7018 POSTER

NFkB Activity Modulates the Oncogenic Potential of Stat3 in Prostate Cancer Development

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Background: Prostate cancer is one of the most frequent tumours in the Western world. Approximately 27000 men die each year from prostate cancer in USA. The Jak/Stat pathway (Jak − Janus kinase, Stat − signal transducer and activators of transcription) is an important signaling cascade in prostate cancer. Stat3 seems to play an essential role in regulation of proliferation, apoptosis, angiogenesis and drug resistance in prostate cancer. The NF-kB pathway is a key player in inflammation. Deregulation of components of the NFκB cascade was observed in metastatic prostate cancer with activated Jak/Stat. Stat3 signaling was shown to cause growth inhibition and apoptosis of cancer cells. Although there has been evidence for an oncogenic function of Stat3, observations from several laboratories suggest the opposite. Under certain conditions activation of Stat3 leads to decreased growth of prostate cancer cells in vitro and can exert an inhibitory effect on prostate cancer xenografts.
Material and Methods: We conditionally deleted PTEN in prostate epithelial cells ($PTEN^{\Delta PEC}$) taking advantage of Cre-recombinase under a prostate-specific probasin (PB) promoter (ARR_2PB). To investigate the role of Stat3 in prostate cancer, we crossed $PTEN^{\Delta PEC}$ mice with Stat3 floxed mice (obtained from Valeria Poli) or with mice harbouring a constitutively activated Stat3 ($Stat3^C$). We analysed $PTEN^{\Delta PEC}$ $Stat3^C$ mice by immunohistochemistry and immunofluorescence. Quantification of protein expression in tissue sections were measured using HistoQuest™ and TissueQuest™ software. In addition, we quantified RNA and protein expression using qRT-PCR and Western Blot techniques.
Results: Loss of Stat3 in $PTEN^{\Delta PEC}$ resulted in accelerated tumour growth, massive inflammation and increased angiogenesis. In contrast, constitutive active Stat3 in $PTEN^{\Delta PEC}$ mice led to decreased tumour formation. The $PTEN^{\Delta PEC}$ $Stat3^{C/+}$ mice showed decreased inflammatory infiltrates (mast cells and T-cells) when compared to $PTEN^{\Delta PEC}$ mice. Western blot analysis of $PTEN^{\Delta PEC}$ $Stat3^{C/+}$ mice revealed significant downregulation of IKKα, IKKβ and p65 when compared to $PTEN^{\Delta PEC}$ mice.
Conclusions: Stat3 in prostate cancer cells interferes with tumour growth. Activation of NFκB in $PTEN^{\Delta PEC}$ mice promotes inflammation and interactions between stromal and tumour cells. In further experiments we will focus on the molecular link between Stat3 and NFκB in prostate cancer development.

7019 POSTER

Potential Value of HOXB13 as a Progression Marker for Recurrent Prostate Cancer

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Background: Many patients with prostate cancer have disease recurrence after surgical removal of tumours and fail to respond to androgen-ablation therapy. Even with the help of a number of clinical/pathological factors, it is not possible to predict which patients will fall into this category. The results of our previous studies demonstrated that the HOXB13 homeodomain protein plays an important role in the development of prostate cancer and the progression of this malignancy. In addition, HOXB13 has been reported to predict estrogen-resistant breast cancer tumours. The purpose of this study was to study whether HOXB13 could be a molecular marker used to predict prostate cancer recurrence.
Materials and Methods: To examine the role of HOXB13 as a molecular marker with clinical/pathological data, the expression of HOXB13 was compared using immunohistochemistry in 57 organ-confined prostate cancer tumours obtained by radical prostatectomy.
Results: There was no significant correlation between the expression of HOXB13 and most clinical/pathological parameters including the tumour margin, invasion, pathological stage, and risk level. The HOXB13 expression level correlated with the Gleason score and there was a positive tendency for it to correlate with the preoperative PSA level. Accordingly, the tumour specimen from four patients that ultimately had biochemical failure (PSA >0.2 ng/mL) all showed a high expression of HOXB13, while their risk levels were either intermediate or high.
Conclusions: This is the first report that HOXB13 may increase the predictability in recurrent prostate cancer when it combined with other clinical/pathological factors. However, more extensive study with larger patient pool is required to confirm the clinical value of HOXB13 as a prognostic marker for prostate cancer.

