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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).

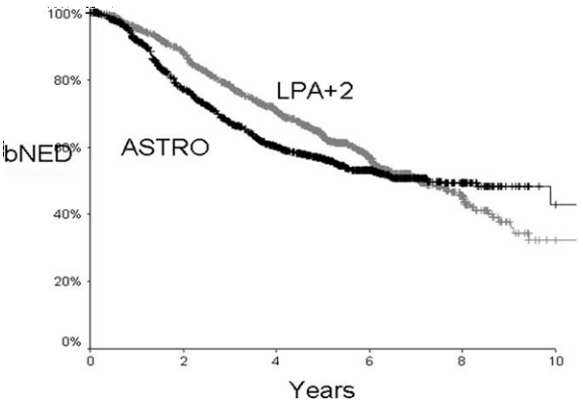

Fig. 1

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.