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Original Article

Moderately Hypofractionated Radiotherapy in Node-positive Prostate Cancer

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Abstract

Aims: Node-positive prostate cancer is a unique subgroup, with varied practice on locoregional treatment. Definitive treatment with hypofractionated radiotherapy has not been widely reported. We have routinely used standard regimens of hypofractionated radiotherapy for node-positive disease and report our results of toxicity, biochemical control and survival.

Materials and methods: Medical records of patients diagnosed with prostate cancer between February 2011 and April 2016 with radiologically involved pelvic nodes on magnetic resonance imaging/computed tomography without distant metastases were analysed. All patients were treated with long-term androgen deprivation therapy (ADT) and hypofractionated radiotherapy. Acute and late toxicities were assessed using Radiation Therapy Oncology Group acute and late morbidity scoring criteria. Biochemical control and survival were computed using Kaplan–Meier survival statistics.

Results: In total, 61 patients were identified with node-positive disease, with a median age of 68 years and a median initial prostate-specific antigen level of 40.1 ng/ml. Most, 50 (81.9%), had T3 disease; 47.6% had Gleason 8–10 disease. All were treated with hypofractionated intensity-modulated radiotherapy, predominantly 60 Gy/20 fractions/4 weeks, with a dose of 44 Gy/20 fractions to the pelvic nodes. Twenty-five patients (41%) who had residual radiologically enlarged nodes after 3–6 months of ADT received nodal boost to the involved nodes, to a dose of 54–60 Gy as simultaneous boost. Incidences of late grade 2 + gastrointestinal and genitourinary toxicities were 13.1 and 18%, respectively, with no grade 4 toxicities. With a median follow-up of 48 months, 15 (24.6%) patients developed biochemical failure, with only four locoregional failures. The 4-year biochemical control rate was 77.5% and overall survival was 91%. Patients who had residual enlarged nodes after initial ADT had worse biochemical control (53.9% versus 93.1% at 4 years, $P < 0.001$).

Conclusion: Moderately hypofractionated radiotherapy using an established fractionation schedule with long-term ADT for node-positive prostate cancer patients is feasible and results in excellent biochemical control rates at 4 years, with acceptable late toxicity rates. The response to initial ADT predicts outcomes.

Key words: Hypofractionated radiotherapy; node-positive; prostate cancer

Introduction

The presence of regional nodal metastases in prostate cancer is categorised as stage IV disease. Radical intent radiotherapy has been used in addition to androgen deprivation therapy (ADT), with retrospective series and database analyses showing a clear potential for improvement in outcomes [1,2]. Similar improvements have been noted with adjuvant radiotherapy in large population-based series in the post-radical prostatectomy setting for pathologically node-positive disease [3]. Despite the fact that there has been no prospective comparison of radiotherapy + ADT versus ADT alone in the clinical node-positive setting, treatment practices around the world have increasingly adopted radiotherapy into the standard treatment, alongside the widespread adoption of conformal treatment with intensity-modulated radiotherapy (IMRT).

Whereas most of the reports of radiotherapy in node-positive disease have been with standard fractionation, there has been a major shift in the dose-fractionation practices in non-metastatic prostate cancer. Following initial radiobiological hypotheses of a low α/β ratio for prostate cancer, there are now several randomised controlled trials that have shown the non-inferiority and safety of moderate hypofractionation schedules [4–6,17]. The greatest experience is with the use of 60 Gy/20

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fractions/4 weeks as used in the CHHiP and the PROFIT studies. However, the feasibility and the results of treatment with moderately hypofractionated radiotherapy have not been widely reported in node-positive disease, apart from a single series from Belgium [7].

Since 2011, we have routinely used standard regimens of hypofractionated radiotherapy for node-positive disease in our centre, and report our results of toxicity, biochemical control and survival.

