Clinical Outcomes of Dose-escalated Radiotherapy for Localised Prostate Cancer: A Single-institution Experience

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Abstract. Background/Aim: To report the outcomes of patients with prostate cancer treated with dose-escalated radiotherapy over a 15-year period at our Institution. Patients and Methods: Patients with biopsy-proven cT1-4N0M0 disease who received radical external beam radiotherapy (EBRT) were reviewed. The endpoints were 5-year overall survival (OS), freedom from biochemical failure (FFBF) and late treatment toxicities. Results: A total of 236 patients were eligible. Median follow-up was 70 months. Low-, intermediate- and high-risk disease was found in 9%; 29% and 62% of patients, respectively. The median radiation dose was 73.8 Gy. Overall 42% of patients had dose escalation to >74 Gy. Five-year OS and FFBF were 95.2%/81.6%/75.4% and 95.0%/98.0%/82.0% for low-/intermediate-/high-risk patients, respectively. Dose escalation to >74 Gy did not improve FFBF (hazard ratio=0.97, 95% confidence interval=0.43-2.19, \( p=0.93 \)) and was associated with a 4.3-fold increase in the odds of grade 3 or more rectal bleeding (\( p<0.01 \)). Conclusion: Dose escalation to >74 Gy did not improve OS or FFBF but was associated with a higher rate of grade 3 or more rectal haemorrhage.

Prostate cancer is one of the most common types of cancer among men in Singapore, accounting for one in every seven cancer diagnoses (1). Following a rising incidence in recent years, more than 4,000 new cases were diagnosed between 2011-2015, in part due to an ageing population as well as enhanced awareness and opportunistic screening (2-4).

External beam radiotherapy (EBRT) is one of the curative treatments for clinically localised prostate cancer, with disease-specific survival comparable to that for radical prostatectomy (5, 6). Long-term toxicities following RT, particularly relating to bowel function, remain problematic (7). The advent of intensity-modulated radiotherapy (IMRT) as the standard of care for delivery of prostate EBRT has resulted in improved biochemical control through dose escalation whilst reducing treatment-related toxicity (8-10). However, to date there are limited reports detailing the treatment of prostate cancer utilising modern RT techniques in an Asian population, despite the trend of increased disease burden. This study aimed to review both the clinical and toxicity outcomes of RT dose escalation in a patient cohort treated at a tertiary centre in Singapore.

Patients and Methods

Patients. Approval for this study was obtained from the Institutional Review Board (NHG 2017/00934). Patients with biopsy-proven prostate cancer who received curative-intent EBRT with or without androgen deprivation therapy (ADT) at our Institution between January 2002 and December 2015 were retrospectively reviewed. Pelvic computed tomography/magnetic resonance imaging, and bone scan were used for staging. Patients with clinical/radiological nodal or distant metastases were excluded. Patients who received prostate brachytherapy were excluded. D’Amico classification was used to categorise eligible patients into low-, intermediate- and high-risk groups based on initial prostate-specific antigen (PSA) level, tumour stage (American Joint Cancer Committee seventh edition) and Gleason score (11).

Radiotherapy. All patients received EBRT in 1.8-2.0 Gy daily fractions, 5 days a week, with bladder and bowel preparation according to Department protocol. Treatment was delivered via 3-dimensional conformal (3D-CRT) technique or IMRT from 2006 onwards. The planning target volume (PTV) for patients treated with IMRT consisted of the clinical target volume (CTV) with a 1-cm circumference except for posterior prostate-rectum interface where a 0.5 cm margin was adopted. Prior to 2009, patients with low-, intermediate- and high-risk prostate cancer were treated to a standardised dose of 73.8 Gy in 41 fractions. After 2009, the dose...

