/CT and 3%, 70%, 30%, 95%, 95% for CT. In zonal-based analyses ^{11}C-choline PET/CT sensitivity, specificity, PPV, NPV and accuracy were 25%, 94%, 37.5%, 6%, 13%, while CT showed 3%, 57%, 25%, 11%, 13%. Finally ^{11}C-choline PET/TC detection rate was 8%, 18%, 29%, respectively for 0.9-4.9 mm, 5-9.9mm, ≥10mm LN metastases, higher than CT detection rate. Our data suggest that ^{11}C-choline PET/CT, providing few false-negative and false-positive than CT, is particularly useful in evaluating patients with nodal enlargement or nodes with borderline sizes; moreover, it can identify lymph node metastases <10 mm more reliably than CT does. ^{11}C-choline PET/CT detected bone marrow metastases and lung nodes. The limited number of patients was the major limitation of this study. Although this is a preliminary report, and other studies are needed to confirm our results, at present ^{11}C-choline PET/CT seems to be a promising imaging technique for the detection of lymph node metastases, more sensitive and specific than CT. ^{11}C-choline CT/PET is useful for prognostic information and preoperative management for bladder cancer patients.

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PRESERVATION OF THE SMOOTH MUSCULAR INTERNAL (VESICAL) SPHINCTER AND OF THE PROXIMAL URETHRA DURING RETROPUBIC RADICAL PROSTATECTOMY: DESCRIPTION OF THE TECHNIQUE AND EARLY RESULTS

E. Brunocilla, C.V. Pultrone, R. Schiavina, G.C. Rocca, M. Borghesi, V. Vagnoni, Z. Zukerman, D. Diazzi, G. Martorana

University of Bologna, Dept. of Urology, Bologna, Italy

Introduction and Objectives: 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. We describe our technique for preservation of the smooth muscular internal (vesical) sphincter and proximal urethra during radical retropubic prostatectomy. *Methods:* The first steps of the prostatectomy reflect the standard RRP, while for the final phases the procedure continues in an anterograde manner with incision of the fibers of the detrusor muscle at the insertion of the ventral surface of the base of the prostate. At this level, the inner circular muscle of the bladder neck forms a sphincteric ring of smooth muscle that covers the longitudinally oriented smooth muscle component of the urethral musculature that extends distally to the verumontanum: these two proximal structures represent the internal sphincter that envelops and locks the proximal urethra. A blunt dissection is continued until the ring shaped vesical sphincter is separated from the prostate and the longitudinally oriented smooth muscle component of the urethral musculature is identified. The base of the prostate is then gently separated from the urethra and from the bladder until the maximal length of the urethral musculature is isolated and preserved. Finally, an urethra-urethral anastomosis is performed and the ventral stitches are also placed through the circular fibers of the bladder neck. In all cases we perform circumferential biopsies of the proximal urethra and of the base of the prostate. *Results:* From February 2007 to January 2011, 66 patients with organ confined prostate cancer were submitted to RRP with the technique described above.Exclusion criteria were large mid lobe prostate or large prostate volume (>80 cc) and high-risk PCa (defined as PSA> 20 ng/ml or clinical T3 or clinical Gleason score >7).Operative time was 119 minutes.In all cases the catheter was removed after 12 days.In all cases the catheter was removed after 12 days.In all cases the surgical margins at the base of the prostate specimen and at the proximal urethra were negative.We evaluated the percentage of patients with early and global restoration of urinary continence, defined as the use of no pads and no leakage of urine or the use of a dry safety pad: the continence rate was 52.1%, 72.5%, 81.3 and 95.3% at 3, 7, 90 and 120 days respectively after catheter removal. *Conclusion:* The described technique is a feasible and safe method for preservation of the internal urethral sphincter. Despite our positive results and enthusiasm, further studies with larger series are needed to confirm these findings.

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HIGH DOSE RATE BRACHYTHERAPY (HDR-BRT) COMBINED WITH IMAGE-GUIDED INTENSITY MODULATED RADIOTHERAPY (IG-IMRT): A 12 CASES EXPERIENCE

G. Tolento[2], A. Bertaccini[1], M. Giampaoli[1], M. Ntreta[2], F. Romani[3], F. Manferrari[1], R. Schiavina[1], D. Marchiori[4], G. Martorana[1], R. Mazzarotto[2]

[1]U.O. Urologia-Martorana, Policlinico S.Orsola-Malpigli, Bologna;
[2]U.O. Radioterapia-Mazzarotto, Policlinico S.Orsola-Malpigli, Bologna;
[3]U.O. Fisica Medica, Policlinico S. Orsola-Malpighi, Bologna;
[4]Gynepro Medical, Bologna, Italy

Introduction: Radiotherapy represents, together with surgery, a treatment option in patients with localized prostate cancer. Image Guided-Intensity Modulated Radiotherapy (IG-IMRT) with fiducial markers and/or High Dose Rate Brachytherapy (HDR-BRT) allowed to safely deliver high radiation doses to the prostate (1, 2). Furthermore, recently the combination of External Radiation Beam Radiotherapy (EBRT) plus HDR-BRT showed better results than the two separated techniques alone (3). In addition Brachytherapy, due to its characteristic high dose per fraction, might have some radiobiological advantages due to the low alpha/beta ratio of the prostate cancer cells (4, 5). *Aim:* The purpose of this study was to evaluate the feasibility and the early toxicity of a cohort of patients affected by high and very high risk prostate cancer and treated with HDR-BRT combined with EBRT in the Radiotherapy Department in S. Orsola-Malpighi Hospital, Bologna. *Patients and Methods:* Between May 2011 and January 2013, a cohort of 12 patients (mean age 69.5 years) affected by prostate cancer (7 high and 5 very high risk) were treated with HDR-BRT plus IG-IMRT. HDR-BRT was delivered to the prostate in one fraction of 14 Gy *via* temporary transperineal insertion of 16-18 plastic afterloading catheters using a Transrectal Ultra-Sound guided approach. Afterwards each patient received a 5000 cGy IG-IMRT in 25 fraction of 200 cGy targeting the prostate, the seminal vesicles and the pelvic lymph nodes. IPSS-short form and IIEF-5 questionnaires were submitted

to each patient before the treatment and re-submitted at each follow-up. Two years Androgen Deprivation Therapy (ADT) was given to patients; only 2 patients were ineligible due cardiologic and diabetologic comorbidities. *Results:* Among 12 patients, 7 reported acute early toxicity (grade 1 in the RTOG scale) after the treatment. Early toxicity disappeared in 5 patients while in 2 patients it is still present (grade 1 in the RTOG scale). The mean follow-up time was 7.7 months (min 3, max 18 months). At the last follow-up, each patient showed an improvement of the IPSS score (mean basal IPSS 13.3; mean IPSS at last submission 6.3), while 4 patients showed a lowering of the IIEF-5 (mean basal IIEF-5 11.2; mean IIEF-5 at last submission 4, 5). All patients underwent a lowering in the last available measured PSA (mean basal PSA after 1 month of ADT 4.60 ng/mL; mean PSA at last follow-up 0.45 ng/mL). *Conclusion:* Treating patients affected by high and very high risk prostate cancer with HDR-BRT combined with IG-IMRT appears to be feasible and safe. However a longer period of observation of a greater cohort of patients is needed to determine the impact in the Quality of Life and to evaluate the oncological outcomes.