Materials and Methods

Medical records of patients diagnosed with prostate cancer, treated with radiotherapy with or without ADT, between February 2011 and April 2016, were selected from our electronic database. A staging multiparametric magnetic resonance imaging (mpMRI) pelvis and bone scan was carried out in all patients. Patients who had enlarged pelvic nodes reported as metastatic underwent a further staging contrast-enhanced computed tomographic (CT) scan to rule out extra-pelvic disease. None of the patients underwent lymph node dissection/sampling. Patients were labelled as node-positive either on the basis of unequivocal lymphadenopathy or based on a multidisciplinary meeting discussion of radiological findings. Those patients with radiologically involved pelvic lymph nodes (threshold of 1.0 cm in short axis of oval nodes and 0.8 cm for round nodes) on MRI/CT scan, without evidence of extrapelvic lymph nodal metastases or distant metastases, were included in this retrospective analysis.

All patients were treated with long-term ADT with 2–3 years of luteinising hormone releasing hormone agonists or orchiectomy and hypofractionated IMRT. The choice of medical versus surgical castration was primarily driven by patient preference and cost, the latter being the less expensive treatment. ADT was started 3–6 months before the start of radiotherapy.

Radiotherapy was planned with hypofractionated schedules assuming an α/β of 1.5 Gy for prostate cancer, to doses of 60 Gy in 20 fractions, over 4 weeks. The initial four patients were treated to a dose of 65 Gy/25 fractions. All treatments were delivered with daily volumetric image guidance.

All patients underwent planning CT, with intravenous contrast, obtained on a GE Lightspeed 16 slice unit with a standard bladder filling protocol of 500 ml water and a 30 min waiting period. All patients were scanned in the supine position. No immobilisation devices were used. The leg position and the distance between the patellae were recorded and reproduced.

The clinical target volume (CTV) 60 Gy included prostate and bilateral seminal vesicles. Planning target volume (PTV) margins of 7 mm were used in all axes for this CTV. An elective dose of 44 Gy/20 fractions was delivered to the pelvic nodes in all patients including the presacral, internal and external iliac group of lymph nodes, starting from the level of L5–S1, following the nodal atlas of the Radiation Therapy and Oncology Group (RTOG) [8], with a PTV margin of 5 mm.

If the initially enlarged nodes remained identifiable on the planning CT scan after 3–6 months of ADT, they were delineated as gross-nodal CTV with a PTV margin of 5 mm. There was no size threshold; any identifiable residual node in the same anatomical location was delineated individually. The dose prescribed to this volume was either 54 or 60 Gy in 20 fractions based on the proximity to the small bowel, and planned using a simultaneous integrated boost (SIB).

Organ at risk dose constraints were based on departmental protocol, which has been previously published [9]. The volume of bladder receiving an absolute dose (and equivalent dose at 2 Gy per fraction) of 59 Gy (70 Gy), 56 Gy (65 Gy), 53 Gy (60 Gy), 47 Gy (50 Gy) was kept below 10%, 20%, 25% and 35%; the corresponding volumes of rectum were kept below 7%, 15%, 20%, 35%, respectively. These were more conservative than the QUANTEC constraints [10]. For rectum, achievable mean EQD2 V70 was 8%, V65 was 14.68%, V60 was 18.72% and V50 was 29.04%; whereas, the mean EQD2 V70 and V65 for bladder was 6.8 and 10.38%, respectively. The maximum dose to femoral heads was kept at 40 Gy. The volume of bowel bag receiving 45 Gy was kept below 90 cm^3 and the volume of penile bulb receiving 47 Gy was kept under 50%.

Online image guidance was carried out daily before treatment with either megavoltage CT on helical tomotherapy (Accuray Inc) or kilovoltage cone-beam CT on Novalis Tx ® (Varian Inc). The extent of imaging included prostate and gross nodes and the goal was to first match the prostate and then to verify and make minor adjustments to keep the nodal disease within the PTV margin.

After radiotherapy, patients were followed up with serum prostate-specific antigen (PSA) and a clinical examination at 3 monthly intervals during the first 2 years, then 6 monthly. Acute and late toxicities were assessed using RTOG acute and late morbidity scoring criteria. For each symptom, the maximal recorded grade was defined as the grade of late toxicity.