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prescriptions and target volumes were as follows. Low-risk patients were treated to 78 Gy in a single phase with CTV including the whole prostate. Intermediate- and high-risk patients were treated in two phases to a total of 79.2 Gy: Phase one CTV encompassed the whole prostate and bilateral seminal vesicles to 54 Gy in 27 fractions, phase two boosted the prostate and proximal seminal vesicles by an additional 25.2 Gy in 14 fractions. Additional whole pelvis irradiation was given to patients with >15% risk of pelvic lymph node involvement according to the Roach formula (12). Where prescribed, 48.6 Gy in 27 fractions was delivered to the pelvic lymph nodes during phase one with a simultaneous integrated boost technique.

**ADT.** In addition to EBRT, intermediate- and high-risk patients received ADT in the form of luteinizing hormone-releasing hormone agonist as a subcutaneous injection for 4-6 months and 2-3 years respectively. At least 2 months of neoadjuvant ADT is given prior to initiation of RT.

**Data collection.** Clinical data were obtained through institutional electronic medical records and RT databases. Information recorded included details pertaining to patient demographics (age, ethnicity, performance status), disease characteristics (histology, Gleason score, PSA level, clinical T stage), RT parameters (technique, total dose, dose-fractionation, whole pelvis irradiation), ADT (type, timing and duration), long-term complications (incidence of rectal bleeding/haemorrhagia, cardiotoxicity in patients who received ADT as indicated by acute myocardial infarction (AMI) or abnormal echocardiograms, as well as treatment outcomes (biochemical recurrence, pattern of locoregional/distant metastasis, cause of death). Follow-up data based on patients’ clinical records were collected until their time of death or the most recent review up to August 2018.

**Follow-up.** Patients were followed up post RT completion as per department protocol at 6 weeks, 3-monthly until the end of year 2, 6-monthly until the end of year 5 and annually thereafter until end of year 10. PSA testing was performed at every follow-up visit. Restaging work-up was carried out if clinically indicated.

**Clinical outcomes.** The primary endpoint was 5-year overall survival (OS), defined as the time from first treatment to death due to any cause or the last follow-up. The secondary endpoint was 5-year freedom from biochemical failure (FFBF) as per Phoenix definition, *i.e.* a documented PSA rise by 2 ng/ml or more above the nadir level (13).

**Toxicity outcomes.** Treatment toxicities were graded based on Common Terminology Criteria for Adverse Events (CTCAE) version (v) 4.03 (14). We focused on rates of rectal haemorrhage, haemorrhagia as well as incidence of urethral stricture post RT. Grade 2 rectal haemorrhage was defined as rectal bleeding requiring medical intervention (*e.g.* steroid enemas) with/without a single elective endoscopic evaluation with argon plasma coagulation/no intervention. Patients who underwent two or more sessions of argon plasma coagulation, rectal formalin application, hyperbaric oxygen therapy with/without blood transfusion(s) as a result of rectal bleeding were coded as experiencing grade 3 adverse events. For radiation cystitis, patients who developed gross haemorrhagia necessitating elective endoscopic intervention (*e.g.* cystodiathermy),

| Characteristic | Value |
|---------------|-------|
| Follow-up duration, months | 70.1 (1.43-169) |
| Age at diagnosis, years | 72 (48-89) |
| ECOG performance status, n (%) | 0 28 (11.9) 1 193 (81.8) 2 15 (6.3) |
| Smoking habit, n (%) | Current smoker 11 (4.7) Never smoker 45 (19.1) Ex-smoker 48 (20.3) Unknown 132 (55.9) |
| Use of aspirin, n (%) | Yes 50 (21.2) No 186 (78.8) |
| Pre-existing ischaemic heart disease, n (%) | Yes 20 (8.6) No 314 (71.2) |
| MRI pelvis/prostate, n (%) | Yes 75 (31.8) No 161 (68.2) |
| CT abdomen/pelvis, n (%) | Yes 151 (64.0) No 85 (36.0) |
| Bone scan, n (%) | Yes 212 (89.8) No 24 (10.2) |
| Histology, n (%) | Acinar adenocarcinoma 232 (98.3) Other 2 (0.8) Unknown 2 (0.8) |
| Gleason grade group, n (%) | 1 62 (26.6) 2 52 (22.3) 3 36 (15.5) 4 39 (16.7) 5 44 (18.9) Unknown 3 (1.3) |
| Pre-treatment PSA, ng/ml | Median (range) 17.3 (0.87-530.4) |

