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Early experience of a multicentre phase I/II study of hypofractionated radiotherapy (55 Gy/16 fractions/4 weeks) for localized prostate cancer

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Objective: To determine the late rectal toxicity of hypofractionated radiotherapy (hypoRT) of 55 Gy/16 (3.44 Gy-fraction, 4/wk) in the treatment of localized prostate cancer.
Method: This study began in Sep 2004 for patients with T1-T2 prosate cancer, Gleason score $\leqslant 6$ and PSA <20, or Gleason score 7 and PSA <15, and up to 6 mo. neoadjuvant LHRH. After TRUS-guided insertion of three gold markers, patients undergo 3D conformal planning (4- or 6-field), supine with full bladder. PTV = prostate $\pm$ adjacent 1 cm seminal vesicles +10 mm margin (except 5 mm rectum). If rectal DVH exceeds constraints (D50 = 37 Gy, D35 = 45 Gy, D25 = 51 Gy, D15 = 55 Gy), IMRT (5- or 7-field) is used. Daily orthogonal pre-treatment aSi-EPIs of target (gold markers) are taken and isocentre adjusted if mismatch >3 mm (2 mm AP). EPIs are repeated during treatment if feasible. Planned sample size is 72 patients from three centres over 2 years. Stopping rule applies if risk of RTOG grade 3 toxicity exceeds 10%.
Results: 18 have completed treatment prescribed. Two patients developed ciprofloxacin-resistant E.coli UTI following insertion of gold markers. One patient required IMRT. EPIs during treatment were available for 215 fractions delivered on 14 patients. 10 fractions (4.7%) were delivered with targeting error >5.0 mm in any direction. Compared to pre-treatment EPIs, average intra-fraction target organ motion up to 2.5 mm was observed for some patients. Average treatment time per fraction is 19 min. One grade 3 rectal bleeding has been observed at 6-month follow up.
Discussion: Accrual and follow up are on-going. HypoRT requires a robust image-guided treatment process incorporating verification images during treatment to confirm targeting accuracy. Patients with significant intra-fraction motion may require alternative set-up strategies to minimize errors due to over-correction during set-up. Clinical outcomes of this dose-fractionation regimen will provide data to better estimate fractionation sensitivity of prostate cancer and normal tissues.

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A comparison of 3D conformal radiotherapy and IMRT treatment plans in prostate cancer

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Introduction: The concave dose distributions for prostate cancer produced by intensity modulated radiotherapy (IMRT) plans present a significant advantage over 3-D conformal radiotherapy (3DCRT). The high dose region wraps around the overlapping rectum in the planning target volume (PTV) and thus conforms the dose to the target volume, and achieves a higher level of rectum sparing. This gives increased scope for dose escalation. This study compared inverse planned IMRT with 3DCRT technique for the treatment of prostate cancer.
Methods: CT studies of 30 randomly selected prostate patients were planned and calculated on a Nucletron (Helax) TMS treatment planning system. All patients were scanned in a supine position without using rectal immobilisation and with a comfortably full bladder. The target volumes consisting of CTV (prostate and seminal vesicle), PTV2 (prostate+1.0 cm margin) and PTV1 (CTV+1.0 cm margin) were outlined. 3DCRT was carried out in 2 phases using 4 fields. Inverse planned IMRT was carried out using step-and-shoot technique with 5 non-opposing fields. The dose prescribed to the isocenter for all plans was 74 Gy as a standard. In IMRT plans with favourable dose volume parameters (DVPs), the prescribed dose was increased to 78 Gy. The coverage of various target volumes (dose to 90% of the volume, D90%) and the sparing of the rectum and bladder were assessed and analysed statistically using Wilcoxon assigned rank test.
Results: The optimum dose volume constraints (DVCs) used in this work were found to be: PTV2 – (95% d, 97% v) and (105% d, 5% v). CTV – (90% d, 95% v) and (95% d, 5% v). PTV1 – (80% d, 95% v) and (90% d, 5% v). Rectum – (50% d, 5% v). Bladder – (50% d, 5% v). Compared with 3DCRT, CTV coverage was comparable in the two plans (P value = 0.40) PTV1 coverage was significantly improved in IMRT plans (P value < 0.001). Although the PTV2 coverage was better in 3DCRT plans (P = 0.02), the minimum D 90% was 67 Gy and the average D 90% was 72 Gy in IMRT plan. Rectum D 25% and bladder D 20% were comparable in both plans (P = 0.2, &0.12). Rectum D 66%, & D 50%, bladder D 50% and D 33% were significantly lower in IMRT plans (P < 0.002). The volume of the rectum and bladder that received 50 Gy and 70 Gy or more were significantly reduced in IMRT plans (P < 0.007). In some patients, the DVPs for the rectum and bladder were significantly lower than their pre-specified tolerance level. This gave the scope to increase the prescribed dose to 78 Gy. In these patients, despite the higher prescribed dose, rectum D 66%, & D 50%, and bladder D 50% were still significantly lower in IMRT plans than in 3DCRT (P < 0.01). Other DVPs were comparable to those in 3DCRT (P < 0.8).
Conclusion: IMRT plans gave comparable target volume coverage to 3DCRT with better rectum and bladder sparing. For higher dose plans, the coverage was far better with more sparing of the rectum and bladder so dose escalation with IMRT plans should be considered.

