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Expression and clinical relevance of the lung resistance protein in germ cell testicular tumours

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Background: LRP was first described in a non-P-glycoprotein-mediated multidrug resistance lung cancer cell line. A prognostic role of LRP was suggested in ovarian cancer, and diffuse large B-cell lyphomas, but not in breast cancer. LRP expression and its clinical relevance in germ cell tumours (GCTs) are unknown.

Material and methods: LRP mRNA was determined by RT-PCR. LRP protein was detected by immunohistochemistry (IH) and Western blotting methods (WB). Seventy primary testicular tumours were evaluated. Tumour response to treatment and patient's clinical parameters were recorded. Ficher's exact test was used for statistical evaluation.

Results: LRP immunostaining was detected in 29 (41%) out of 70 primary testicular cancers; in 6 (40%) of the 15 seminomatous and 23 (42%) of 55 nonseminomatous (NS) cases. In the NS group 8 pure teratomas, 2 embryonal carcinomas, and 13 teratoma components of mixed tumour showed LRP expression. Among the mixed type of tumours 3 seminomas, 4 embryonal carcinoma components were also positive against LRP antibody. Pure teratoma and teratoma component of mixed tumour expressed significantly higher LRP compared with other subtypes of tumour (p=0.02). 22 out of 34 tumour expressed LRP protein and mRNA examined by WB and RT-PCR. In 18 of 22 tumour expressing LRP protein and mRNA were also positive by IH. The sensitivity and specificity of IH compared to RT-PCR and WB was 82% and 100% respectively. No correlation between LRP immunostaining and clinical staging was demonstrated (p=0,22). Sixteen patients (8 pure teratomas, 5 mixed tumour 4 with teratoma components and 3 others) with advanced stage disease received primary chemotherapy. Six patients died (5 pure teratomas and 1 mixed tumour with teratoma component) due to chemoresistance, however no significant association between LRP expression and chemoresistance was established (P=0,2),

Conclusion: LRP expression occurs in GCT and IH is a reliable method to evaluate LRP expression in testis cancers. We did not find correlation between LRP expression, and clinical drug resistance. However the high association of LRP immunostaining and teratomas suggests that LRP may contribute in chemoresistance, in this tumour type, which should be further evaluated.

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Long-term results following one course of adjuvant chemotherapy for high-risk stage I non-seminomatous germ cell tumors: the Spanish germ cell cancer group experience

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Purpose: Patients (pts) with clinical stage I non-seminomatous germ cell tumor (NSGCT) with pathologic high-risk features have a recurrence risk on observation of approximately 40%. This study evaluates the long-term efficacy of the administration of one course of adjuvant chemotherapy in a series of pts treated in a multi-institutional setting.

Material and Methods: From October 1994 to May 1999, 21 pts with clinical stage I NSGCT with vascular invasion (15 pts); or invasion beyond the albuginea, into the epididymis or the spermatic cord (6 pts), were treated in 9 hospitals with one course of cisplatin 100 mg/m2, etoposide 400-500 mg/m2 and weekly bleomycin 30 mg (BEP), after orchidectomy.

Results: Median time of follow-up was 61 months, with all pts followed-up for at least 3 years. All the pts have remained alive and free of disease to date. The actuarial event-free survival at 5 years was 100%. No grade 3 and 4 hematological toxicity was observed. Non-hematological toxicity was mild, and consisted mainly of nausea, vomiting and alopecia. No significant long-term sequelae were found.

Conclusion: After long-term follow-up, the administration of one course of BEP appears to be an effective therapeutic alternative for clinical stage I pts with high-risk of relapse. Comparison with adjuvant treatment with two cycles of BEP would be of interest.

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Does prostate cancer dedifferentiate over time?

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Background: It remains uncertain whether prostate cancer dedifferentiates over time. To illuminate further insight into this unanswered question, we have examined whether there is any histological upgrading from radical prostatectomy (RP) to local recurrence in patients with clinically isolated, biopsy proven, local recurrence following RP.

Method: Retrospective, single institution study. A total of 43 patients with clinically isolated, biopsy proven, local recurrence following RP were retrospectively analyzed to assess the change in Gleason score (GS) from RP to local recurrence. Central pathology review was undertaken for both RP and local recurrence biopsy specimens. The changes in primary and secondary Gleason grade (GG), and any potential correlation between the extent of GS change and other variables were also examined.