7020 POSTER

Survival After Biochemical Failure − the "Far Away" in Prostate Cancer

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Background: The biochemical relapse-free survival is the goal of the studies that analyze the effectiveness of local treatments for prostate cancer (CaP). However, patient's evolution after biochemical recurrence (BR) is a poor studied parameter. We analyze and compare the survival of patients initially treated with surgery or radiotherapy (RT) following diagnosis of RB.
Material and Methods: We report the experience of HGU Gregorio Marañón in follow up and treatment of patients with RB criteria, focusing in survival from recurrence, patterns of progression and efficacy of salvage therapies.
Results: 366 patients with RB treated with surgery (267) or RT (99) were considered eligible for analysis. Time to RB from initial diagnosis was higher in irradiated patients (51.5 vs 35.5 months). However, the median survival from RB to death or latest news was 62 months in the surgery group and 22 months in the RT cohort ($p = 0.00$). After a median follow up of 91 months, the 8 yr cause-specific survival was 93.5% in operated patients and 88% in those treated with RT ($p = 0.01$). 35 patients (9.5%) died of CaP.
In the surgical group, 162 patients (60.5%) received RT as salvage therapy. 13% of the operated and 27% of irradiated patients did not received treatment after RB. In patients treated with radical RT, only 17% had a local salvage treatment (cryotherapy or brachytherapy) and 56% received androgen deprivation ± chemotherapy. After RB, 41 operated patients (15%) and 21 after RT developed metastases, mainly in bone.
The poorest outcome was observed in patients who developed RB during adjuvant hormonotherapy after RT and in patients with persistent elevated PSA after prostatectomy. Patients undergoing salvage RT after RB obtained the best survival rates.
Conclusions:
– In prostate cancer patients, median survival after RB is fairly long (51 months) and higher in operated patients.
– After RB, 15−20% of patients develop metastases.
– Defining criteria for treatment of irradiated patients with RB will help us to optimize their management and improve survival rates.

7021 POSTER

Multidisciplinary Management of Castration Resistant Prostate Cancer (CRPC) in France − a Survey Comparing Practices and Assessing Collaboration Between Urologists and Oncologists

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Background: In France, multidisciplinary meeting to discuss individuals' cases is mandatory and helps collaboration between urologist and oncologist. The primary goal of this study was to analyze the putative differences in management of castration resistant prostate cancer (CRPC) among urologists and oncologists and to assess the quality of the collaboration.
Material and Methods: This nationwide study was performed from May to November 2010. A 24-items questionnaire was sent to the members of the French association of urologists (AFU) and to the oncologists involved in the management of CRPC patients. Answers from 450 urologists and 150 oncologists were expected. Information on the mode of clinical practice, local multidisciplinary meeting setting and management of CRPC was requested. The completed questionnaires were anonymously collected

either on a dedicated website or by mail. Descriptive statistics was used to summarize the data and describe responses.
Results: A total of respectively 458 and 158 questionnaires were collected from urologists and oncologists. A weekly multidisciplinary meeting is hold respectively by 33 and 46% of urologists and oncologists. Less than 3% of physicians meet less than once a month. CRPC is defined by the use of both PSA dosage and level of testosterone by respectively 66% and 78% of urologists and oncologists. In CRPC patients: bone scan plus CT scan is prescribed by 78% of oncologist and 48% of urologists; respectively 43% and 41% of urologists and oncologists primarily proposes hormonal manipulation and 12% and 21% an enrollment in a clinical trial. Only 24% of urologists and 48% of oncologists consider that the presence of metastasis is necessary to prescribe chemotherapy. Most of the oncologists would like to see the patient earlier on in the disease history, and 33% think that they see the patient too late. Among urologists, 72% believe to deliver correct information on chemotherapy to the patient, whereas 61% of oncologists consider that patients are not clearly informed about chemotherapy when referred from urology.
Conclusion: To our knowledge, this is the 1st study assessing cooperation between physician involved CRPC management. Multidisciplinary meeting is an effective tool to collaborate and to promote common treatment guidelines. Some work should be done to improve the communication to the patient and to smooth the patient referral from the urologist to the oncologist.

7022 POSTER

Intraoperative Rectal D2cc Monitoring Reduces Rectal Doses More Than Using V100 Alone in Real Time Dynamic LDR Prostate Brachytherpy

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Background: The 2007 ESTRO/EAU/EORTC guidelines in prostate brachytherapy recommend using the rectal D2cc (RD2cc) as the primary parameter for this organ at risk rather than rectal V100 (RV100). The real time technique allows intraoperative calculation of rectal D2cc and V100. This study examines the effect of switching from RV100 as the primary parameter to RD2cc with dynamic real time adjustments to optimise dose. Low RV100 volumes are easily achievable pre-implant and are always higher on post-implant dosimetry (PID).
Methods: Rectal dosimetry of 261 patients undergoing brachytherapy at the Royal Berkshire Hospital was examined. The initial 150 patients underwent the proceedure with intraoperative calculation of Prostate D90, Prostate V150, Rectal V100 and Urethral D10. Rectal D2cc was calculated retrospectively in this group. After the introduction of the 2007 recommendations, Rectal D2cc replaced Rectal V100 as the primary parameter. Both were calculated prospectively in a further 142 patients. Post-implant dosimetry was performed for all patients on CT scans at day 30.
Results: The recommendations state that RD2cc should be less than the prescription dose, which is 160 Gy in the real time technique at this centre.