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The new RTOG-ASTRO biochemical relapse definition is a more appropriate endpoint for multivariate analysis of prostate cancer outcomes

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Background: In early 2005 the RTOG and ASTRO adopted a new definition of PSA relapse (bNED) following radiation therapy treatment of prostate cancer. The new definition ("lowest PSA to date+2", 'LPA+2') is a rise of 2 ng/ml greater than the nadir, and henceforth replaces the ASTRO definition, in use since 1997. Although it has been shown by others to be more accurate than ASTRO, it has not been studied as the endpoint of multivariate analysis. This study compares the two definitions on a large mature dataset.
Materials and methods: From a prospective database of 1885 men treated since 1994, 1002 patients were selected who had been treated prior to April 2000, and who had complete staging information available. Most of those excluded did not have percent positive core (PPC) data. bNED was calculated according to both ASTRO and LPA+2 definitions and standard multivariate statistics were performed on those factors significant on univariate analysis. Radiation dose was categorized above or below-at the median dose of 66 Gy. Androgen deprivation therapy (ADT, both neoadjuvant and adjuvant) duration was expressed in months (including zero, where none was used). PSA was log-transformed. For both definitions the validity of the proportional hazard assumption was explored for the use of ADT.
Results: The median follow-up of the 1002 eligible patients was 5 years. The ASTRO bNED rate at 4 years was 10% higher than the LPA+2 (70% v. 60%), after 7 years the curves cross, and by 10 years the ASTRO bNED was 10% lower than the LPA+2 (32 v 42%), see figure 1. The LPA+2 definition showed proportional hazards, whereas the ASTRO definition did not. On multivariate analysis both definitions gave similar results (see table 1) but neoadjuvant androgen deprivation therapy (ADT) was only marginally significant with ASTRO (p = 0.047), but was clearly significant with LPA+2 (p = 0.001).

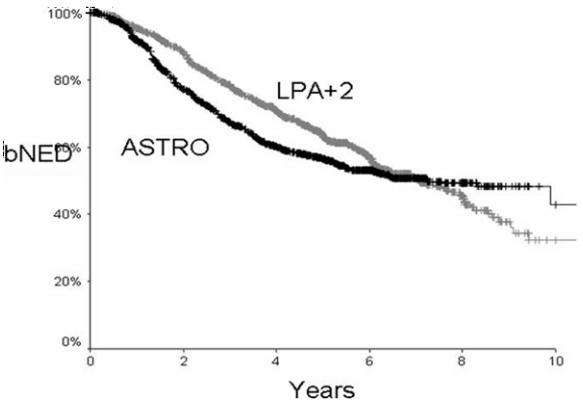

Fig. 1

Conclusions: Multivariate analysis with the LPA+2 definition is statistically sound, unlike the ASTRO definition which does not fulfill the proportional hazards assumption. Both show similar outcomes with multivariate analysis, with the exception of neoadjuvant ADT usage. This likely results from the false scoring of biochemical relapse with the ASTRO definition due to slight PSA rises while testosterone is recovering after cessation of ADT. ASTRO underestimates biochemical control rates for the first 5–6 years of follow-up. The LPA+2 definition does not show the plateau seen with the ASTRO definition.

