Radiotherapy and Oncology 123 (2017) 459–465

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate cancer radiotherapy

Improved outcomes with dose escalation in localized prostate cancer treated with precision image-guided radiotherapy

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ARTICLE INFO

Article history:
Received 11 January 2017
Received in revised form 12 March 2017
Accepted 1 April 2017
Available online 20 April 2017

Keywords:
Prostate cancer
Dose escalation
Radiotherapy
Image guided radiotherapy

ABSTRACT

Background and purpose: Dose-escalated radiotherapy (DE) improves outcomes in localized prostate cancer (PCa). The impact of DE in the context of image-guided radiotherapy (IGRT) remains unknown. Herein, we determined outcomes of three sequential cohorts treated with progressive DE-IGRT.
Materials and methods: We analyzed data from 1998 to 2012. Patients treated with radical radiotherapy were included, with three sequential institutional schedules: (A) 75.6 Gy, (B) 79.8 Gy, (C) 78 Gy, with 1.8, 1.9 and 2 Gy/fraction, respectively. IGRT consisted of fiducial markers and daily EPID (A, B) or CBCT (C).
Results: 961 patients were included, with median follow-up of 6.1y. 30.5%, 32.6% and 36.9% were treated in A, B and C, respectively. Risk category distribution was 179 (18.6%) low-, 653 (67.9%) intermediate- and 129 (13.5%) high-risk. PSA, T-category, androgen deprivation use and risk distribution were similar among groups.
BCR (biochemical recurrence) was different ($p < 0.001$) between A, B and C with 5-year rates of 23%, 17% and 9%, respectively (HR 2.68 [95% CI 1.87–3.85] and 1.92 [95% CI 1.33–2.78] for A and B compared to C, respectively). Findings were most significant in the intermediate-risk category. Metastasis, cause-specific-death and toxicities were not different between cohorts.
Conclusion: Our findings suggest continuous BCR improvement with progressive DE-IGRT. Prospective validation considering further DE with IGRT seems warranted.
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External beam radiotherapy (EBRT) is an effective curative treatment modality for localized prostate cancer (PCa). In five randomized studies, higher dose of EBRT (i.e. dose-escalation [DE]) has been consistently shown to improve biochemical control rates and clinical progression-free outcomes [1–7]. Although not observed in original trials, a recent population-based study showed improved overall survival (OS) for intermediate- and high-risk PCa patients treated with DE (>74 Gy) [8], highlighting the importance of determining the role of DE in the modern era. Technological improvements to EBRT delivery over the last three decades have enabled progressively higher doses with increasing accuracy and precision, better avoidance of surrounding organs-at-risk (OAR) and therefore decreased treatment-related toxicities [9]. However, the impact of many of these advances on oncologic outcomes remains to be demonstrated.

Improvements in radiotherapy planning, target definition, and dose-calculation systems initially translated into the clinical use of 3D-conformal radiotherapy (3DCRT) which successfully reduced treatment-related toxicities [10] and supported subsequent developments. Of these, robust optimization algorithms and the capability of radiation beam-shaping rapidly crystalized in the adoption of today's widely-used intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). Expectedly, IMRT showed further improvements in resulting dose distributions translating in better toxicity profiles [9,11,12]. However, consistent anatomical alignment during treatment delivery while using very highly-conformal techniques for a moving target such as the prostate has remained a concern [13].

A more recent breakthrough in our field has been image-guidance (IG) to reduce geometric uncertainties, and to increase the precision and accuracy of EBRT treatments. In PCa, IG can be achieved by kV/MV orthogonal imaging of intra-prostatic fiducial

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http://dx.doi.org/10.1016/j.radonc.2017.04.003
0167-8140/

markers or volumetric cone-beam CT (CBCT) [14]. Addition of daily IG to 3DCRT has been associated with significant reductions in gastrointestinal (GI) toxicity [15], and reduction in both genitourinary (GU) and GI symptoms when added to IMRT, despite the use of higher prescription doses [16]. Importantly, in a single institution experience the addition of IG to DE IMRT was associated with improvement in biochemical control outcomes [17]. Nonetheless, the benefit of DE in the context of precise daily IGRT remains undetermined.

In our institution, daily IG was put into practice simultaneously to 3DCRT implementation for PCa, and preceded subsequent DE schedules and IMRT/VMAT use. In this study, we aimed to compare disease-specific outcomes and toxicity profiles among three sequential cohorts treated with progressive DE schedules in the context of curative-intent IGRT for localized PCa.

Materials and methods

From July 1st, 1998 to December 31st, 2012 patients who were treated with prostate-only 3DCRT or IMRT for T1-3N0M0 prostate cancer with radical radiotherapy at Princess Margaret Cancer Centre were included (Table 1). All patients had reviewed biopsy-proven prostate adenocarcinoma with in-house available blocks for translational studies, and were staged according to the American Joint Committee on Cancer staging (AJCC) criteria. Patients were categorized into low-, intermediate-, and high-risk groups according to National Comprehensive Cancer Network (NCCN) criteria. Intermediate-risk group was further sub-categorized into favorable and unfavorable groups according to the Zumsteg–Spratt classification [18]. Toxicity was collected from regular follow-up visits using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 definitions. Androgen deprivation therapy (ADT) use was defined as LHRH agonist or antagonist administered prior to and/or concurrent with the radiation treatment.