**CT:** Computed tomography; ECOG: Eastern Cooperative Oncology Group; MRI: magnetic resonance imaging; PSA: prostate specific antigen; *D’Amico risk categories: Low-risk: Gleason score <6, PSA <10 ng/ml and clinical stage T1c or T2a; Intermediate-risk: Gleason score 7 or PSA 10-20 ng/ml or clinical stage T2b; High-risk: Gleason score 8-10 or PSA >20 ng/ml or clinical stage T2c, T3, T4.**
blood transfusion or hospitalisation were coded as experiencing grade 3 adverse events. Required treatment (if any) for urethral strictures diagnosed post RT was documented.

**Statistical analysis.** Univariable and multivariable Cox proportional hazard regression models were performed to identify independent factors with significant impacts on patient survival. OS was calculated using the Kaplan-Meier method. The statistical level of significance for all tests was set at 0.05. Analyses were performed using STATA version 14 (Stata Corp., College Station, TX, USA).

## Results

### Patient characteristics.

A total of 236 eligible patients were identified, with a median follow-up period of 70.1 months (range=1.43-169) as shown in Table I. The median age at diagnosis was 72 (range=48-89) years. The majority of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 (93.6%). According to D’Amico risk classification, 21 (8.9%), 69 (29.2%) and 146 (61.9%) patients had low-, intermediate- and high-risk disease respectively.

### RT and ADT.

Treatment characteristics are outlined in Table II. The median prescribed radiation dose was 73.8 Gy (range=70.2-82.2 Gy). IMRT technique was used in 204 (86.4%) patients, while 3D-CRT was used to treat the in the remaining 32 patients (13.6%). The full prescribed course of RT was completed in 233 (98.7%) patients. Dose escalation to 74 Gy or more was achieved in 99 (42.0%) patients. Whole pelvis radiation was given in 173 (73.3%) patients.

ADT was given to 206 (87.3%) patients mainly in the form of 1- and 3-monthly subcutaneous leuprolide at a dose of 3.75 mg and 11.25 mg or subcutaneous goserelin at a dose of 3.6 mg and 10.8 mg lasting for the planned duration of hormone therapy. Of the patients who received ADT, 164 (79.6%) had more than 6 months of treatment.

### Patterns of recurrence.

Overall, 24 (10.2%) patients developed biochemical recurrence during follow-up, most (87.5%) of whom had high-risk disease. Distant metastases developed in 27 (11.4%) patients in the same time period. Of these, 19 (70.4%) had disease to bone, 5 (26.3%) to lung, 8 (33.9%) to lymph nodes below diaphragm, 3 (10.3%) to lymph nodes above diaphragm, and 1 (3.4%) to the liver. There were no local recurrences detected in the prostate.

### Cause of death.

At the end of the follow-up period, 45 (19.1%) patients had died, of whom four (8.9%) as a consequence of metastatic prostate cancer, all of whom had high-risk disease. Seven deaths (15.6%) were attributed to cardiac causes including AMI, all had been treated with ADT (mean duration=2.6 years) and five had pre-existing ischaemic heart disease.

### Clinical and toxicity outcomes.

The overall 5-year OS for all patients was 79.2%. For low-, intermediate- and high-risk patient groups, the 5-year OS was 95.2%, 81.6% and 75.4%, and the 5-year FFBF was 95.0%, 98.0% and 82.0% respectively (Table III). The Kaplan-Meier survival estimates for FFBF and OS by risk categories are shown in Figures 1 and 2.