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RESEARCHING THE MORE EFFICIENT MODEL FOR CALCULATING THE PSA VELOCITY IN ORDER TO DETECT A PROSTATE CANCER: AN EXPLORATIVE STUDY

A. Bertaccini[1], M. Giampaoli[1], F. Manferrari[1], R. Schiavina[1], D. Marchiori[2], G. Martorana[1]

[1]U.O. Urologia-Martorana, Policlinico Sant'Orsola-Malpighi, Università di Bologna;
[2]Gynepro Medical, Bologna, Italy

Introduction: The introduction of PSA into the urological clinical practice has led to an always more common use of its "derivatives". Since the original description by Cartel *et al*. (1), PSA Velocity gained importance, although sometimes with conflicting evidences (2), as a diagnostic tool in order to identify which patients should undergo a prostate biopsy (3-5). However, there is not an actual agreement about which formulas to use and how many PSA dosages to consider in the calculation. *Aim:* Purpose of this retrospective exploratory study was to evaluate the most suitable system to calculate the PSA Velocity, in particular which kind of formula to use and which monitoring PSA lapse of time to consider. *Patients and Methods:* This retrospective explorative study was conducted in a cohort of 103 patients (mean age of 65,7 years) scheduled for a prostate biopsy in the Urology Clinic, Sant'Orsola-Malpighi Hospital, Bologna. All available measured PSA were collected from the patients who underwent a PSA dosing at least 3 times in the past 2 years. PSA Velocity was calculated using two different mathematic models: first using the average of the PSA increases over time then through the slope of the least square regression line (PSA VelocitySlope (3)) obtained from PSA *vs*. Time. The previous two formulas were applied either in all the available measured PSA (mean of 7 dosed PSA values in a mean lapse of time of 4.4 years) either in the PSA values measured in the last 2 years alone (mean of 5 dosed PSA values). *Results:* Among 103 patients, 39 (mean PSA: 7.51 ng/mL; C.I.95% 5.75-9.26) were found positive for a Prostate Cancer while 64 were found negative (mean PSA: 7.20 ng/mL; C.I.95% 6.09-8.41). At the receiver operating characteristic (ROC) analysis the PSA VelocitySlope calculated with all the available PSA measurements evidenced the best score (AUC 0.58; C.I.95% 0.46-0.68). PSA Velocity with all the available PSA measurements (AUC 0,51; C.I.95% 0.39-0.63), PSA VelocitySlope calculated with last 2 years PSA (AUC 0.51; C.I.95% 0.40-0,62) and to the PSA Velocity with the last 2 years PSA (AUC 0.50; C.I.95% 0.38-0.61) showed lower scores. The PSA alone showed the lowest AUC (AUC 0,48; C.I.95% 0.36-0.60). *Conclusion:* PSA Velocity calculated through the slope of the least square regression line of PSA *vs*. Time appears to be more useful if obtained from the largest pool of PSA measurements. However, further studies are needed to be conducted in order to validate and standardize an optimal PSA Velocity calculation.

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NARROW BAND IMAGING (NBI) TURBT: DOES IT IMPROVE DETECTION RATES? SINGLE CENTRE PRELIMINARY EXPERIENCE

Roberto Giulianelli, Barbara Cristina Gentile, Giorgio Vincenti, Stefano Nardoni*, Luca Mavilla, Luca Albanesi, Francesco Attisani, Gabriella Mirabile, Francesco Pisanti, Davide Granata, Manlio Schettini

Division of Urology, Nuova Villa Claudia, Rome, Italy

Introduction: Bladder cancer treatment is considered as the most expensive tumour treatment regarding the cost per patient per year as well as lifetime cost per patient. According to literature, 50% to 70% of the NMIBC (non-muscle invasive bladder cancer) patients display recurrence after the initial endoscopic treatment. Many cases of early recurrences are determined by the incomplete tumor removal through trans-urethral resection. NBI is an optical image endoscopy technique designed to enhance the contrast between mucosal surfaces and microvascular structures without the use of dyes. The aim of this study was to compare the predictive power of the white light (WL) versus NBI TURBT detection rate, in the diagnosis of non-muscle invasive bladder cancer. *Materials and methods:* From June 2010 to December 2011, 513 consecutive patients, 342 male and 171 female, affected by non-muscle invasive, primitive or recurrence bladder tumours, underwent WL and NBI bipolar TURBT. All patients provided written informed consent prior the study. The study was conducted in accordance with good clinical practice and the Declaration of Helsinki, including the most recent amendments (Edinburgh, 2000). Results as shown in Tables I and II.

Table I.

Patients characteristics (%)	Positive WL TURBT (%)	Positive NBI TURBT (%)	Lesions positive only NBI TURBT (%)
Primitive lesions	156 (50.6%)	127 (41.2%)	43 (13.9%)
Recurrence lesions	176 (85.8%)	91 (44.3%)	29 (14.1%)
Unifoc lesions	205 (69.2%)	91 (30.7%)	32 (10.8%)
Multif lesions	82 (37.7%)	135 (62.2%)	40 (18.4%)
<3 CM	242 (75.8%)	77 (24.1%)	46 (14.4%)
>3 CM	127 (65.4%)	67 (34.5%)	26 (13.4%)

TableII.

Neoplasms (pts)	WL cystoscopy (%)	Increased detection rate before NBI cystoscopy (%)	Detection rate before WL TURBT (%)	Increased detection before TURBT NBI (%)
PUMNPL	67 (13.06%)	40 (7.7%)	75 (14.6%)	34 (6.6%)
Ta	204 (39.7%)	132 (25.7%)	204 (39.7%)	108 (21.05%)
T1	71 (13.8%)	67 (13.06 %)	85 (16.5%)	67 (13.06%)
CIS	7 (1.36%)	9 ((1.75%)	7 (1.36%)	9 (1.75%)
PUMNPL primitive	27 (5.26%)	23 (4.48%)	32 (6.23%)	16 (3.1%)
Ta primitive	138 (26.9%)	78 (15.2%)	132 (25.7%)	49 (9.55%)
T1 primitive	46 (8.9%)	37 (7.21%)	57 (11.1%)	40 (7.79%)
Cis primitive	7 (1.36%)	6 (1.16%)	7 (1.36%)	6 (1.16%)
PUMNPL reccurence	20 (3.89%)	8 (1.55%)	21 (4.09%)	9 (1.75%)
Ta reccurence	66 (12.8%)	54 (10.52%)	72 (14.93%)	43 (8.38%)
T1 reccurence	25 (4.87%)	30 (5.84%)	28 (5.45%)	27 (5.26%)
Cis	0 (0%)	3 (0.58%)	0 (0%)	3 (0.58%)

Conclusions: Combination of NBI cystoscopy and NBI TURBt seems to provide a better diagnostic and therapeutic approach to bladder tumours, especially in Ta and T1 lesions. The detection rate after NBI TURBT versus WL TURBT improved significantly (42.5%, $p<0.01$). NBI TURBT improved overall detection rate in multifocals and over 3 cm lesions (by 62.2% and 34.5%, respectively) than unifocals and less 3 cm lesions (by 30.7% and 24.1%, respectively). For multifocals and less than 3 cm lesions the ability to detect tumors which are not visible in the white light TURBT was increased with the use of NBI by 18.4% and 14.4% compared to unifocals and over 3 cm lesions [10.8% and 13.4% ($p<0.01$)] respectively. Despite the overall high rate of NBI, false positive were 99 pts. (19.2% before NBI cystoscopy and 93 pts (18.3%) before NBI TURBT).