Table 1

Factor	ASTRO p value	LPA+2 p value
PSA	< 0.0001	< 0.0001
T Stage	0.0002	0.0003
Gleason	< 0.0001	< 0.0001
Radiation dose <>66 Gy	0.0066	0.001
PPC	< 0.0001	0.0001
Neoadjuvant – ADT	0.047	0.0011
Adjuvant – ADT	< 0.0001	< 0.0001

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Duration of toxicity following permanent I125 prostate brachytherapy

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Background: Convenience and a favourable toxicity profile have made prostate brachytherapy increasingly popular in the treatment of low risk prostate cancer (PC). However, toxicity may not be as low as initially thought with the current techniques. This study looks at the time course of the common toxicities following permanent I125 prostate brachytherapy.
Methods: 249 patients (pts.) with low risk PC treated between October 1998 and October 2004 are currently being followed post implant. The prescribed dose was 145 Gy MPD. A urethral sparing technique was used which aimed at keeping the urethral dose to less than 150% of the prescribed dose. Implants were done using preloaded needles with either loose or linked seeds. At each visit pts were questioned about sexual function, and genitourinary and gastrointestinal symptoms. Post-implant dosimetry was performed 1 month following the implant. Follow up occurred every 3 months in the first year, every 4 months in the second year, and every 6 months thereafter.
Results: Of the 249 pts., 3 pts. were lost to follow-up, and 1 had not returned for his 1 month post-implant dosimetry follow-up visit. The remaining 245 men had a median age of 67 years (range: 47–84 years) and a median follow-up of 24.1 months (range: 3.5 – 57.7 months). Forty percent received adjuvant hormones treatment. The toxicity profile is as follows:

GI pts.			GU pts.	
Grade	Acute	Late	Acute	Late
1	16	28	27	123
2	3	10	17	59
3	0	0	7	16

Ninety-one percent experienced some deterioration in urinary function and 27% experienced some rectal toxicity. Diarrhea and bloody discharge, and frequency, nocturia and dysuria were the most commonly reported rectal and bladder toxicity, respectively. The average duration of acute and late grade 1/2 rectal toxicities was 2.9/2.5 and 7.1/7.7 months, respectively. The average duration of acute and late grade 1/2/3 urinary toxicities was 3.0/2.8/2.3 and 14.5/11.0/11.5 months, respectively. Ninety-six men were known to have normal sexual functioning prior to implant, 53 developed some level of erectile dysfunction, and 29 became impotent, 15 post hormones. The median time from treatment to impotency was 6 months. Ten pts. regained functioning (5 with Viagra), with a median duration of impotency of 12.6 months. Positive correlations were found between the D90 (P = 0.005) and V100 (P = 0.004), and urinary symptom severity. No other relationships between severity and dosimetric values were noted.
Discussion: Brachytherapy was tolerated well, with low to moderate urinary, bowel and sexual toxicity in most pts lasting between 3 and 15 months. Elevated dosimetry values appear to be an indication of higher severity grade for urinary toxicity but not rectal toxicity. While almost all symptoms eventually resolved, the duration was longer than expected.

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Risk adapted management in clinical stage a (CS-A) nonseminomatous testicular tumors (NSTT): a critical appraisal