Univariable analysis showed that Gleason grade group 4 and 5 [hazard ratio (HR)=2.22, 95% confidence interval (CI)=1.05-4.66, p=0.036; and HR=2.34, 95% CI=1.16-4.74, p=0.018], D’Amico high-risk category (HR=5.69, 95% CI=1.38-23.40, p=0.016) and ECOG PS 2 (HR=17.86, 95% CI=4.96-64.24, p=0.001) were significantly associated with

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**Table II. Treatment characteristics (N=236).**

| Characteristic                                      | Value                  |
|-----------------------------------------------------|------------------------|
| Prescribed radiation dose, Gy*                      | Median (range)         |
|                                                     | 73.8 (70.2-82.2)       |
| Radiation technique, n (%)                          |                        |
| 3D-CRT                                             | 32 (13.6)              |
| IMRT or Arc therapy                                | 204 (86.4)             |
| Dose escalation to ≥74 Gy, n (%)                    |                        |
| Yes                                                 | 137 (58.0)             |
| No                                                  | 99 (42.0)              |
| Whole pelvis radiation therapy, n (%)               |                        |
| Yes                                                 | 173 (73.3)             |
| No                                                  | 59 (25.0)              |
| Unknown                                             | 4 (1.7)                |
| Neoadjuvant; concurrent/adjuvant ADT, n (%)         |                        |
| Yes                                                 | 206 (87.3)             |
| No                                                  | 30 (12.7)              |
| ADT duration ≥6 months (N=206), n (%)               |                        |
| Yes                                                 | 164 (79.6)             |
| No                                                  | 42 (20.4)              |

3D-CRT: 3-Dimensional conformal radiation therapy; IMRT: intensity-modulated radiation therapy; ADT: androgen-deprivation therapy. *Equivalent dose in 2 Gy fractions.

**Table III. Clinical outcomes.**

| D’Amico risk group | 1-Year | 3-Year | 5-Year | 1-Year | 3-Year | 5-Year |
|--------------------|--------|--------|--------|--------|--------|--------|
| All                | 97.5   | 88.5   | 79.2   | 100.0  | 95.2   | 95.0   |
| Low-risk           | 100.0  | 95.2   | 95.2   | 100.0  | 95.2   | 95.0   |
| Intermediate-risk  | 97.1   | 89.5   | 81.6   | 100.0  | 100.0  | 98.0   |
| High-risk          | 97.3   | 87.1   | 75.4   | 96.5   | 92.0   | 82.0   |

OS: Overall survival; FFBF: freedom from biochemical failure (Phoenix criteria).
an increased hazard of death. RT technique (IMRT vs. 3D-CRT) and dose escalation to ≥74 Gy were not significantly associated with OS on both univariable and multivariable analyses (Table IV).

On the other hand, only Gleason grade group 3 and 5 (HR=3.80, 95% CI=1.40-10.31, p=0.009, and HR=3.75, 95% CI=1.47-9.58, p=0.006) were significantly associated with an increased risk of biochemical failure (Table V). Dose

Figure 1. Freedom from biochemical failure by prostate cancer risk category according to Kaplan-Meier survival estimates.

Figure 2. Overall survival by prostate cancer risk category according to Kaplan-Meier survival estimates.
escalation to ≥74 Gy did not significantly improve FFBF (HR=0.97, 95% CI=0.43-2.19, p=0.93).

The cumulative incidence of grade 3 rectal bleeding and haematuria were 9.3% and 1.7%, respectively. There were no grade 4 or 5 toxicities reported (Table VI). The median onset of grade 3 rectal bleeding from start of EBRT was 14.7 months (range=6.2-58.7 months). Logistic regression showed that dose escalation to ≥74 Gy increased the odds of developing grade 3 or more proctitis by 4.3 times (p=0.004). No positive correlation was demonstrated between RT technique (IMRT vs. 3D-CRT), whole pelvis RT or the use of aspirin (Table VII). Urethral stricture developed in 14 (5.9%) patients, of which nine (64.3%) required intervention such as dilatation and optical urethrotomy.