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NARROW BAND IMAGING (NBI) CYSTOSCOPY: DOES IT IMPROVE DETECTION RATE? PRELIMINARY EXPERIENCE IN A SINGLE CENTRE

Roberto Giulianelli, Barbara Cristina Gentile, Giorgio Vincenti, Stefano Nardoni*, Luca Mavilla, Luca Albanesi, Francesco Attisani, Gabriella Mirabile, Francesco Pisanti, Davide Granata, Manlio Schettini

Division of Urology, Nuova Villa Claudia, Rome, Italy

Introduction: The standard method used to diagnose bladder neoplasms and monitor patients for recurrence is white-light (WL) cystoscopy. Undetected tumours may appear later as a recurrence, and some of them may become invasive, highlighting the need for developing better endoscopic methods to detect recurrent bladder tumours. NBI is an optical image endoscopy technique designed to enhance the contrast between mucosal surfaces and microvascular structures without the use of dyes. The aim of this study was to compare the predictive power of white light (WL) cystoscopy versus NBI cystoscopy for the diagnosis of non-muscle invasive bladder cancer. *Materials and methods:* From June 2010 to December 2011, 513 consecutive patients, 342 male and 171 female (Table I), affected by non-muscle invasive bladder tumours, underwent WL plus NBI cystoscopy . All patients provided written informed consent prior the study. Inclusion criteria were primitive bladder neoplasms (positive to ultrasounds or urinary cytology) and/or recurrent non-muscle invasive bladder neoplasms in follow-up. Exclusion criterion was gross hematuria at the time of cystoscopy. *Results* are shown in Table II. The use of NBI cystoscopy improved detection rate in more than 45% of the patients (231 patients with primitive and recurrent lesions visible with NBI). In 20.4% (105 pts) the lesions were visible only by the use of NBI cystoscopy. NBI cystoscopy increased the ability to detect multifocal and >3cm lesions not visible by WL in 29.4% and 34.3% respectively. *Conclusion:* The use of NBI cystoscopy increased the overall detection rate in 45.02% ($p<0.01$), the overall focality detection rate in 47.17% ($p<0.01$) and the overall dimension detection rate in 44.9% ($p<0.01$) of the patients.

Table I. *Patient's characteristics*.

Sex (M/F)	333/180
Age (mean, yrs)	66.4
Smockers/Non-Smockers	342/171
Primitive lesions	310
Recurrent lesions	203
Unifocal lesions	296
Multifocal lesions	217
<3 cm	318
>3 cm	195

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EN BLOC TURB WITH PLASMAKINETIC BUTTON TURIS: IS IT A BETTER TREATMENT OPTION?

Roberto Giulianelli, Barbara Cristina Gentile, Luca Mavilla, Luca Albanesi, Francesco Attisani, Gabriella Mirabile, Francesco Pisanti, Davide Granata, Giorgio Vincenti, Manlio Schettini

Division of Urology, Nuova Villa Claudia, Rome, Italy

Introduction: The aim of the transurethral resection of bladder tumor (TURBT) is to completely remove the tumor and to determine its stage by identifing detrusor muscle invasion. Conventional endoscopic resection removes tumors in piecemeal and the adequacy of TURBT is often identified later only by the subsequent histopatological examination. Presence of detrusor is a surrogate for the completeness of resection but the absence of detrusor muscle in TURBT specimen in up to 50% of the cases has been reported. Restaging TURBT has shown presence of residual disease in up to 76% of cases. The aim of this study was to evaluate

Table II.

Neoplasms	Overall visible lesions with WL cystoscopy (%)	Overall visible lesions with NBI cystoscopy (%)	Visible lesions with WL and NBI cystoscopy (%)	Visible lesions only WL cystoscopy (%)	Visible lesions only NBI cystoscopy (%)
Primitive lesions (%)	189 (60.9%)	135 (43.5%)	257 (83.4%)	8 (2.58%)	43 (13.8%)
Reccurence lesions (%)	111 (54.6%)	96 (47.2%)	138 (67.3%)	5 (2.46%)	62 (30.5%)
Unifocal lesions (%)	197 (66,5%)	99 (33.4%)	249 (84.1%)	6 (2.02%)	41 (13.8%)
Multifocal lesions (%)	74 (34.1%)	143 (65.8%)	146 (67.2%)	7 (3.2%)	64 (29.4%)
<3 CM (%)	203 (63.8%)	101 (19.6%)	275 (86.4%)	5 (1.5%)	38 (11.9%)
>3 CM (%)	97 (49.7%)	130 (66.6%)	120 (61.5%)	8 (4.1%)	67 (34.3%)

the adequacy of en bloc TURB specimen by the presence of the detrusor muscle. We performed en-bloc TURBT using the Plasmakinetic Button Turis Gyrus system. *Materials and Methods:* From June 2010 to December 2011, 513 consecutive patients, 342 male and 171 female, affected by non-muscle invasive bladder tumours, underwent white light (WL) plus NBI bipolar TURBT. In 26 pts we performed en bloc NBI bipolar TURBT. All patients provided written informed consent prior to the study. All procedures began by performing a white light cystoscopy, and after this, the use of NBI confirmed what had been seen and revealed eventual more suspicious areas. All endoscopic resections were performed with a button loop and Olympus Gyrus bipolar generator (Olympus, Tokyo, Japan), in saline, with 30 degrees optic. Resection of each lesion was carried out with white light, whilst the resection of surgical margins and bed of resection were performed using only NBI light.

Primitive T Neoplasms (pts)	Unifocal	Multifocal	<3 cm	>3 cm
PUNMPL (pts)	39	10	49	0
Ta LG (pts)	67	35	59	43
TaHG (pts)	17	40	15	42
T1LG (pts)	12	3	10	5
T1HG (pts)	21	51	16	56
CIS	6	7	11	2
Recurrences T neoplasms (pts)				
PUNMPL (PTS)	24	6	30	0
TaLG	53	29	61	21
TaHG	18	15	22	11
T1LG	9	6	11	4
T1HG	27	13	31	9
cis	2	1	3	0

Results: Of 26 patients in the en-bloc group, 25 (96.1%) had detrusor muscle in their initial specimen. In the en-bloc group, the procedure could be completed without any bladder perforation as observation was much better due to better hemostasis. Median catheterization time was 30 hours (24-36), mean hospital stay was 42 hours (36-48), mean bleeding loss was 0.9 gr/dl (0.3-1.5) and no death occured during peri-or post-operative follow-up. Early adverse events were dysuria (52.1%), urgency (15.3%), haematuria (11.5%) and AUR with re-catheterization (3.8%). No second look hemostatic endoscopy was performed. *Conclusion*: An ideal TURBT would mean complete resection of the visible tumor, resection of the surrounding healthy looking mucosa for up to 1 cm and then removal of the detrusor muscle. Inadequate TURBT, is not only judged by the absence of muscle in the specimen, but also by the rate of recurrence at the same site. It is common knowledge that recurrence is seen in 50-80% of non-muscle-invasive bladder cancer mostly during the first year.

