RESEARCH ARTICLE

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Retrospective Analysis of Clinical Outcomes of Stereotactic Body Radiation Therapy for Localized Prostate Cancer at an Asian Cancer Specialist Centre

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Abstract

Introduction: The current treatment options for localized prostate cancer are radical prostatectomy and external beam radiotherapy (EBRT) with stereotactic body radiation therapy (SBRT) gaining interest as a treatment option compared to standard fractionation radiation therapy. This present study is a retrospective study evaluating the correlations between the biochemical efficacy, and treatment toxicity in SBRT for localized prostate cancer. **Methods:** All organ-confined prostate cancer patients treated with SBRT from 2010 to 2018, at Beacon Hospital, Malaysia were included in this study. Patient demographics, dosimetric parameters, and disease information were retrospectively collected. The primary endpoint was biochemical recurrence-free survival assessed using the Phoenix definition (Nadir + 2 ng/mL). Toxicity outcomes were scored using the Radiation Therapy Oncology Group scale. **Results:** Fourty-nine patients who met the inclusion criteria (5 low-, 13 intermediate- and 31 high-risk according to the D'amico Risk Classification) received SBRT. The most common dose regime was 34-35Gy in 5 fractions (n=18). Other dose regimes were 24Gy in 3 fractions and 25-33Gy in 5 fractions. Median follow-up was 45.4 months. The median pre-treatment prostate-specific antigen (PSA) was 11.22 ng/mL, which decreased to a median PSA of 0.1 ng/mL by 2 years post-treatment. Out of the 49 cases, only 1 case of biochemical recurrence occurred, yielding a 3- and 5-year overall survival of 100%, and a 3- and 5- year biochemical recurrence-free rate of 100% and 95.2%. Acute grade III urinary toxicities occurred in 1 (2%); whereas acute grade I urinary and rectal toxicities were seen in 22 (44.9%) and 7 (14.3%) patients respectively. Grade I and grade III late rectal toxicities occurred in 3 and 1 patients respectively, while 3 and 1 patient reported late grade I and III urethral stricture respectively. **Conclusion:** SBRT for clinically-localized and locally advanced prostate cancer provided promising outcomes with low toxicity and good biochemical control.

Keywords: Stereotactic body radiotherapy- localized prostate cancer- outcome- survival

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Introduction

Prostate cancer (PCa) has been reported to have the highest burden of cancer, indicated by the highest disability-adjusted life-years (DALYs) globally, reflecting the confluence of its high incidence, high cure rate, and treatment associated morbidity (Soerjomataram et al., 2012). Subclinical prostate cancer is common in men aged 50 years and above, and most patients with PCa are diagnosed with clinically localized disease, with the majority having low to intermediate risk of disease (National Comprehensive Cancer Network, 2020). The current management options for PCa includes definitive external beam radiotherapy (EBRT), radical prostatectomy, brachytherapy and watchful waiting for patients with low- and intermediate-risk disease; with radiation demonstrating a near 98% of overall cure rate (Hannan et al., 2014).

Typically, definitive EBRT has been delivered in small daily doses of 1.8 to 2.0 Gy spread across 39-45 fractions (Brenner and Hall, 1999). However, there have been a number of studies suggesting a link between higher doses per fraction and increased sensitivity of PCa to radiation by virtue of a low α to β ratio (a proxy for radiosenstivity) (Brenner and Hall, 1999), implicating that hypofractionation may potentially improve isoeffective oncologic results within a shorter time frame. Studies utilizing moderate hypofractionation has demonstrated it to be non-inferior in terms of both efficacy and safety when compared to conventionally fractionated radiation (Dearnaley et al., 2016; Lee et al., 2016; Catton et al., 2017).

Ultra-hypofractionation, or more commonly known as Stereotactic radiation (SBRT) is a form of EBRT in

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which large doses of radiation is delivered per fraction over a short period of time. Since the introduction of this technique in 2000, multiple trials have been conducted and reported favourable outcomes (King et al., 2013; Kishan and King, 2017), which then led to the recommendation from National Comprehensive Cancer Network, NCCN on adopting this technique should the institution demonstrate adequate technology, physics and clinical expertise, although randomized phase III data is still lacking.