AMI developed in 28 (11.9%) patients during follow-up, eight (28.6%) of whom had documented pre-exiting ischaemic heart disease (IHD). ADT was given to 26 (92.9%) patients for an average of 1.8 years. The mean interval of onset of AMI after first RT fraction was 4.0 years. The use of ADT did not appear to be significantly associated with increased odds of developing AMI during or after treatment [odds ratio (OR)=4.40, 95% CI=0.58-33.63, p=0.153].

### Discussion

In our study of 236 patients with node-negative non-metastatic prostate cancer who underwent definitive EBRT with or without ADT, 5-year OS was 95.2%, 81.6% and 75.4%; and FFBF was 95.0%, 98.0% and 82.0% for low-, intermediate- and high-risk patients, respectively. This is comparable with internationally published data (5, 15, 16). To our knowledge this is the largest series reporting prostate cancer outcomes after RT in South-East Asia.

This cohort comprised a sizable number of D’Amico high-risk patients (61.9%) and the majority were treated with IMRT (86.4%). Although dose escalation to between 74-80 Gy has been shown to improve FFBF in multiple previous trials (17-20), particularly in patients with intermediate- to high-risk disease (9, 21, 22), our results suggest that there was no significant reduction in biochemical recurrence or survival benefit seen at 5 years. The reason for this apparent difference may be two-fold. Firstly, our study included a significant proportion of patients treated with ADT. Long-term results from several large randomised trials have demonstrated that ADT reduced biochemical failure and improved OS in patients with intermediate- to high-risk disease (23-26). However, ADT use was typically excluded in the aforementioned dose-escalation trials (17, 18, 21, 22), accounted for only a small proportion of the cohort (19), or was limited to a short duration (neoadjuvant and concurrent) (20). In our study, 87.3% of the patients received ADT and 79.6% were treated for more than 6 months in duration. This may have contributed to overall better biochemical and survival outcomes, neutralising the potential benefit of dose escalation. Secondly, the median follow-up of 70 months (5.8 years) in our study was relatively shorter than the
average for dose-escalation trials which regularly followed-up patients for more than 10 years, thereby accruing a larger number of events (biochemical recurrences and deaths) which may in turn translate into therapeutic benefit.

Controversy remains concerning the association between ADT use and cardiovascular complications. Mechanisms proposed include insulin resistance and impaired arterial vasculature function secondary to induced hypogonadism. Results from large observational studies suggest that men more than 65 years of age are especially susceptible (27-29). However, conflicting evidence from multiple randomised phase III trials showed that neoadjuvant, and adjuvant as well as total longer duration of ADT (up to 28 months) were not associated with increased cardiovascular mortality (30-32). With regards to cardiac morbidity, in a large propensity-matched analysis of more than 19,000 ADT users and non-users, Alibhai et al. found ADT not to be associated with increased AMI at 6.5 years of follow-up (33). Our results were in line with this. However, owing to the fact that the number of events in our study was fairly small (28 AMIs and seven cardiovascular-related deaths), longer follow-up of a larger patient population is required for a more definitive conclusion.

Late rectal and bladder toxicity are common after prostate EBRT, frequently manifesting as haemorrhage secondary to formation of friable neovasculature and non-healing mucosal ulceration, on the background of fibrosis and chronic ischaemia (34, 35). Multiple patient (e.g. anticoagulation, comorbidities such as diabetes mellitus, inflammatory bowel disease) (31, 36), disease and radiation characteristics (e.g. total dose, dose per fraction, irradiated organ-at-risk volume, delivery modality) (9, 10, 35, 37) have been suggested to play a part. Unfortunately, there is considerable variation amongst studies looking at the incidence of chronic radiation proctitis/cystitis owing to the lack of consensus on its reporting and definition. Furthermore, significant heterogeneity in patient selection, dose/modality of radiotherapy, presence or absence of adjunct use such as rectal balloon, concomitant use of ADT and duration of follow-up limits the value of direct comparison.