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SUNITINIB IN METASTATIC RENAL CELL CARCINOMA: RESULTS OF A MONOCENTRIC EXPERIENCE

Elisa Zanardi[1], Marco Maruzzo[1], Umberto Basso[1], Fable Zustovich[1], Pasquale Fiduccia[1], Antonella Brunello[1], Anna Roma[1], Patrizia Farina[1], Elisabetta Bezzon[2], Alberto Banzato[3], Filiberto Zattoni[4], Vittorina Zagonel[1]

[1]Oncologia Medica 1, Istituto Oncologico Veneto IOV, IRCCS, Padova;
[2]Radiodiagnostica Oncologica, Istituto Oncologico Veneto IOV - IRCCS, Padova;
[3]Cardiologia, Istituto Oncologico Veneto IOV, IRCCS, Padova;
[4]Urologia, Università degli Studi di Padova, Padova, Italy

Background: Sunitinib is a multi-target tyrosine-kinase inhibitor largely used for the treatment of metastatic renal cell carcinoma (mRCC) in first or subsequent lines therapy. *Patients and Methods:* From March 2006 to September 2012, we retrospectively reviewed clinical data of patients with mRCC treated with sunitinib at our Institution. *Results:* We evaluated 106 patients, median age 63 years (range 27-89), 70% males, with clear cell histology (89%), and with prior nephrectomy (87%). Sunitinib was used either as first (70%) or second or further line of treatment after cytokines or targeted therapies. The median number of cycles received was 8 (1-49). In the first line treatment median PFS and OS were 15.0 months (95% CI=9.8-20) and 35 months, respectively. In the second or further line PFS and OS were 15 months (11.7-18.2) and 25 months, respectively. The prognostic relevance of Motzer risk score was maintained in all the lines of treatment. Patients who received at least 4 cycles at standard dose (50 mg/d 4 wks on/2wks off) had a significantly better PFS and OS compared to patients who did not (PFS 23.0 *vs*. 12.0 months p=0.012, OS 49.0 *vs*. 16.0 months p=0.006). Among the patients treated in first line, the 18.9% had a disease progression within three months from starting sunitinib (primary refractory), while 25.7% were treated for more than 24 months (long term responders). Grade 3 or 4 toxicities were found in 35% of the patients but only 6.6% (7 patients) discontinued treatment because of unacceptable toxicities. *Conclusion:* Sunitinib is an active and feasible drug in a large population of mRCC patients. In our group of patients we observed PFS, and OS results apparently superior compared to pivotal trials (1, 2). These results can be explained by patients selection, better management of drug toxicities, less strict criteria for radiological progression, and availability of further sequential treatments. Patients receiving at least four full dose cycles achieved statistically significant better outcomes.

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MULTIPARAMETRIC CAD SYSTEM FOR MR PROSTATE CANCER DETECTION

Valentina Giannini[1], Simone Mazzetti[2], Anna Vignati[1], Christian Bracco[2], Michele Stasi[2], Filippo Russo[1], Enrico Bollito[3], Daniele Regge[1]

[1]Department of Radiology,
[2]Dept. of Medical Physics , IRC@C: Institute for Cancer Research at Candiolo, Candiolo;
[3]Dept. of Pathology, University of Turin at San Luigi Gonzaga Hospital, Regione Gonzole 10, Orbassano, Italy

Introduction/Background/Aim: Prostate specific antigen (PSA)-based screening reduces the rate of death from prostate cancer (PCa) by 31%, but this benefit is associated with a high risk of overdiagnosis and overtreatment. As prostate transrectal ultrasound-guided biopsy, the standard procedure for prostate histological sampling, has a sensitivity of 77% with a considerable false-negative rate, more accurate methods need to be found to detect or rule out significant disease. Prostate magnetic resonance (MR) imaging has the potential to improve the specificity of PSA-based screening scenarios as a non-invasive detection tool, in particular exploiting the combination of anatomical and functional information in a multiparametric framework. The study present aims at increasing the objectivity and reproducibility of prostate MRI interpretation by developing an automated interpretation approach for ultimate use in computer-aided diagnosis (CAD), which combines T2-w, Dynamic Contrast-Enhanced (DCE) and Diffusion-Weighted (DW) parameters, in order to calculate a pixel-wise malignancy probability map. This method can be of benefit to improve the diagnostic accuracy of the radiologists, reduce reader variability and speed up the reading time, automatically highlighting probably cancer suspicious regions. *Patients and Methods:* The dataset used in this study comprised 10 patients of the IRC C (Cardiolo, Italy) (mean age: 64 years) with 11 lesions (mean volume: 0.79±0.43 cc). Inclusion criteria were positive biopsy and a PSA level greater than 4 ng/ml. *MRI protocols and reference standard*. Axial T2-w, DW, and DCE sequences were performed at 1.5T MR using an endorectal coil with integrated pelvic phased multi-coil array (Signa LX, GE Healthcare, Milwaukee, WI). Within 3 months, all patients underwent radical prostatectomy. Foci of cancer were contoured by the pathologist and histological samples digitalized. An experienced radiologist compared the acquired sequences with histopathologic sections and outlined a ROI on the T2-w images in correspondence with each foci of cancer. Non-tumoural prostate regions of the peripheral gland were also selected for each patient to sample benign tissue behaviour on multi-parametric MR imaging. *CAD pipeline*. MRI data were processed with software packages in-house developed using Matlab® or C++ algorithms. First, automatic image registration was performed to correct for misalignment between images coming from different MR sequences. Registration should correct for voluntary and involuntary movements during the DCE, as well as for image distortion due to the magnetic susceptibility in the DW images. Having all the datasets registered, each pixel could be represented like a vector containing scalar values, such as T2-w image intensity, quantitative physiological parameters (*i.e.* K_{ep}, K_{trans}) obtained from DCE-MRI datasets, and values of apparent diffusion coefficient maps obtained from DWI images. Next, all these parameters were fed into a linear SVM classifier in order to provide a classification that maximizes the detection of true positives while at the same time minimizing the false positive benign area. A parametric color-coded map of the prostate gland was then created; colors were assigned based on the probability of presence of cancer in each pixel. *Results:* The mean area under the ROC curve for the SVM classifier was 0.93±0.09, sensitivity 87.2% and specificity 89.2% at the best cut-off point. Figure 1 shows an example of the output probability map for one suspected lesion.