Nonetheless, this treatment technique has not been widely adopted because of concerns over long-term safety and efficacy. There have been many reports on the short-term outcome of SBRT on prostate, but studies with longer follow up are still lacking. To date, this is the first study in Malaysia that has looked at the real-world outcomes of SBRT on men with prostate cancer.

Materials and Methods

Patients

This is a retrospective observational cohort study where all patients received treatment between January 1, 2009 to 31 December 2018 for prostate cancer treated with Cyberknife Robotic Radiosurgery System at Beacon Hospital, Petaling Jaya were included in this study. 81 patients were identified for this study. Cases were identified through the hospital's registry with further data retrieved from the radiotherapy records. Foreign patients, patients with metastatic disease and/or recurrent disease as well as concurrent malignancies; and patients with incomplete data sets were excluded from this study.

Treatment

Stereotactic body radiotherapy was delivered with a robotic arm–mounted linear accelerator (Accuray, Inc., Sunnyvale, CA, USA). Gold fiducial makers were placed in the prostate for real-time motion tracking during treatment. Organs at risk (OAR) were contoured and included bladder, rectum and femoral head. Dose volume constraints for the different OARs were determined according to the report of the American Association of Physicists in Medicine (AAPM) Task Group 101 (Benedict et al., 2010), with recommended maximum point doses for rectum and bladder of 28.2 Gy each in 3 fractions; and 38 Gy for rectum and 50 Gy for bladder in 5 fractions respectively. The clinical target volume (CTV) included the prostate and proximal 1 cm of the seminal vesicles depending on the risk. A margin of 2 mm in all other directions were added to the CTV to create the planning target volume (PTV).

In this study, the doses of SBRT ranged from 24 Gy to 34 Gy in 3 to 5 fractions (with 46 out of 49 patients [93.9%] receiving 5 fractions). Treatments were delivered on consecutive days and the prescribed dose was normalized to 65–85% isodose line. Patients' follow up information were retrospectively collected from the clinical notes and prostate-specific antigen (PSA) level information were also collected as recorded during routine surveillance.

Data collection

Medical records along with patient's histopathology reports (HPE) were abstracted. Patient demography to include age, ethnicity and nationality, tumour characteristics to include size, laterality, grade, staging; and treatment given and survival were all analysed descriptively. Ethics approval was obtained from Medical Research Ethics Committee (MREC ID: NMRR-19-2932-49404 (IIR)).

Statistical Analysis

Patients were stratified into low-, intermediate- or high risk as per the D'Amico Risk Classification based on initial PSA level, tumour stage and Gleason score (D'Amico et al., 1998). Biochemical recurrence (BCR) is defined using the Phoenix definition of a PSA level of 2ng/mL or higher than lowest post-SBRT value (nadir) (Roach et al., 2006). Additionally, physician-scored toxicity event outcomes were scored retrospectively, focusing on genitourinary (GU) and gastrointestinal (GI) toxicities. Scoring criteria for toxicities were done based on the Radiation Therapy Oncology Group (RTOG) criteria (Cox et al., 1995). Acute toxicity was defined as an adverse event occurring within the first 90 days after completion of SBRT.

All analyses were performed using MedCalc for Windows, version 19.0.4 (MedCalc Software, Ostend, Belgium). Two tailed p value of <0.05 was considered statistically significant. Kaplan-Meier analysis was done to perform estimate BCR-free survival, distant metastasis free survival and overall survival, with time to event set using the first day of SBRT as the starting point. This framework was also used to estimate the cumulative evidence of grade 3 or higher GU or GI toxicities. The log-lank test and Cox proportional-hazard model were used for univariate and multivariate analyses.