Biochemical failure was defined according to the Phoenix criteria [11]. Clinical or biochemical control was calculated from the date of registration in the prostate cancer clinic to the date of biochemical relapse. All patients had a diagnosis of prostate cancer at the time of registration. Locoregional relapse and distant failure were detected on imaging (CT abdomen/thorax and bone scan or prostate-specific membrane antigen [PSMA] positron emission tomography [PET] when available). Overall survival was defined from the date of registration to the date of death from any cause. Survival was computed using Kaplan–Meier statistics using the SPSS version 20 statistical software (IBM corporation).

Results

In total, 61 patients with node-positive disease were identified between February 2011 and April 2016. The details of patient characteristics and treatment are shown in Table 1. The median age of the patients was 68 years, with a median initial PSA level of 40.1 ng/ml. Most patients (50/61)

Table 1
Patient, disease and treatment characteristics

Median age (years)	68 (51–83)
Median initial PSA (ng/ml)	40.14 (0.05–864.7)
Tumour stage	
T2	8 (13.1%)
T3a	26 (42.6%)
T3b	24 (39.3%)
T4	3 (4.9%)
Gleason Score	
6	8 (13.1%)
7	24 (39.3%)
8–10	29 (47.6%)
Median of predicted likelihood of lymph nodal metastasis (Roach formula)	47.34% (1.78–100%)
Androgen deprivation therapy	
LHRH analogue	35 (57.4%)
Orchiectomy	26 (42.6%)
Radiotherapy dose fractionation	
60 Gy/20 fractions/4 weeks	57 (93.4%)
65 Gy/25 fractions/5 weeks	4 (6.6%)
Nodal boost (54–60 Gy)	25 (41%)

PSA, prostate-specific antigen; LHRH, luteinising hormone releasing hormone.

had T3 disease. By virtue of their Gleason score and PSA, the likelihood of lymph nodal metastases by the Roach formula was high.

The initial four patients were treated to 65 Gy/25 fractions/5 weeks (iso-effective dose at 2 Gy of 76.24 Gy). Patients treated from February 2012 onwards were prescribed a dose of 60 Gy/20 fractions/4 weeks (iso-effective dose at 2 Gy of 77.25 Gy). Twenty-five patients (41%) who had residual radiologically enlarged nodes after 3–6 months of ADT or orchiectomy received nodal boost to the involved nodes to either 54 Gy or 60 Gy using SIB.

Treatment was well tolerated, with none of the patients suffering grade 3 or 4 acute gastrointestinal or genitourinary reactions and no toxicity-related treatment interruptions. Incidences of late grade 2 and 3 gastrointestinal toxicity were six (9.8%) and two (3.3%), respectively. Incidences of late grade 2 and 3 genitourinary toxicity were eight (13.1%) and three (4.9%), respectively. There were no grade 4 toxicities.

With a median follow-up of 48 months, 15 (24.6%) patients developed biochemical failure, with only four patients failing locoregionally and the rest with distant metastases. Among locoregional failures there was one patient who had local failure only, one who had regional nodal failure and para-aortic nodal failure, and the remaining two patients had regional failure together with bone metastases. The median duration to biochemical failure was 33 months. The 4-year clinical/biochemical control rate was 77.5% and the projected 5-year clinical/biochemical control rate is 74.3%. The 4-year overall survival is 91%.

No statistically significant difference was found in biochemical failure rates across the patients who had a higher Gleason score (8–10) versus lower (6–7) or between patients treated with orchidectomy versus 2–3 years of luteinising hormone releasing hormone agonists. However, patients who had residual enlarged nodes after 3–6 months of ADT and required nodal boost had poorer biochemical clinical/biochemical control rates (4-year rates 53.9% versus 93.1%; $P < 0.001$).