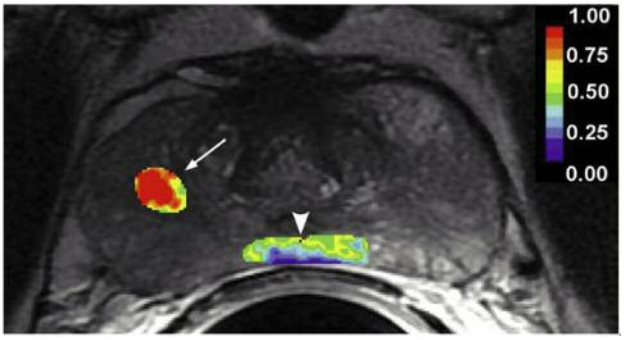

Figure 1. *Malignancy likelihood map of a malignant (plain arrow) and a normal (arrowhead) region. Red colour means a probability p≥0.8, green and blue p<0.5*

Discussion and Conclusion: The promising results, obtained from a dataset of 10 patients, should be validated on a larger cohort of subjects, but they suggest that the discrimination on a voxel basis between benign and malignant tissues is feasible with good performances. This method can be of benefit to improve the diagnostic accuracy of the radiologist, reduce reader variability and speed up the reading time, automatically highlighting probably cancer suspicious regions.

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A DIALYZED, ELDERLY PATIENT WITH POOR PERFORMANCE STATUS TREATED WITH SUNITINIB FOR METASTATIC CLEAR CELL CARCINOMA

Donatello Gasparro[1], Sara Tarasconi[2]

[1]Medical Oncology Unit, University Hospital; Parma,
[2]Emergency Department, University Hospital, Parma, Italy

Introduction: Patients with metastatic renal cell carcinoma often present impaired renal function as a consequence of surgical treatment. Sometime the impairment of renal function is so severe to require haemodialysis, and in this case the patients are often considered unfit for cytoreductive treatment. In the last few years the advent of some targeted agents has permitted to manage this cohort of patients with efficacious and well tolerated treatment. The efficacy and toxicity profile of the treatment are similar to those in the general population of patients with metastatic renal cell carcinoma (mRCC). We present a case report of an elderly patient with end-stage chronic renal failure requiring dialysis and poor performance status. *Methods:* In May 2008, a 76 year old man was referred to our institution. In 1998 he underwent right nephrectomy for renal cell carcinoma, with subsequent onset of end stage chronic renal failure requiring haemodialysis. He was subjected to follow up until November 2007 when he underwent radical cystectomy and prostatectomy for Papillary Urothelial cancer of the bladder (PT2a-Nx-Mx). A staging computed tomography scan (TC) showed multiple retroperitoneal abdominal nodules (in infrahepatic space and infiltrating the psoas muscle) so he was referred to our institution. We decided to perform an US-guided biopsy, obtaining histological diagnosis of renal clear cell carcinoma metastases. In consideration of performance status (PS 2), advanced age and dialytic treatment we were undecided between starting specific treatment or only best supportive care. The long disease-free interval after nephrectomy and the presence of severe back pain induced us to start a treatment with Sunitinib, despite the lack of data from literature about feasibility of this therapy in dialyzed patients. In consideration of advanced age and performance status (PS 2) we decided for a 25% dose reduction. In July 2008 the patient began the treatment with Sunitinib 37.5 mg daily for 4 weeks followed by a 2 weeks break. From the third cycle, we further reduced the dose to 25 mg daily (for 4 weeks followed by a 2 weeks break) because of the onset of grade III asthenia. The patient continued the treatment with the same schedule until December 2011 for a total of 27 cycles. In December 2011, despite stable disease, the patient asked for discontinuation of the therapy. *Results:* After two cycles, a restaging CT scan revealed a partial response, with a significant reduction in size of the nodules. The subsequent ultrasound and radiological (CTscan) evaluations showed the disappearance of some nodules and further dimensional reduction of others. After the discontinuation of the treatment we observed a slow, progressive increase of the dimension of the metastases. Back pain disappeared after the first cycle and to date is still absent. The most severe adverse effect was grade III asthenia (due to the dialytic treatment performed three times a week). *Discussion:* Our case demonstrates, in agreement with other literature reports, that treatment with Sunitib is feasible in patients with chronic renal failure requiring haemodialysis. Poor performance status and advanced age must not be considered exclusion criteria for cytoreductive treatment, especially in metastatic renal cell cancer carcinoma with a long disease –free interval after primary treatment.

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LONG TERM SAFETY OF FIRST LINE SUNITINIB THERAPY IN PATIENTS WITH ADVANCED RENAL CELL CANCER

Vittorio Ferrari[1], Daniela Nonnis[1], Francesca Consoli[1], Francesca Valcamonico[1], Giuseppina Arcangeli[1], Laura Ferrari[1], Anna Scalvini[1], Alfredo Berruti[2],

1Oncologia Medica, Spedali Civili di Brescia, Università degli Studi di Brescia;
[2]Dipartimento di Specialità Medico-Chirurgiche, Scienze Radiologiche e Sanità Pubblica, Azienda Ospedaliera Spedali Civili, Brescia, Italy

Background: Vascular-endothelial growth factor (VEGF) pathway plays a significant role in the pathogenesis of renal cell carcinoma (RCC). The development of target agents blocking this molecular mechanism has consistently modified the prognosis of RCC patients, with a significant number of long-term survivors. Sunitinib has an established role in the first line therapy of advanced RCC. While the acute and intermediate toxicities of the drug are largely known, the long term safety is poorly defined. The aim of

this study was to describe the tolerability of the drug when administered continuously for a very long time period. *Methods:* A mono-institutional retrospective study including 85 consecutive patients with renal cell carcinoma (RCC) was conducted at The Department of Medical Oncology at Spedali Civili of Brescia from 2006 to 2012. All these patients were treated with sunitinib as first line therapy until progression. The end-point was the evaluation of long term side effects beyond 18 months of treatment. Results: We identified at least 13 patients who were treated as first line therapy with sunitinib for more than 18 months. The median duration of this treatment was 29 months (range: 22-62 months). Overall survival was 52 months (range: 22-89 months). For the 18th month onwards no dose reduction was necessary. The main side effect was persistent asthenia G1-2 (NCI-CTCAE *vs*. 4.0) in all patients. These patients experienced similar grade gastrointestinal (diarrhea, taste changes) toxicity, hand-foot syndrome and hair discoloration before and after the cut-off date of 18 months. However, some of the side effects experienced in the first months such as skin discoloration and mucositis improved spontaneously with the prosecution of the treatment. Hypertension and hypothyroidism were controlled by the adequate medical treatment during the entire period of observation. No pts discontinued the treatment due to toxicity. Conclusion: These preliminary results suggest that long-term use of sunitinib is feasible and some of the side effects experienced in the first period may disappear with the prolonged use. Given the many emerging treatment options for advanced RCC, the safety in long-term survivors warrants greater attention.