	Number	Median Rectal Post-implant D2cc (Gy) (% of 160 Gy)	% implants with RD2cc at <160 Gy	Median Intropeative Rectal V100 cc	Median Post-implant Rectal V100 cc	Median Post-implant Prostate D90 Gy
Using rectal V100 as primary parameter	150	127.7 (79.8%)	88.0%	0.17	1.04	171.8
Using rectal D2cc as primary parameter	142	87.7 (54.8%)	97.7%	0.01	0.42	174.6
Significance level of differenc in medians (t-test)		<0.001		<0.001	<0.0001	0.055

These data show that significant reductions in rectal D2cc and V100 can be achieved by modifying intropeative dosimetry alerts. Adding in calculation of rectal D2cc and prostate V100 has allowed a 40 Gy reduction in median post-implant rectal D2cc and a decrease in rectal V100 by 59.6%. These reductions can be safely achieved without compromise to the prostate D90.
Conclusions: The use of RD2cc intraoperatively allows a significant reduction in rectal dose, over and above that achievable when using RV100 as the primary rectal parameter. Using RV100 as the primary parameter may give a false sense of security that the rectal volume irradiated is as low as is reasonably achievable.

7023 POSTER

On Board Imaging Shifts in Prostate Cancer Patients Treated Using External Beam Radiation Therapy

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Background: External beam radiotherapy (EBRT) in prostate cancer using intensity modulated techniques requires daily on-board image (OBI) guidance to correct eventual shifts in three dimensions. There are few data on what factors influence on the shifts values. Finding predictors of prostate's higher mobility would help in treating such patients.
The aim of the study was to assess the differences in shifts in cranio-caudal, lateral and antero-posterior dimensions in daily image-guided radiotherapy with intention-to-treat in prostate cancer patients and to determine if several planned organ volumes may impact the extent of the shift.
Materials and Methods: 51 patients were treated using EBRT with cone-beam computed tomography (CBCT) imaging due to prostate cancer from November 2010 to March 2011. The data were obtained from 39 patients planned to treat possibly on full bladder and empty rectum. The volume of bladder, rectum and clinical target volume (CTV) was measured for planning. Daily OBI was performed using CBCT and shifts in 3 dimensions were registered, the mean and maximum shifts on each dimension from each patient were calculated.
Results: The median of mean shifts was 0.33 cm on cranio-caudal dimension, 0,275 cm on lateral and 0.26 on antero-posterior. No maximum shifts greater than 2.4 cm were observed in the study group. No statistically significant correlations between CTV nor bladder and rectum volume on planning were noted (p- values for Spearman rank order correlations for maximum and mean lateral shifts greater than 0.22, >0.2 cm for cranio-caudal and >0.08 for antero-posterior). Higher incidences of maximum corrections were done on craniocaudal dimension (mean 0.88 cm 95%Confidence interval 0.66–1.11) in contrast with lateral dimension (mean 0.54 cm 95% CI 0.43–0.66) ($p = 0.01$). Antero-posterior shifts (mean 0.70 95% CI 0.54–0.86) did not differ from the cranio-caudal or lateral directions ($p = 0.36$ and 0.23 respectively).
Conclusions: The shifts on each 3 dimensions using CBCT are usually lower than 0.3 cm. There is no possibility to predict using the CTV, bladder or rectum volume on planning whether the patient would require greater corrective shifts in any dimension. Shifts in cranio-caudal dimension seem to require corrections more often than those in other dimensions.

7024 POSTER

Dose Escalated Radiotherapy for Prostate Cancer With Proton Boost

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Background: With the attractive physical features of proton beams and due to the increasing evidence for an advantage of hypofractionated treatment in prostate cancer (PC), a treatment schedule with a hypofractionated proton boost (PBT) combined with conformal external beam radiotherapy (EBRT) was introduced 2002 in our institution as an alternative to dose escalation with high dose-rate brachytherapy (HDR-BT). The outcome of 267 patients treated between 2002–2008 with regards to biochemical failure, overall survival and late side effects is evaluated.
Material and Methods: A cohort study of 64 low-risk, 98 intermediate, and 105 high-risk PC patients treated at the Department of Oncology, Uppsala Sweden. The schedule was 20 Gy in 4 fractions with PBT followed by 50 Gy in 2 Gy fractions delivered by EBRT. Assuming a value of α/β of 3 Gy and RBE of 1.1 the equivalent dose in 2 Gy fractions for the schedule is 87 Gy. A transperineal boost to the prostate with protons was administrated at the Svedberg Laboratory in Uppsala with a single, fixed, horizontal beam with 180 MeV energy. All EBRT were delivered with photon beams at energies $\geqslant$ 6 MV. For accurate positioning four gold markers were placed in the prostate. Of the high-risk patients 74%, whereas of the intermediate group 46% received hormonal deprivation during a median time of 7 and 5 months respectively. Median follow-up time is 48 months.
Results: Median age was 65 y (46−79 y) and median PSA 10 ng/ml (1.7–158 ng/ml) for the whole group. The median volume of the prostate measured by TRUS was 37cc (15–120 cc). No grade III or IV rectal toxicities were observed according to EORTC scoring criteria. Genitourinary problems at baseline of grade II and III were observed in 14% and 8% of patients respectively. Late toxicity is under evaluation. Totally 25/267 (9.4%) of the patients had biochemical relapse: none of the low-risk, 5/98 (5%) intermediate and 20/105 (19%) of high-risk patients. Only 3 patients (all high-risk) have died in PC and 243 (91%) of the patients are still alive.