Results

Patient Characteristics and Treatment

Patient demographic and treatment characteristics are presented in Table 1. A total of 49 patients were included in this study. The median age of patients was 68 years (range, 48–85 years). The majority of the patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 (58%). The median initial PSA was 11.2 (range, 0.1–625) ng/ml and most patients (83.6%, 41/49) had disease confined to prostate (clinical stage ≤T2c), of which 8/49 (16.3%) were Stage 1, 19/49 (38.8%) Stage IIA, 14/49 (28.6%) Stage IIB and 8/49 (16.3%) Stage III based on AJCC TNM staging. According to D'amico risk classification, 5 (10.2%), 13 (26.5%), 31 (63.3%) patients had low-, intermediate- and high-risk disease respectively.

RT and ADT

Treatment characteristics are also outlined in Table 1. The median prescribed radiation dose was 34 Gy (range=24-35 Gy). Most of the patients (71.4%) received 3400 cGy, followed by 3500cGy (14.3%) and the treatment was delivered on consecutive days for all patients.

Fourty (81.6%) patients received neoadjuvant,

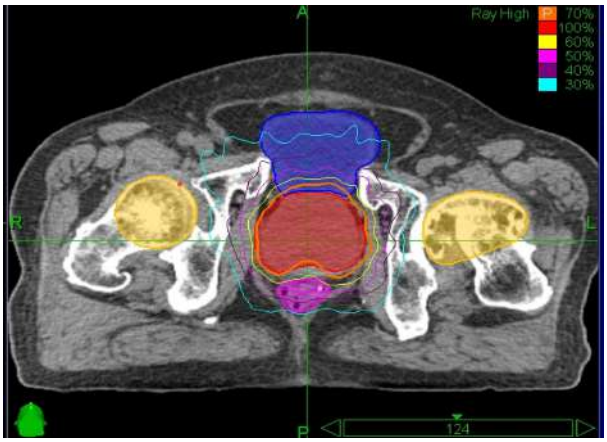

Figure 1. 34 Gy Delivered to the 70% Isodose Line, Tumor Coverage 97.66%, and Conformality index 1.23.

concurrent and adjuvant androgen deprivation therapy (ADT). ADT was given to patients mainly in the form of 1- and 3-monthly leuprolide at a dose of 3.75 mg and 11.25mg respectively or subcutaneous goserelin at a dose of 3.6mg and 10.8mg respectively lasting for the planned duration of hormone therapy. All of the patients had more than 6 months of treatment. A total of 22 men (44.9%) received ADT before radiation, with rates ranging from 20% (1 of 5) in patients with low-risk disease to 7.6% (1/13) and 64.5% (20 of 31) in patients with intermediate- and high-risk disease, respectively. The median duration of ADT until radiation was 1.8 months (range, 0.1-10 months). Meanwhile, 37 patients (75.5%) received concurrent and adjuvant ADT, with rates ranging from 60% (3/5) in the low-risk group to 84.6% (11/13) and 74.2% (23/31) in the high-risk group. The median duration of concurrent and adjuvant ADT was 15 months (range, 4 months to 36 months).

Recurrence and Disease Progression

Overall, 1 patient (2%), with high-risk disease, developed biochemical recurrence during follow up. The same patient also developed distant metastases to the bone in the follow up period, though there were no local recurrences detected in the prostate.

At the end of the follow-up period, none of the treated patient had died as a consequence of metastatic prostate cancer, yielding a prostate-cancer specific survival of 100%.

Follow up

The median follow-up period overall was 45.4 months (interquartile range [IQR], 23.2-71.0 months), and follow-up periods by risk group were as follows: low-risk, 67.65 months (IQR, 57.1-83.1 months); intermediate risk, 46.1 months (IQR, 29.7-68.3 months); and high-risk, 44.1 months (IQR, 16.9-71.8 months).