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LONG TERM RESPONSE WITH SUNITINIB FOR METASTATIC RENAL CELL CARCINOMA REFRACTORY TO BEVACIZUMAB

Franco Morelli, Lucia Lombardi, Annamaria Capotorto, Evaristo Maiello

Department Haematology-Oncology IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy

Background: Multitargeted tyrosine kinase inhibitors (TKIs) have significantly extended the overall survival (OS) and progression free survival (PFS) of patients with metastatic renal cell carcinoma (mRCC). The sequential use of TKIs has been an effective strategy to prolong PFS. This strategy is supported by the results of several retrospective studies, all indicating that there is limited or no cross resistance among the TKIs. *Patients and Methods:* A 58 year old man with mRCC developed progressive bone metastases after 12 weeks of treatment with the VEGF-binding agent bevacizumab in combination with IFN-a. *Results:* The patient had stable disease after 12 weeks (two cycles) of sunitinib at the dose of 50 mg/day on a 4 week-on/2 week off schedule. He has continued therapy for more than 30 months and with the exception of mild fatigue and nausea, the treatment has been well tolerated. One year after beginning sunitinib, the patient developed hypertension (G2) requiring a dose reduction to 37.5/day with the same schedule. Re-escalation to the standard dose occurred within 10 weeks when hypertension was controlled with medical management. *Discussion and Conclusion:* This case illustrates the potential for patients with mRCC to derive long term benefit from sunitinib when used after bevacizumab. The patient's extented follow up period highlights the tolerability of sunitinib and the durability or response at the dose of 50 mg/day.

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IMPACT OF TREATMENT WITH TYROSINE KINASE INHIBITORS ON BRAIN METASTASES FROM RENAL CELL CARCINOMA

M Bassanelli, A Felici, S Giacinti, A Baldoni, AM Aschelter, P Marchetti

Department of Oncology, Faculty of Medicine and Psychology, Sapienza University, Sant'Andrea Hospital, Via di Grottarossa 1035-1039, 00189, Rome, Italy

Background: Brain metastases (BM) occur in 2% to 17% of patients with Renal Cell Carcinoma (RCC). Transport of Tyrosine Kinase Inhibitors (TKIs) across the blood-brain barrier is limited and radiotherapy (whole-brain or stereotactic radiosurgery) is the treatment of choice to achieve a local brain control. *Case Report:* We report the case of a 83 years-old man, who underwent in 1993 a radical right nephrectomy for RCC (stage III according to AJCC). Follow-up was negative until 2007, when a CT scan revealed a lung nodule in the middle lobe. Considering the long disease free survival and the single metastatic site, the patient underwent a right lung wedge resection. The histology confirmed a metastasis from renal clear cell carcinoma. After surgery, the patient began a follow-up programme. In December 2008 a spiral CT showed progressive disease in mediastinal and hilar nodes and a physical examination revealed a single skin lesion on the left forearm that was surgically removed resulting as metastatic site of RCC. Patient's performance status was good and he was classified in favourable risk group according to the MSKCC and Heng's score criteria. In February 2009 he started Sunitinib

50 mg daily (4 weeks on and 2 weeks off). A CT scan performed after three months of treatment showed a stable disease (SD), while a partial response (PR) in all node sites was achieved after 8 cycles. A right frontal BM of 17 mm was highlighted on a MRI brain scan performed on July 2010. Due to the PR on mediastinal and hilar lymph nodes, despite the brain progression, we decided to treat BM with stereotactic radiotherapy (18 Gy, 1 fr), and to continue Sunitinib at the same dose-schedule. Patient remain stable for 8 cycles more. A total of 16 cycles was administrated and the main toxicities experienced were: hyperglycemia, hypertriglyceridemia, stomatitis, asthenia and diarrhea of grade 2 and nausea, hand-foot syndrome, thrombocytopenia and hypertension of grade 1. In November 2011 a CT scan showed new lung metastases and a second line therapy, with Everolimus at 10 mg daily, was started. A SD was achieved and maintained until October 2012 when lung progressive disease appeared. Considering the good performance status, the prior therapies and the prolonged disease control with the previous TKI treatment we decided for a third line therapy with Axitinib (5 mg twice daily). At the first CT evaluation lung and nodal metastases were stable and this therapy is currently ongoing. *Conclusion:* The clinical outcome of our patient was not influenced by brain metastases and a multimodal approach appeared to be the best way to prolong his progression-free survival. Some retrospective series confirmed that the outcome of RCC patients was influenced by extracerebral metastases rather than the diagnosis of BM, but largest studies are needed to clarify the best clinical strategy in this setting.

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FATIGUE IN METASTATIC RENAL CELL CARCINOMA (mRCC): CLINICIAN-REPORTED *VS.* PATIENT-REPORTED OUTCOME

Mimma Rizzo, Giacomo Cartenì

UOSC di Oncologia, Azienda Ospedaliera di Rilievo Nazionale "A. Cardarelli", Napoli, Italy

Introduction: Fatigue is a feeling and a state of tiredness that exceeds the norm and is experienced as clearly unpleasant. The assessment of fatigue may be useful to monitor the effectiveness of interventions. Therefore, fatigue was recently reported (1) as the main single reason for a patient to prefer Pazopanib over Sunitinib in mRCC. Fatigue may be reported as a CTC-AE (mild/moderate/severe/life-threatening) item as well as a score obtained from a Quality of Life (QoL) questionnaire (*i.e.* FACT-Fatigue). The aim of this analysis was to verify if clinician-reported and patient-reported levels of fatigue are suitable to conduct to the same therapeutic decisions. *Methods:* CTC-AE Fatigue rates were reported from the Pazopanib *vs*. Best Supportive Care (BSC) (2), and from Pazopanib *vs*. Sunitinib (PISCES (1) and COMPARZ [3]) studies; relative and absolute effects were calculated using the RevMan5 and GRADE-PRO software. FACT-Fatigue scores were reported when available. *Results:* The administration of Pazopanib increased by more than 2 times (as compared to BSC) the risk of fatigue (RR: 2.23; 95% CL: 1.26 to 3.93), with an absolute effect of 119 more fatigue episodes every 1000 patients treated (95% CL: 26 more to 283 more). When Pazopanib and Sunitinib were compared in a randomized basis, the absolute estimate of the effect was limited to 67 fewer fatigue episodes in favour of Pazopanib every 1000 patients treated (pooled analysis of PISCES and COMPARZ studies; Table I).

Table I. *Fatigue in Pazopanib Vs Sunitinib studies.*

Fatigue events by treatment	Relative effect Relative Risk (95% CL)	Absolute effect Fatigue episodes/ 1000 patients (95% CL)
Pazopanib: 348/707 Sunitinib: 389/696	0.8807 (0.7970 to 0.9731)	67 fewer (15 fewer to 113 fewer)

The differences between treatments in terms of FACT-Fatigue mean change from baseline were 2.49 (PISCES) and 2.32 (COMPARZ) in favour of Pazopanib, both scores being below the M.I.D (Minimal Important Difference that patients perceived as important in either benefit or harm, and that would lead clinicians to consider a change in patients therapy). *Conclusion:* It is in clinicians duty to decide if the increase in CTC-AE fatigue rates and FACT-Fatigue scores is clinically relevant when determining the benefit-to-harm ratio of a candidate treatment. Anyway, the patient-preference outcome (of the PISCES study) seems not mirroring the evidence previously presented; possibly, the lack of validation of this questionnaire may have played a role.