This difficulty is emblematic of the accuracy and consistency of radiation toxicity results analysis across multiple studies through time. Zhen et al. investigated the utilisation patterns of three most commonly used standards for grading tissue toxicities induced by radiation (38). They found that the CTCAE system (39) has been gaining in vivo 34: 757-765 (2020)
lung, breast and prostate studies, alongside the Radiation Therapy Oncology Group grading scale (40). In our study, the CTCAE grading system was chosen given that it is the most up-to-date, comprehensive and developed by drawing on the strengths of previous instruments. Focus was placed on the incidence of rectal bleeding and haematuria, which lends itself to further endoscopic investigation. The cause of symptoms, radiation-induced or otherwise, may be determined more objectively. This is in contrast with other symptoms such as urinary frequency or urgency which may be indicative of or compounded by background prostatic hyperplasia.

When managing patients presenting with radiation-induced rectal haemorrhage or haematuria, many clinicians may elect to withhold any antiplatelet or anticoagulation agents. Interestingly, the daily use of aspirin (100 mg) approached significance as a protective factor for more than grade 3 rectal bleeding (OR=0.26, \( p=0.072 \)) in our study. Aspirin is a commonly used drug in the prostate cancer population, and, through mechanisms not yet completely elucidated, has been associated with 5-year FFBF benefit in high-risk patients treated with both EBRT and radical prostatectomy, and OS benefit for the Gleason 9-10 subset (41, 42). Data are conflicting, however, regarding its potential role in exacerbating acute and late toxicities. Choe et al. reported that 79 patients who received warfarin or clopidogrel during prostate EBRT had significantly increased risk of developing more than grade 3 bleeding toxicity (15.5% vs. 3.6%, \( p<0.0001 \)), and that use of IMRT modality in this group actually further enhanced the bleeding risk (31). On the other hand, Mikell et al. showed that in 210 patients on low-dose aspirin during EBRT, acute genitourinary toxicity was reduced (OR=0.73, \( p=0.40 \)) (43). In addition, there was a trend towards reduced late gastrointestinal toxicity (OR=0.69, \( p=0.056 \)), echoing the results of the current study. This suggests a possible unique anti-inflammatory effect of aspirin (over other antiplatelet/anticoagulation agents) which counteracts radiation-induced acute and late tissue injuries, which warrants further investigation.

The strengths of this study are: Firstly, target volume contouring was standardised in accordance to the Radiation Therapy Oncology Group contouring atlas (43). Secondly, all treatment plans were subjected to peer review within 1 week of escalation RT. Thirdly, the follow-up in our study was relatively short. Longer follow-up is needed to detect any differences in OS and FFBF in patients treated with dose-escalation RT.

In conclusion, our results demonstrated favourable survival and biochemical outcomes for clinically localised prostate cancer treated with EBRT, in a cohort that consisted of >60% with high-risk disease. Whilst dose escalation to beyond 74 Gy did not appear to increase biochemical control or improve OS, it came at a cost of increased rectal haemorrhage. Further prospective studies are needed to explore the value of dose escalation in risk-matched patient cohorts treated with and without ADT. Longer follow-up is required to refine survival and late toxicity outcomes. Harmonisation of radiation toxicity scoring and reporting within the research community is imperative to inform future developments in prostate cancer management.

**Conflicts of Interest**

The Authors declare no conflicts of interest with regard to this study.

**Authors’ Contributions**

KM: Data collection, interpretation of data, manuscript writing; KL: Interpretation of data, revision of article; CCL: Interpretation of data, revision of article; DC: Interpretation of data, revision of article; KHO: Interpretation of data, revision of article; YYS: Interpretation of data, revision of article; JT: formulated the protocol, data collection, data analysis, interpretation of data, article writing.

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