Results: Median age at the time of local recurrence was 67 years (range: 55-78). RP was performed between 1983 and 1998. Pathological stage was PT2 in 13, PT3a in 24, and PT3b in 6. 28 patients had positive surgical resection margins, while 15 did not. 8 had a short course (< 3 months) of hormone therapy prior to RP. Initial GS at the time of RP was 5, 6, 7, 8, and 9 in 1, 3, 29, 1, and 9 patients, respectively. Median interval between RP and local recurrence was 3.6 years (range: 0.3-17.7; mean: 4.2 years). Clinical evidence of relapse was confined to the prostate bed, as all had normal bone scan and CT scan of abdomen and pelvis. At the time of local recurrence, GS was upgraded in 13, unchanged in 23, and downgraded in 7. Excluding 8 receiving hormone prior to RP, GS was upgraded in 11, unchanged in 20, and downgraded in 4. Primary GG was upgraded in 10, unchanged in 28, and downgraded in 5. The extent of GS change was correlated with the interval between RP and local recurrence (p=0.08), but not pathological T stage or age.

Conclusion: There was a trend, though not statistically significant (p=0.36), toward a higher GS at the time of local recurrence. This trend was more pronounced when restricted to the 35 patients who did not have hormone prior to RP (p=0.08). The extent of GS change was associated positively with the elapsed time to local recurrence. The above findings are suggestive of cellular dedifferentiation over time. The main drawbacks of the study are selection bias and a small sample size.

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Concordance/Discordance of pathological evaluation of radical prostatectomy (RP) specimen between a community hospital and a tertiary teaching hospital

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Purpose: 1. To examine concordance or discordance between a community hospital (CH) and a tertiary teaching hospital (TTH) with respect to the grade, margin status, and tumor extent in RP specimens.

2. To assess and compare the completeness of a pathology report with respect to the aforementioned factors.

Materials and Methods: A phase II study, evaluating the combination of post-operative radiotherapy plus 2-year androgen ablation as either adjuvant or salvage therapy, accrued a total of 154 post-RP patients. All underwent retropubic RP for prostate adenocarcinoma as primary therapy. 113/154 RP cases were performed at a community hospital and the basis of this study. Their RP specimens were centrally reviewed by the Sunnybrook and Women's College Health Science Centre (a TTH) as a part of patient screening for study eligibility. The original CH pathology reports were compared with the central TTH consultative review with regards to concordance and completeness.

Results: Gleason score (GS): GS ranged from 4 to 9 in CH pathology reports. In TTH review, GS ranged from 6 to 9. 29% had GS 6 or less in CH reports, while only 17% did in TTH review. The highest concordance rate was for GS 7 at 87%. The lowest concordance rates were for GS 6 and 8. 62% of GS 6 were upgraded to GS 7 in TTH review. 11.5% of CH reports did not give GS, while 0.88% (due to marked anti-androgen treatment effect) did not in TTH review.

Resection margins and Tumor extent are shown in the table.

Abstract 886 – Table

	Bladder neck resection margin	Apical resection margin	Peripheral resection margin	Capsular penetration	Seminal vesicles involvement
Concordance rate for positive margin	76%	95%	94%	85%	81%
Concordance rate for negative margin	83%	74%	66%	59%	96%
Conversion rate from negative to positive margin	7%	18%	34%	34%	2%
Conversion rate from positive to negative margin	24%	3%	4%	15%	16%
% of missing information in CH reports	27% (10% of these had positive margin on review)	22% (20% of these had positive margin on review)	12% (50% of these had positive margin on review)	33% (38% of these had capsular penetration on review)	1%

Conclusions: In the TTH review, there was a trend toward GS upgrading. There was a significant discordance rate in the evaluation of resection margins and capsular penetration. Also a significant proportion of CH reports had missing information with regards to resection margin status and tumor extent. The study suggests the importance of central review of RP specimens by a TTH and the need of a standardized reporting system for RP specimens.

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Impact of mean rectal dose on late rectal bleeding following conformal radiotherapy for prostate cancer: dose volume effect

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Purpose/Objective: To identify clinical and dosimetric factors predictive of a higher risk of grade 2 late rectal bleeding in patients with localised prostate cancer treated with three-dimensional conformal radiotherapy (3D-CRT) in a prospective dose escalation study.

Methods and Materials: We performed a retrospective analysis of clinical records and dose-volume histograms of 107 patients with T1c-T3 prostate cancer treated at this institution with 3D-CRT and a minimum follow-up of one year. Twenty-one patients were treated at dose level I (70 Gy), 57 patients were treated at dose level II (72 Gy) and 29 patients at level III (75.6 Gy). The mean ICRU reference dose was of 76.49 Gy, range 69.80 to 82.62 Gy. All dose prescriptions were to ICRU point (dose level I) or to the minimum isodose surface encompassing the planning target volume (PTV) (dose levels II and III). Neoadjuvant and 2-years adjuvant androgen suppression were given to 16 and 27 high-risk patients respectively. Late rectal bleeding were graded according to RTOG toxicity scores adapted for rectal bleeding.