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LONG TERM STABLE DISEASE IN A POOR-RISK RENAL CELL CARCINOMA (RCC)

M. Pagano, N.M. Asensio Sierra, C. Boni

Oncology Unit, Azienda Ospedaliera S.Maria Nuova - IRCCS Reggio Emilia, Italy

Introduction: Treatment options have increased considerably for patients with advanced RCC with introduction of vascular endothelial growth factor (VEGF) and mammalian target of rapamycin/mammalian target of rapamycin-containing complex 1 (mTOR/TORC1) inhibitors (1-4). Temsirolimus is an inhibitor of mammalian target of rapamycin kinase, a component of the intracellular signaling pathways involved in the growth and proliferation of cells. The initial choice of therapy for individual patients is based on clinical risk determined by validated prognostic models and on evidence of benefit derived from clinical trials within risk categories (5, 6). These prognostic factors are well established: high serum lactate dehydrogenase >1.5 ULN, low hemoglobin, high corrected serum calcium >10 mg/dL, time from diagnosis to treatment <1 year and Karnofsky Performance Status ≤60-70. Patients with 3 or more risk factors are defined as poor risk and represent about 20% of patients with advanced RCC. The median survival time in this group is approximately of 5 months. Despite the number of molecules now available in the clinical practice in the subgroup of patients with poor prognosis renal cancer, temsirolimus therapy seems to be the one offering greater advantage in terms of overall survival (OS) (7). We present a case of a patient long-term responsive to treatment with temsirolimus. *Case Report:* On December 2011, a 49 year-old female patient underwent left radical nephrectomy for clear cell renal carcinoma G3 according to Furmhan, pT2Nx M1 (bilateral lung and brain). At physical examination a right breast nodule (2.5 cm) was found and a biopsy showed an infiltrating breast ductal carcinoma: (IDC) G3, ER 100%, PgR 50%, TTF1 negative, Ki 67 10%, HER2 negative, cT2cN0. To clarify the nature of the lung metastasis a biopsy was performed, confirming a renal origin. The laboratory analysis showed iron deficiency anemia (Hb 8.4 gr/dl), IgG monoclonal gammopathy, LDH values 294 U/L, and Calcium 8.2 mg/dL. In January 2012, the patient was treated with brain radiotherapy (20 Gy in 4 fractions). At the end of radiotherapy the patient showed Grade 3 asthenia. After evaluation of prognostic factors (anemia, Karnofsky 70, time from diagnosis to treatment inferior to one year) on February 2012, treatment with weekly temsirolimus at a total dose of 25 mg was started. For breast cancer treatment, the surgical option was not considered due to the poor performance and advanced RCC, and therapy was continued with an aromatase inhibitor. *Results:* Response to treatment was evaluated with total body CT scans every 3 months. After 48 weeks of temsirolimus a stable disease was observed until today. Changes in triglycerides and cholesterol values were observed (45 mg/dL *vs*. 160 mg/dL; 93 mg/dL *vs*. 246 mg/dL respectively) without requiring medical treatment. Blood glucose levels didn't changed. During treatment, LDH values showed an initial exponential growth, reaching values greater than 900 U/L after the first month of therapy. Then LDH values were stabilized gradually reaching constant values of 400 U/L. The Hb levels increased during the course of treatment achieving stable values of >11 gr/dL. Gradual improvement of clinical condition, with a significant rising of Karnosfky PS was observed. Treatment was in general well tolerated. *Discussion and Conclusion:* In the trial that compared Temsirolimus with Interferon alfa, treatment with Temsirolimus was associated with a moderate prolongation of overal survivall in patients with poor prognosis advanced RCC. The median OS was 10.9 months with temsirolimus *versus* 7.3 months in the group with interferon alfa; median progression-free survival times were 3.8 and 1.9 months respectively (7). Here we reported a case of a prolonged response to Temsirolimus with a relevant still lasting 13 months stable disease. Temsirolimus was well tolerated; the triglycerides and cholesterol increased values, may have been influenced by concomitant therapy with an aromatase inhibitor. Our result in this particular case made us wonder for how long we will have to continue Temsirolimus therapy in presence of disease stabilization, in the absence of data from literature.

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MAGNETIC RESONANCE AS AN EARLY INDICATOR OF CLINICAL OUTCOME IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

Riccardo Ricotta[1], Angelo Vanzulli[2], Sara di Bella[1], Maria Olga Giganti[1], Barbara Colnago[2], Lisa Pietrogiovanna[1], Antonella Verrioli[2], Dario di Trapani[3], Francesco Sozzi[3], Aldo Massimo Bocciardi[3], Salvatore Siena[1]

[1]Divisione Oncologia Falck,
[2]Divisione di Radiologia,
[3]Divisione di Urologia,
Ospedale Niguarda Ca' Granda, Milano, Italy

Background: Treatment with multitargeted tyrosine kinase inhibitors (TKIs), has significantly improved the clinical outcome of patients with metastatic renal cell carcinoma (mRCC). In the era of targeted therapies, a rapidly growing body of knowledge has generated criticisms regarding timing and parameters for cancer response assessment. An early identification of patients who are likely to benefit from treatment remains of paramount importance. Preliminary studies conducted by our group and others have shown that an early tumor shrinkage ≥10% represents a predictive imaging marker of clinical outcome to targeted drugs in mRCC and other solid tumors (1-3). The purpose of our study was to determine whether an early radiologic assessment by magnetic resonance imaging (MRI) after 2 weeks of therapy was able to select patients with mRCC who derived benefit from treatment with TKIs. *Patients and Methods:* Since October 2009, 19 patients with mRCC were treated with TKIs at Ospedale Niguarda Ca' Granda. Seventeen patients were treated with sunitinib (11 in first and 6 in second-line setting, respectively), 1 patient received pazopanib (first-line) and 1 patient sorafenib (third-line). According to Memorial Sloan-Kettering Cancer Center classification, 4 patients were low risk and 15 were intermediate risk. All patients were evaluated by unenhanced MRI at baseline and week 2 after the beginning of the treatment with TKIs and by contrast-enhanced computed tomography (CECT) within 8-12 weeks (first examination), then every 12-16 weeks according to clinical practice. We defined early response as a tumor shrinkage ≥10% at week-2 MRI, while response by CECT was defined according to Response Evaluation Criteria in Solid Tumour (RECIST 1.1). *Results:* Twelve patients (63.2%) presented some degree of tumor shrinkage by week-2 MRI, ranging from 3.2 to 32.5% (mean reduction (SD) of diameter of target lesions was 11.5% ± 10%). Early response was observed in 6/19 cases (31.6%) and 100% of these patients had a disease control rate (DCR) by first CECT, compared with 69% among early nonresponders (9/13). Median PFS was 114 weeks (95% CI, 0-239.7) *vs*. 27.1 weeks (95% CI, 23.4-30.8) for patients with [n=6 (31.6%)] or without [n=13 (68.4%)] early response, respectively (Log Rank p=0.065). The percentage of patients who were progression-free after 6 months from the beginning of the treatment was 100% (5/5 evaluable patients) *vs*. 50% (6/12 evaluable patients) for early responders *vs*. early nonresponders, respectively (p=0.1, Fisher exact test 2-tailed). The results in terms of OS are still pending. *Conclusion:* Our data indicate that the dimensional reduction of tumor burden is assessible by MRI after 2 weeks of therapy with TKIs. The present results suggest that detection of an early response may be associated with a prediction of clinical outcome, although this study has the limitation of the cohort-type design and of a small population evaluated. Therefore, the findings should be considered hypothesis, and prospective clinical studies aimed to comparison with standard radiologic criteria are needed.