Treatment outcome and PSA kinetics

Out of the 49 patients, 1 patient, with high-risk disease, experienced BCR with a 5-year cumulative BCR incidence of 4.8% and the same patient developed distant metastases (DM) (2.0%), corresponding to a 5-year DM rate of 4.8%. The actuarial 5-year BCRFS was 95.2%. For low-, intermediate- and high-risk patient groups, the 5-year BCRFS was 100%, 100% and 91.7% respectively, with the hazard ratio for 5-year biochemical recurrence in the high-risk group, 1.0998; 95% confidence interval [CI], 0.08156 to 14.8308; P=0.6873. The median nadir PSA was 0.1ng/mL (range 0.0 – 5.2 ng/mL), and the median time to nadir was 18 months (0.0 – 34.0 months) in all patients. The median OS for the patients is not reached, with a 5-year OS of 100%. The actuarial five-year distant metastasis free survival rate (DMFS)

Table 1. Demographic Profile of Cohort

Characteristic	Value	
Age at diagnosis, years		
Median (range)	68 (48-85)	
Ethnicity, n (%)		
Malay	11 (22.4)	
Chinese	25 (51.0)	
Indians	6 (12.2)	
Others	7 (14.3)	
ECOG, n (%)		
0	21 (42.9)	
1	28 (57.1)	
Clinical Staging (TNM, AJCC), n (%)		
I	8 (16.3)	
IIa	19 (38.8)	
IIb	14 (28.6)	
III	8 (16.3)	
T Stage (TNM, AJCC), n (%)		
T1c	6 (12.3)	
T2a	10 (20.4)	
T2b	12 (24.5)	
T2c	13 (26.5)	
T3a	3 (6.1)	
T3b	5 (10.2)	
Gleason score, n (%)		
6	14 (28.6)	
7 (3+4, 4+3)	23 (46.9)	
≥8	12 (24.5)	
PSA at diagnosis (iPSA), ng/mL		
Mean (SD)	28.1 (88.4)	
Median (range)	11.2 (0.1 – 625.0)	
D'Amico Risk Classification (%)		
Low Risk	5 (10.2)	
Intermediate Risk	13 (26.5)	
High Risk	31 (63.3)	
Prescribed radiation dose, Gy		
Median (range)	34 (24-35)	
Neoadjuvant; concurrent/adjuvant Androgen Deprivation Therapy use, n (total,%)	ADT Use	Without ADT
Low risk	2 (40)	3 (60)
Intermediate risk	2 (15.4)	11 (84.6)
High risk	5 (16.1)	26 (83.9)

was 95%. For low-, intermediate- and high-risk patient groups, the 5-year DMFS was 100% and 100% and 91.7% respectively.

A total of 22 men (44.9%) received ADT before radiation, with rates ranging from 20% (1 of 5) in patients with low-risk disease to 7.6% (1/13) and 64.5% (20 of 31) in patients with intermediate- and high-risk disease, respectively. The median duration of ADT until radiation was 1.8 months (range, 0.1-10 months). Meanwhile, 37 patients (75.5%) received concurrent and adjuvant ADT, with rates ranging from 60% (3/5) in the low-risk group to 84.6% (11/13) and 74.2% (23/31) in the high-risk group. The median duration of concurrent and adjuvant ADT was 15 months (range, 4 months to 36 months).

To evaluate the PSA declining kinetics after SBRT excluding the effect of recurrence, 1 patient with biochemical recurrence were excluded. In the remaining 48 patients, the median nadir PSA value was 0.1, 0.1 and 0.09 ng/mL and median time to nadir was 7, 5 and 8 months after SBRT in low-, intermediate- and high-risk groups, respectively. There were no statistically significant differences in nadir value or time to nadir according to the risk groups (p=0.5).

Toxicity

Severe toxicities were uncommon in our study. Acute grade III GU toxicities occurred in 1 (2.0%) patient; whereas acute grade I GU and GI toxicities were seen in 22 (44.9%) and 7 (14.3%) patients respectively. Grade I and grade III late GI toxicities occurred in 3 and 1 patients respectively, while 3 and 1 patient reported late grade I and III urethral stricture respectively. No patients experienced grade ≥ 4 GU or GI toxicities, in both acute and late settings.