Results: Six of the 107 patients (6%) experienced grade 2 rectal bleeding and only one patient (1%) at dose level II had grade 3 complication. The clinical variables considered for analysis were: age, pretreatment PSA, Gleason score, T stage, history of diabetes mellitus and gastrointestinal (GI) diseases, administration and type of hormonal therapy and presence of acute rectal symptoms during radiation therapy. The dosimetric variables considered were: mean ICRU dose, rectal volume, the maximal dose and mean dose to the rectal volume (Dmax and Dmean), NTCP and the volumes (percentage and absolute) of rectum receiving more than 30Gy, 40Gy, 50Gy, 60Gy, 72Gy, 75Gy, 78 Gy and 80Gy. On univariate analysis, only dosimetric factors were significantly correlated with grade 2 rectal bleeding: 1) rectal volume ($p=.024$), 2) rectal Dmean ($p<.0005$), 3) the percentage of rectal volume exposed to >30 Gy ($p=.005$), >40 Gy ($p=.001$), >50 Gy ($p=.001$), >60 Gy ($p<0.0005$) and >72 Gy ($p=.016$), and 5) a higher NTCP ($p=0.001$). The results of multivariate logistic regression analysis indicated that both, the rectal Dmean (Exp(B): 1.268; CI 95%: 1.084-1.482; $p=.003$) or V60 (Exp(B): 1.105; CI 95%: 1.036-1.179; $p=.002$) correlated with grade 2 rectal bleeding.

Conclusion: The present study confirms a clear evidence of dose volume effect and the importance of intermediate doses (60 Gy) on the risk of rectal bleeding at this dose level. The predictive value of mean rectal dose could be explained by its strong correlation with intermediate doses and because its real value is less dependent on setup variability and internal organ motion.

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Cranial nerve palsies in metastatic prostate cancer- results of base of skull radiotherapy

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Background: Cranial nerve dysfunction caused by metastasis to the base of skull is a relatively infrequent but debilitating complication of prostate cancer that is traditionally treated by external beam radiotherapy and high dose steroids. There is very little data on response to therapy in the literature.

Methods: We examined the Royal Marsden Hospital prostate cancer database for patients with prostate cancer who were treated with external beam radiotherapy to the base of skull for cranial nerve palsies between 1st January 1995 and 31st December 2002. Data obtained included radiological findings, radiation dose and fractionation, biomarkers, and response to treatment.

Results: A total of 32 patients with a median age of 73 years (range 49-85) were identified as fulfilling the inclusion criteria. Increased uptake of isotope was seen in the base of skull in all patients on bone scan. The most common palsies were of the 6th, and 12th cranial nerves. Palsies were unilateral in all cases and multiple in 3 patients (9%). All patients were treated to the mid-plain using parallel-opposed beams of 6 Mev photons or Cobalt-60. Twenty seven patients (84%) received 20 Gy in 5 fractions in 7 days, with 3 patients (9%), treated with 30Gy in 10 fractions. All patients bar one were treated with a median Dexamethazone dose of 6mg daily in addition to radiotherapy. Sixteen patients (50%, 95% CI: 34-66%) had a response to therapy, 50% of which had complete resolution of symptoms. The median survival following base of skull radiotherapy was 3 months (range 1-36) with 14 patients (44%) living less than 2 months after completion of therapy.

Conclusions External beam radiotherapy is an effective modality in the palliation of cranial nerve palsies secondary to base of skull involvement by metastatic prostate cancer with a response rate of 50% in this series. Patients with this manifestation of prostate cancer have a very poor prognosis.

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Estrogens and a phytoestrogen (genistein) induce hypersensitivity of prostate carcinoma cell lines to low dose radiation in vitro

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As prostate carcinomas tend to express estrogen receptors (especially type β), we tested the potential of a combined therapy with an estrogen (estradiol) and a predominantly estrogen receptor β-stimulating phytoestrogen (genistein, a soy product) and radiation in LNCaP and PC-3 cells *in vitro*. The advantage of genistein compared to estradiol is its better tolerance in male patients.

With colony forming assays, we tested the clonogenic survival of the cells after incubation with different concentrations of genistein and estradiol and subsequent irradiation.

To evaluate the receptor expression of the employed passages of LNCaP cells, we isolated RNA, transcribed it into cDNA, and performed a hot start RT-PCR.

The influence of the combined treatment on cell cycle distribution was measured by FACS analysis after staining the cells with DAPI.