Departmental standard included three prostate-only dose-fractionation schedules over time, namely (A) 75.6 Gy (1.8 Gy per fraction for 42 fractions), delivered by six-field 3DCRT, with intraprostatic fiducial markers and daily IG by electronic portal imaging device (EPID); (B) 79.8 Gy (1.9 Gy per fraction for 42 fractions), delivered similar to (A); and (C) 78 Gy (2 Gy per fraction for 39 fractions), delivered by IMRT or VMAT, with daily CBCT image-guidance. All patients were planned and treated with a bowel and bladder protocol. For target and OAR delineation, dedicated CT simulation image sets were used as per institutional policy. MRI was not used routinely in these cohorts.

In patients treated with EPID-based IG, three gold fiducials were implanted into the base, mid-portion and apex of the prostate under trans-rectal ultrasound guidance and local anesthesia, at least three days prior to CT simulation. Image guidance was performed by MV imaging prior to each radiation fraction. Patient position was corrected if the discrepancy was 3 mm or more in any direction. Cone beam CT (CBCT) became the institutional standard during spring 2007. Volumetric CBCT was acquired prior to radiation delivery on each fraction, and corrections made according to same thresholds based on fiducials' or soft-tissues discrepancies.

For the entire period of this study, clinical target volume (CTV) was defined as the prostate, and the base (1–2 cm) of the seminal vesicles in select cases, and subsequently a planning target volume (PTV) was created by adding 1 cm isotropic expansion in all directions, except 7 mm posteriorly. In group A, patients were treated with 6 beam coplanar 3DCRT technique (two laterals, two anterior obliques, two posterior obliques), using 18 MV photon energy and multi-leaf collimators (MLC). Dose prescription was to the ICRU point [19]. Group B was planned and treated similar to group A [20]. Group C was treated with IMRT or VMAT technique, with 99% of CTV volume receiving the prescription dose (78 Gy), so that 99% of PTV volume (D99%) would receive at least 95% of the prescription dose [21].

Follow up after radiation was done according to institutional policies, with physical examination and PSA ascertainment every 3–6 months for the first 5 years and annually afterward. Primary endpoint was biochemical recurrence (BCR), defined by Phoenix criteria (nadir PSA plus 2 ng/mL) [22]. Metastasis-free rate, prostate-cancer-specific survival and overall survival were secondary endpoints. Data on dead/alive status was gathered from provincial Cancer Care Ontario (CCO) registry. The information on BCR, metastasis and cause of death were collected from patients' electronic medical records. The times to BCR, metastasis and survival were calculated from the start of radiation treatment (RT) to the date of respective event, or to the last PSA analysis/clinical visit date in cases where no event was observed. With the exception of overall survival, all other endpoints had competing events. The competing risk event for BCR was death without BCR, for metastasis was death without metastasis and for cause-specific death was death from other causes.

Table 1
Patient characteristics and their distribution among three dose schedules.

	Total (n = 961)	75.6 Gy (n = 293)	79.8 Gy (n = 313)	78 Gy (n = 355)	p value (Between dose schedules)
Age Median (Range)	71.63 (44.58–86.78)	70.6 (49.7–83.7)	71.8 (44.6–83.7)	72.2 (48.3–86.8)	**0.0024**
PSA < 10	652 (68%)	190 (64.8%)	218 (69.6%)	244 (68.7%)	0.49
PSA [10–20]	263 (27%)	91 (31.1%)	78 (24.9%)	94 (26.5%)	
PSA > 20	46 (5%)	12 (4.1%)	17 (5.4%)	17 (4.8%)	
cT1	424 (44%)	133 (45.4%)	135 (43.1%)	156 (43.9%)	0.34
cT2	520 (54.3%)	158 (53.9%)	173 (55.3%)	189 (53.2%)	
cT3	17 (1.7%)	2 (0.7%)	5 (1.6%)	10 (2.8%)	
GS 3–6	281 (29.2%)	84 (28.7%)	104 (33.2%)	93 (26.2%)	**0.0021**
GS 3 + 4	406 (42.2%)	102 (34.8%)	141 (45%)	163 (45.9%)	
GS 4 + 3	196 (20.4%)	74 (25.3%)	50 (16%)	72 (20.3%)	
GS 8–10	78 (8.2%)	33 (11.3%)	18 (5.8%)	27 (7.6%)	
LR	179 (18.6%)	52 (17.7%)	64 (20.4%)	63 (17.7%)	0.48
IR	653 (67.9%)	194 (66.2%)	213 (68.1%)	246 (69.3%)	
HR	129 (13.5%)	47 (16%)	36 (11.5%)	46 (13%)	
fIR	248 (37.9%)	66 (34%)	90 (42.3%)	92 (37.4%)	0.23
ufIR	405 (62.1%)	128 (66%)	123 (57.7%)	154 (62.6%)	
ADT	100 (10.4%)	39 (13%)	26 (8%)	35 (10%)	0.12

PSA: serum prostate-specific antigen (ng/mL); GS: Gleason score; LR: low risk; IR: intermediate risk; HR: high risk; fIR: favorable intermediate risk; ufIR: unfavorable intermediate risk; ADT: Androgen deprivation therapy.
Significant p values (<0.05) are highlighted with bold font.