Discussion

The management of node-positive prostate cancer has posed a dilemma to oncologists over the years, partly due to a paucity of level I evidence regarding the preferred line of treatment. Traditionally, ADT alone had been the cornerstone of treatment in pathologically confirmed node-positive disease, without any further local therapy [12].

Retrospective institutional reviews [1,13] and analysis of the SEER database [2] have shown significantly higher biochemical recurrence-free survival rates and overall survival rates with external beam radiotherapy plus ADT, versus ADT alone, in the node-positive cohort. Similarly, Seisen *et al.* [14] published the National Cancer Database review on the role of local therapy for clinically node-positive prostate cancer patients and found superior overall survival of 78.8% versus 49.2% at 5 years, favouring ADT and local therapy, and no significant difference between radical prostatectomy and radical radiotherapy. This trend follows evidence showing a benefit of adding radiotherapy to ADT in the post-prostatectomy setting for pathological node-positive disease [15,16]. Based on these reports, institutions are increasingly offering local treatment, usually radiotherapy, in addition to ADT in all or a subset of patients with clinically or pathologically confirmed node-positive disease.

Hypofractionated radiotherapy using fraction sizes of 2.7–3 Gy per fraction has become a standard of care in treating localised prostate cancer patients, based on the results of recent randomised phase III trials [5,17,18]. The results of these trials confirm earlier calculations of an α/β ratio of prostate cancer of about 1.5 Gy. The fact that the ratio is lower than the surrounding critical structures (i.e. 3 Gy for bladder and rectum), allows delivery of a higher dose per fraction over a shorter overall duration.

The only reported series specifically investigating moderately hypofractionated radiotherapy and ADT in node-positive disease is from Ghent University in Belgium. Most patients (55/80) in their series were clinically node-negative but were found to be pathologically node-positive on a planned pelvic nodal dissection. Of the clinically node-positive patients (25/80), most also underwent lymph node dissection. The median prescription dose was 69.3 Gy in 25 fractions to the primary with an elective pelvic dose of 45 Gy with IMRT and SIB to 65 Gy was administered for radiologically residual nodes after lymphadenectomy. They reported 3-year biochemical recurrence-free survival and clinical recurrence-free survival of 81 and 89%, respectively [7].

The only other study is an early report of very high-risk and node-positive prostate cancer patients treated with stereotactic radiotherapy, reported from Tata Memorial

Hospital in India [19], including 37 patients with PSMA PET/CT identified nodal metastases. The biochemical control at 18 months was 94% for the whole cohort, with acceptable toxicity rates.

We are reporting the results of moderately hypofractionated IMRT in our institutional cohort of radiologically node-positive prostate cancer patients. With a median follow-up of 48 months, the 4-year biochemical control rate was 77.5% in our analysis. The results are encouraging and comparable with the earlier results of Fonteyne *et al.* [7].

The major issue in irradiating pelvic nodal stations is increased toxicity to the bowel, without any proven benefit of the same. Implementation of IMRT and daily image guidance have been helpful in the prevention of higher grade late toxicities. Dose-escalated elective pelvic nodal IMRT has been safely delivered in phase I trials with acceptable grade 2 gastrointestinal and genitourinary toxicities [20,21]. In our series, the incidence of late grade 2 + gastrointestinal and genitourinary toxicities were 13.1 and 18.1%, respectively. This is again comparable with the results from Belgium, where 23% of patients had grade 2 or more gastrointestinal toxicity, whereas 35% patients had grade 2 or more late genitourinary toxicity [7]. Toxicity in the node-positive setting in our cohort is also similar to our earlier report on 101 high-risk patients, where grades 2 or more late gastrointestinal and genitourinary toxicities were recorded in 20.8 and 13.9% of patients, respectively [9]. The toxicity rates are not very different from the hypofractionated arms treating 60 Gy/20 fractions/4 weeks in the PROFIT study using the RTOG criteria, where pelvic nodal radiotherapy was not used [17].