Discussion

A dose of >70Gy in conventionally fractionated radiotherapy for prostate cancer has shown improved biochemical control rates in previous studies, but is often associated with a higher risk of late toxicity, particularly in those who have received higher dose radiation (Dearnaley et al., 2007; Zietman et al., 2005; Zietman et al., 2010). There is growing interest in the use of hypofractionation in prostate cancer. This is based on findings that prostate cancer cells have a low alpha-beta ratio and therefore likely to benefit from a larger doses per fraction (Fowler et al., 2001; Brenner et al., 2002). Hypofractionation also has the advantage of shortening the overall treatment duration, making it much more convenient for patients compared to 8 weeks with conventionally fractionated RT.

In our study, 49 patients with node-negative non-metastatic prostate cancer who underwent SBRT with or without ADT, 5-year OS was 100%; and BCRFS was 95.2%. This finding is comparable with internationally published data (Alicikus et al., 2011; Hamdy et al., 2016; Aizawa et al., 2018). To our knowledge, this is the first study in Malaysia conducted to date evaluating SBRT administered by CyberKnife System in patients with localized prostate cancer.

It is interesting to note the phenomenon known as "benign PSA bounce" was seen in two patients after SBRT, who had at least one sequentially increased PSA value during their follow-up evaluation, typically of small magnitude with subsequent resumption of a declining trend after. One patient with a baseline PSA of 8.03ng/mL saw an initial PSA drop after SBRT, followed by a rise in PSA to 7ng/mL up to 8 months post SBRT before his PSA started to decline and continues to decrease currently at a 1.33ng/mL, with nadir not yet reached at 31 months post RT. For the other patient, who had a PSA baseline of 8.6ng/mL also experienced an initial drop in PSA after SBRT before rising to 8.42ng/mL at 12 months post SBRT then followed by a declining trend and eventually reaching a nadir at 0.02ng/mL at 34 months post treatment.

In our study, SBRT is associated with favourable disease control and safety profile for localized prostate cancer patients from low to high risks group consistent with the results in reported studies with 2-3 years of follow up (King et al., 2012; Chen et al., 2013; Oliai et al., 2013). In the present study, we only included patients with follow up of more than 1 year, hence providing a better overview on the late toxicities associated with SBRT. Our overall 5-year BCRFS of 95.2% is consistent with the results from this systematic review and meta-analysis of over 6000 patients (Jackson et al., 2019). In this meta-analysis of studies that reported rates by risk group, the 5-year BCRFS for low and intermediate-risk disease were 96.7% and 92.1% respectively; in comparison with our own results of excellent 5-year BCRFS of 100% in both groups. Our results are also comparable to those treated with surgery or brachytherapy (Beauval et al., 2016; Boehm et al., 2016; Matzkin et al., 2019; Park et al., 2020). Although 10-year data with a larger patient population are desirable to establish long-term efficacy, the fact that an "ablation" median PSA nadir level was obtained at a minimum post-SBRT follow-up interval of 5-years suggests that the DFS result will be durable and competitive with any other local prostate cancer treatment method described to date.

We reported low rates of Grade 3 late GU and GI toxicities of 2% and 4% respectively, in keeping with those reported in the literature (Jackson et al., 2019). The low rates of GI toxicity are achieved without the use of rectal spacers or balloons. This is likely due to the advantage of the Cyberknife system with real-time fiducial tracking which enabled much tighter margins to be employed, and therefore sparing more normal tissue.

This present study outcomes, along with previous study conducted demonstrated that SBRT is safe and effective for localized prostate cancer, with minimal impact on quality of life during and after treatment (Fuller et al., 2014; Park et al., 2018; Fuller et al., 2020).

In conclusion, despite majority of the subjects in the present study fell under the high-risk category, our findings reported favorable survival and biochemical outcomes for clinically localized prostate cancer treated with SBRT. However, future studies with a longer follow-up period are required to further assess the survival and late toxicity outcomes.

Author Contribution Statement

All authors contributed to protocol/project development and approval final version of manuscript

JST and BJC: data collection and analysis; manuscript writing/editing.

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Conflict of Interest Statement for all authors

All authors certify that they have no conflict of interest.

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