Introduction

The role of pelvic radiotherapy for high-risk localized prostate cancer is controversial as two randomized trials examining this question have not demonstrated an overall survival benefit. However, the lack of benefit may be due to inadequate doses of radiation to the prostate or pelvic lymph nodes in an attempt to respect normal tissue dose constraints, the use of older radiation treatment techniques, as well as inclusion of patients with low risk of pelvic lymph node involvement.

Treating the pelvic lymph nodes to higher doses of radiotherapy using modern radiotherapy techniques such as image-guided intensity modulated radiotherapy (IG-IMRT) may improve prostate cancer control while limiting unnecessary adverse effects.

We have previously published our feasibility and acute toxicity results of dose-escalated IG-IMRT to the pelvic lymph nodes and prostate in men with high-risk or node-positive (N1) prostate cancer. This study reports the long-term outcomes including biochemical control and late toxicity.

Methods and Materials

Men with biopsy-proven prostate cancer and high-risk disease (cT4-4 and/or Gleason 8-10 and/or PSA ≥ 20 μg/L) and >15% estimated risk of lymph node involvement based on the Roach formula, or men with radiological evidence of pelvic nodal metastases were eligible to participate in this phase II single institution prospective study. Patients were recommended a minimum of 24 months of androgen deprivation therapy (ADT).

All patients underwent insertion of 3 intraprostatic fiducial markers prior to CT simulation and a pelvic MRI scan in the treatment position. Standard bladder and bowel preparation protocols were followed, with daily online image-guidance. The prostate CTV was delineated using the co-registered 72 MRI sequences. The pelvic nodal CTV included the obturator, internal iliac, external iliac and common iliac lymph nodes. The presacral lymph nodes were not included in the target volume. Prostate and pelvic nodal PTV have been previously described, as well as organ at risk (OAR) dose constraints.

The planned prescription dose was 55.1 Gy in 29 fractions to the prostate/semenal vesicles (P/SV) and pelvic lymph nodes (PLN), with a sequential boost dose of 24.7 Gy in 13 fractions to P/SV delivered using IG-IMRT. Patients with radiological evidence of pelvic nodal disease were treated using the same regimen, with no attempt to deliver a boost dose to gross disease. Doses were prescribed such that the CTV received 100% - 105% of the prescription dose, and PTV received 95% - 105% of the prescription dose. In order to meet OAR constraints, dose reductions were mandated, with the preference to drop fractions in phase 1, then add these dropped fractions to phase 2, in order to maintain the total prescribed dose of 79.8 Gy to the prostate PTV.

The primary endpoint of this study was late gastrointestinal (GI) and late genitourinary (GU) toxicity using the RTOG scoring criteria. Secondary endpoints were long-term probability of biochemical control (Phoenix criteria) and overall survival. Probabilities of toxicity and biochemical control were estimated using cumulative incidence function.

Differences between cohorts were examined using the log-rank test.

Results

The cumulative incidence of late GI and GU toxicity are shown in Figures 1 and 2. Late GI grade ≥ 3 toxicity at 8 years was 5.8%, and late GU grade ≥ 3 toxicity was 4.5%. During the study period, 7 men developed GI grade 3 late toxicity and there were no GI grade 4 toxicities. Six men experienced GU grade 3 late toxicity and one man developed a GU grade 4 late toxicity (severe haemorrhagic cystitis 6 years after radiation treatment).

At last follow-up visit there were no GI grade ≥ 3 toxicities and two GU grade 3 toxicities. There was no significant difference in late GI nor late GU toxicity between patients receiving pelvic lymph node doses ≤ 50 Gy and > 50 Gy.

The 5-year biochemical control for the entire cohort was 77%, and at 8 years was 62% (Fig. 3a). In the node-negative patients, the 5- and 8-year biochemical control was 82% and 66%, compared to N1 patients at 44% and 36% respectively (Fig. 3b). Overall survival was 92% at 5 years and 81% at 8 years, and significantly lower in those with N1 disease.

Conclusions

The role for pelvic radiotherapy continues to be investigated and we await the results from the currently accruing trials. There may be an additional benefit in tumour control by increasing the dose to the pelvic lymph nodes, and this study demonstrates that dose-escalation using IG-IMRT to treat both the pelvic lymph nodes and prostate/semenal vesicles combined with androgen deprivation therapy is feasible and results in acceptable late toxicity and disease control comparable or slightly improved compared to standard dose pelvic irradiation using 2D/3D-conformal techniques.

References