We used a clinical rather than a pathological approach to categorisation of a patient as having node-positive disease based on interpretation of initial imaging with mpMRI imaging and after discussion at a dedicated uro-oncological multidisciplinary team meeting. Most of these patients had high Gleason scores and had locally advanced disease (>T3a) and the likelihood of nodal metastases was high according to the Roach formula [22]. We did not verify with biological imaging, e.g. PSMA PET, as this was not available in our centre during the treatment of this cohort. Currently, PSMA PET/CT is used for the confirmation and detection of metastatic disease in a subset of patients with high-risk features, according to recommendations by the multidisciplinary team. Lymphadenectomy or sampling for radiologically node-positive disease is not a standard practice in our institution.

Elective nodal volumes were based on the RTOG pelvic nodal contouring guidelines, with the superior border limited to the L5–S1 interface. Common iliacs were not specifically included, because it was felt that failure patterns in these patients would be predominantly systemic. It could be debated whether it would be more appropriate to cover the region around the vessels up to the bifurcation of the aorta. In our cohort, all the patients treated had involved nodes below the division of the common iliac into internal and external iliac vessels (below the level of S1). Volumes were not routinely extended to the common iliac bifurcation. Although two of the failures included nodal disease in the region of the aortic bifurcation, at the margin of the pelvic field, they were accompanied by para-aortic or distant metastases.

The main difference between our series and that from Belgium is the lymphadenectomy for diagnosis and treatment in patients at high risk of nodal metastases. In that series, most patients were clinically node-negative and represent a cohort who we would usually treat as node-negative without proceeding for a lymphadenectomy and would not have included in this audit. Our treatment protocol is identical for a high-risk localised or node-positive patient.

A safety-oriented approach was followed to administer nodal boost to only the residual/detectable nodes on the planning CT scan, after 3–6 months of ADT. A dose of 54 Gy/20 fractions was prescribed to residual nodes when they were close to bowel (iso-effective dose at 2 Gy of 64.8 Gy) and 60 Gy/20 fractions to nodes away from bowel (iso-effective dose at 2 Gy of 77.25 Gy). The dose of 54 Gy (EQD2 64.8 Gy) was chosen as doses in the range of 65 Gy have been used in older randomised trials showing a benefit of adding ADT to radiotherapy alone in high-risk patients [23]. The patterns of failure, with only four of the 61 patients failing locoregionally, suggest that this dosage schedule is effective for regional control. Patients who had residual nodes requiring boost doses fared far worse than those who had resolution of nodes with 3–6 months of ADT. Failure of complete regression of nodes is probably related to a poorer biology or more extensive initial nodal metastases. However, it is important to note that even in this cohort of patients with residual nodes with ADT, reasonable regional control was achieved with nodal boost doses of radiotherapy, with only 2/25 patients failing regionally.

Our study was retrospective in nature and therefore may be associated with unknown biases. However, as the treatment protocol for node-positive disease has remained standard over the course of time, and is followed for all patients, this cohort represents the clinical scenario faced in our practice.

The ongoing PRIME trial in India (NCT03561961, clinicaltrials.gov) is assessing the non-inferiority of extreme hypofractionated stereotactic body radiotherapy to moderately hypofractionated radiotherapy in high-risk and node-positive prostate cancer and will provide high-quality prospective data on outcomes in node-positive prostate cancer treated with hypofractionated radiotherapy.

With 4 years of follow-up, our results suggest that radical-intent treatment with moderately hypofractionated radiotherapy and long-term ADT does achieve good results in node-positive disease. However, longer follow-up will show us if these results are sustained and if this treatment is potentially curative in most patients. These results also indicate that moderately hypofractionated radiotherapy can be considered practical and safe in this setting, just as it has been found in node-negative disease.

Conclusions

Moderately hypofractionated radiotherapy is safe and effective when added to long-term ADT for radiologically

node-positive prostate cancer. Outcomes are better for those patients who have complete regression of nodes with an initial 3–6 months of ADT.

Conflict of Interest Statement

The authors have no conflicts of interest to declare or financial disclosures.

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