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Background: We previously reported that the patients (pts.) in CS-A NSTT who underwent retroperitoneal lymphadenectomy (RPLA) are more likely to relapse if their preorchiectomy AFP was >80 ng/ml, if they have >80% embryonal carcinoma or if there was microvascular tumor invasion (ISW 165:555, 1995). The aim of the present study is analysis of experience with surveillance in comparison to primary RPLA and cisplatin (CDDP)-based chemotherapy (CHT) according to risk factors in CS-A NSTT with normal values of serum tumor markers (STM) postorchiectomy.
Material and methods: 195 pts. entered a prospective but nonrandomized study, from 01.81–12.03. The pts. are divided into 3 groups according to primary risk adapted treatment. Arm A (n = 60) – surveillance. Arm B (n = 65) – "nerve sparing" RPLA with 2 cycles of adjunctive CDDP-based CHT in PS-B1/B2. Arm C (n = 70) – only 2 cycles of CDDP-based CHT in high risk (HR) group of pts. (as defined above).
Results: Arm A – 9/21 pts (42.9%) with HR relapsed (4 RPLN, 2 RPLN+lung, 1 inguinal LN+lung, 2 only elevated STM) within median free interval (MFI) of 12.3 months (M)(range 3–46) with CR following applied therapy in 6 pts (66.6%)(8 pts. necessitate surgery). Alive and free of disease (AFD) are 18 pts. (85.7%) at median follow-up (MFU) of 12.3 years (range 3.5–20.6). 6/39 pts. (15.4%) with low risk (LR) (without previously mentioned criteria) relapsed within MFI of 6.8 M (range 3–10) (3 RPLN, 1 lung, 2 only elevated STM) with universal CR following applied CHT. All pts are AFD after MFU of 9 years (range 1.9–18.7) (p < 0.05). Arm B – Relapses following RPLA in HR PS-A occurred in 7/35 pts. (20%) within MFI of 8.3 M (range 2–23) (5 lung, 1 RPLN, 1 only elevated STM with CR following CHT± surgery in 4 pts. (57.1%). 11 pts. with LN metastasis had universal survival. Overall, relapses occurred in 9/46 pts. (19.2%) with survival in 41 pts. (91.1%) at MFU of 14.6 years (range 8.75–17.25). Among 19 pts. with LR, only 2 pts. (10.5%) had LN metastases, whereas relapse rate was null in 17 fully available pts after MFU of 10.8 years (range 8.6–15.8) (1 lost of FU at 26 M, 1 died of other malignancy at 90 M). 18/46 pts. (39%) I n HR received adjunctive CDDP-based CHT vs 1/19 (10.5%) in LR group of pts. (p < 0.05). Arm C – 1/70 pts. (1.4%) HR pts. treated with primary CHT relapsed at 12 M in the lung and died despite salvage CHT and surgery. AFD are 69 pts. (98.6%) at MFU of 5.5 years (range 1.5–13.7).
Conclusions: We conclude that the pts in CS-A NSTT are not necessarily helped by initial RPLA. According to the results of the present study optimum therapy for HR pts are 2 cycles of CDDP-based CHT. Surveillance policy is acceptable mode of treatment in strictly selected group of pts with LR.

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Early death from comorbid illnesses among curatively-treated prostate cancer patients

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There is a need to better identify those patients with prostate cancer who may not benefit from treatment because they will die of other causes before their cancer becomes symptomatic. We sought to identify which comorbid illnesses are the most important to consider when advising patients about treatment options.
We conducted a population-based case-cohort study of patients diagnosed and treated for cure with radiotherapy or prostatectomy in Ontario, Canada between 1990 and 1998. Cases consisted of a random sample of 587 patients who died within 10 years of a cause other than prostate cancer. The comparison cohort consisted of 1655 patients randomly selected from all treated patients in the Ontario Cancer Registry (OCR). Data were collected from medical charts at the treating hospital or cancer centre and supplemented from physician office charts as needed. The sampling frame and some key variables were obtained using the OCR linked to electronic clinic and census data. Analyses were stratified by treatment type: radiotherapy or surgery. In addition to investigating the role of separate comorbid illnesses, we calculated patient's total comorbidity burden using the Cumulative Illness Rating Scale (CIRS).
The most common causes of death were heart disease (36.6%) and respiratory disease (18.4%). Overall, the disease ultimately causing death was identified as a comorbid illness (at cancer diagnosis) in 51.1% of cases; this proportion was 92.6% for cases dying of respiratory disease and 37.2% for heart disease deaths. Across both treatment groups and after controlling for age, comorbid disease was statistically significantly associated with at least a 2-fold increase in the risk of death in those with: moderate to severe cardiac, severe hematopoietic, moderate to severe respiratory, severe lower GI, and moderate to severe liver disease. For both the radiotherapy and surgery groups, each increment on the CIRS scale (range 0–25) was associated with a 13% increase in the risk of dying after controlling for age.
We identified those illnesses known at prostate cancer diagnosis that will be most likely to lead to an early death among patients being curatively treated for prostate cancer. The results have important implications for