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CARDIOVASCULAR RISK IN CASTRATION RESISTANT PROSTATE CANCER PATIENTS TREATED WITH ABIRATERONE ACETATE OR ENZALUTAMIDE. A META-ANALYSIS

Daniele Alesini, Roberto Iacovelli, Michela Palleschi, Alessia Pochesci, Daniela Modica, Ilaria Attili, Gabriele Piesco, Simone Scagnoli, Valentina Orlando, Enrico Cortesi

Dipartimento di Scienze Radiologiche, Oncologiche ed Anatomo-Patologiche, Day Hospital Oncologico B, Sapienza-Università di Roma, Italy

Background: New hormonal treatments (HT) have demonstrated significant activity thus providing new non-chemotherapeutic options for castration resistant prostate cancer patients. Although these agents seem to have favorable toxicities, they could enhance the well-known cardiovascular toxicity of previous anti-androgen therapies. We performed a meta-analysis to determine the risk of cardiovascular adverse events for CRPC pts treated with new anti-androgen therapies. *Materials and Methods:* MEDLINE/PubMed, conferences and clinicaltrials.gov databases were searched for articles reported from January 2006 to June 2012. Eligible studies were limited to phase III trials of US Food and Drug Administration—approved new hormonal treatment for CRCP (enzalutamide and abiraterone acetate) that reported on patients with cancer, randomized design and adequate information on cardiovascular adverse events. Data extraction was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Statistical analyses were conducted to calculate the summary incidence, relative risk (RR) and 95% Confidence Intervals (CIs) by using random-effects or fixed-effects models on the basis of the heterogeneity of included studies. *Results:* Three randomized controlled trials that enrolled a total of 3482 patients with CRPC met the eligibility criteria for inclusion in the final analysis. A total of 3466 patients were evaluable for safety analysis; among these 2133 received HT (1333 abiraterone acetate and 800 enzalutamide) and 1333 received placebo in the control arms. The incidence of all grade cardiac events was 9.1% (95%CI, 7.9-10.3) in the HT arm compared to 6.9% (95%CI, 5.5-8.3) in the control arm with a RR of 1.15 (95%CI, 0.91-1.46) (I^2=43%; Chi^2=3.52, p=0.17), the RR was higher for abiraterone (1.33; 95%CI, 1.00-1.76) (I^2=0%; Chi^2=0.15, p=0.7), compared to enzalutamide (0.81; 95%CI, 0.53-1.26) but the difference was not significant (p=0.07). The incidence of high grade cardiac events was 2.5% (95%CI, 1.8-3.2) in the HT arm compared to 1.4% (95%CI, 0.8-2.1) in the control arm with a RR (random effect) of 1.26 (95%CI, 0.42-3.79) (I^2=72%; Chi^2=7.21, p=0.03).The RR (fixed effect) was higher for abiraterone (2.21; 95%CI, 1.18-4.17; p=0.01) (I^2=0%; Chi^2=0.03, p=0.87), compared to enzalutamide (0.44; 95%CI, 0.16-1.19) and the difference was significant (p=0.007). *Conclusion:* Abiraterone acetate was found to be related to a small but significant higher incidence and risk of high grade cardiac events compared to the placebo and to enzalutamide.

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THE IMPACT OF FAT INFILTRATION AND RENAL VEIN THROMBOSIS ON CANCER-SPECIFIC SURVIVAL IN T3A KIDNEY TUMORS

A. Baccos, R. Schiavina, G.C. Rocca, M. Borghesi, C. Pultrone, F. Chessa, L. Della Mora, G. Saraceni, M. Cevenini, E. Brunocilla, A. Bertaccini, M. Garofalo, F. Manferrari, G. Martorana

University of Bologna, Dept. of Urology, Bologna, Italy

Introduction & Objectives: The role of fat infiltration and renal vein thrombosis in patients with renal cell carcinoma (RCC) is still controversial. Aim of this study was to evaluate the prognostic impact of these parameters in pT3a RCC patients and to identify possible new prognostic groups. *Patients and Methods:* We analyzed 122 consecutive pT3a patients who underwent radical nephrectomy for RCC between 2000 and 2011 at our Institution. Age, gender, multifocality, kind of presentation, pathological tumor size, margin status, histological subtype, Fuhrman grade, presence of node or systemic metastasis, tumor necrosis, sarcomatoid differentiation, peritumoral fat and/or hilar fat infiltration and renal vein thrombosis were evaluated. CSS rates were estimated using Kaplan Meier survival curves; univariable and multivariable analysis were performed with Cox analysis.

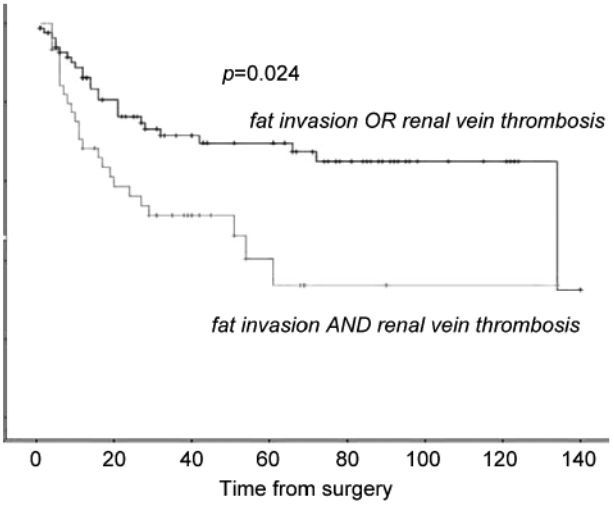

Figure 1.

Results: The mean follow-up was 41.7±35.4 mo, the mean age was 64.1±12.0 yrs, 98 (0.3%) were male, 8 (6.5%) had tumor multifocality, mean tumor size was 7.3±2.8 cm, 67 (54.9%) were incidental, 19 (15.6%) had node metastases, 17 (14%) had systemic metastases, 3 (2.5%) had positive surgical margins, 98 (80.3%) had clear cell RCC, 31 (25.4%) were G2, 67 (54.9%) were G3 and 24 (19.7%) were G4 RCC, 31 (5.4%) had tumor necrosis, 10 (8.2%) had sarcomatoid differentiation. Patients with peritumoral fat and/or hilar fat infiltration (n=63, 51.6%) and patients with renal vein thrombosis (n=18, 14.7%) experienced comparable CSS rates (p>0.05) while patients with both renal vein thrombosis plus fat infiltration (n=41, 33.6%) showed worse CSS than the first group (p=0.02). Finally patients were divided in new prognostic groups: group A, fat invasion or renal vein thrombosis (n=81, 66.3%) and group B, fat invasion and renal vein invasion (n=41, 33.7%) (Figure 1). At multivariate analysis, the new grouping as well as pathological tumor size, margin status, and Fuhrman Grade were independent prognostic predictors of CSS (all p<0.05). *Conclusion:* Patients with both fat invasion and renal vein thrombosis experience worse CSS rates when compared to those with only one factor. This new grouping could be considered in the prognostic classification of pT3a RCC patients.

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