Original article

Treatment response in prostatic neoplastic lesions using CyberKnife (stereotactic body radiation therapy)

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ABSTRACT

Objective: To evaluate the treatment response of CyberKnife stereotactic radiotherapy in patients with prostatic neoplastic lesions.

Patients and methods: This prospective observational study was conducted at Radiology and Cyberknife Robotic Radiosurgery Department of Jinnah Post Graduate Medical Centre (JPMC), Karachi from 22nd June 2019 to 21st June 2020. Males with biopsy-proven prostatic adenocarcinoma with age 55 years or more having Gleason's score of 6 to 8, clinical stage of T1 to T2C, and prostate-specific antigen (PSA) of ≤30 ng/ml were consecutively enrolled. Detailed information regarding PSA concentration, Gleason score, T stage, risk group and ADT (Androgen Deprivation Therapy) usage were noted which were given to high risk patients only for 9 months. Drop in the PSA (biochemical marker) was assessed at baseline, at 3 months and 6 months follow-up.

Results: The median age of the patients was 65 years. The overall median PSA level was 2.7 (0.86-7.3) ng/ml. Majority 49 (90.7%) patients presented with T2 N0 M0 TNM status while only 5 (9.3%) patients presented with T1 N0 M0 TNM status. There were 5 (9.3%) patients with high risk, 26 (48.1%) with intermediate risk, and 23 (42.6%) with low risk. ADT was received by 5 (9.3%) patients. The median PSA at baseline was 10.1 (6.9-18.1) ng/ml which significantly drops to 1.6 (0.8-3.6) ng/ml at 3rd months, and 0.4 (0.2-1.2) at 6th months (p-value <0.01).

Conclusion: The findings showed an adequate treatment response of CyberKnife stereotactic radiotherapy of patients with prostatic neoplastic lesions.

Keywords

CyberKnife stereotactic radiotherapy, Response, Prostatic neoplastic lesions, Prostate-specific antigen, PSA, Androgen deprivation therapy

INTRODUCTION

Prostate cancer is one of most common cancer worldwide in males.[1] It is reported that due to increase advancement of diagnostic modalities, its prevalence is also growing remarkably.[2] The available treatment options to treat patients with capsule confined prostatic cancers are surgical or radiotherapy.[1-4] The radiotherapy management techniques include external beam radiation therapy (EBRT) and brachytherapy (BT).[3,4] With the development of new imaging modalities as computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy or PET-CT, it is more likely to detect a single or limited number or metastases at lower prostate-specific antigen (PSA) concentration level.[5,6] Improvements in the early detection of the disease relapse now allows to diagnose single or organ-limited metastases in patients with rising PSA after primary treatment. Conventional CT and MRI are approximately equivalent in detecting lymph node (LN) metastases, and all nodes exceeding minimal size of 8 to 15 mm could be considered as potentially involved.[7,8] Stereotactic ablative radiotherapy (SABR) is a radiation therapy in which very high doses of radiation are delivered in a small number of fractions. It is a painless and non-invasive procedure which can be used as an effective alternative to surgery. However, there is still dearth of studies on this topic in Pakistan. This study aims to evaluate the treatment response of CyberKnife stereotactic radiotherapy of patients with prostatic neoplastic lesions in local population.

PATIENTS AND METHODS

This prospective observational study was conducted at Radiology and Cyberknife Radiosurgery Department, Jinnah Post Graduate Medical Centre (JPMC), Karachi from 22nd June 2019 to 21st June 2020. Ethical approval was obtained from ethical committee of JPMC (IRB #:21229.) and signed informed consent was obtained from enrolled participants after explaining the pros and cons of the study. The inclusion criteria of the study were; (i) Biopsy proven prostatic adenocarcinoma male with age 55years or more, (ii) Gleason's score 6 to

Conflict of interest: The authors declared no conflict of interest exists.

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8, (iii) clinical stage of T1 to T2c, and (iv) PSA of ≤ 30 ng/ml. Whereas patients with following characteristics were excluded: (i) Prior surgery or radiotherapy for prostate cancer, (ii) Gleason scores 9 or 10 and (iii) clinical stage T3, or more. Risk group was divided in very low, low, intermediate, and high group, very high. The very low-risk group included T1c or lower stage patients with PSA ≤ 10 ng/ml, low-risk group included T1-T2 and PSA ≤ 10 ng/ml, intermediate-risk group comprised T2b or T2c patients with PSA10- 20 ng/ml, high-risk group T3a with PSA >20 ng/ml and very high-risk included T3-T4. Epi info sample size calculator is used for the estimation of sample size taking confidence interval 95%, margin of error 5%, reported percentage of patients without Androgen Deprivation Therapy (ADT) at follow-up 91.4%. The estimated sample size came out to be 54. Patients was irradiated using the CyberKnife system, comprising a 6MV linear accelerator installed on a robotic arm with six degrees of freedom. The system was connected to a robotic couch (six degrees of freedom) and a tracking system allowing correction of the patient position. For this purpose, three markers (Gold Anchors-fiducial marker, 1.5 to 6.0 mm in diameter) were implanted under transrectal ultrasound (TRUS) guidance, in a triangular-like configuration. To compensate for any migration, CT and MRI were done after 1 week of fiducial implant. The treatment plan acquired on the basis of CT pelvis with contrast along with T2 weighted MR images. Detailed information regarding PSA concentration, Gleason score, T stage, risk group and ADT usage were noted. Dietary plan was given to patient to minimize the production of flatulence and feces. Patient was catheterized on day of stereotactic body radiation.

Patients was irradiated with total dose of 36.25 Gy delivered in 5 fractions (7.25 Gy/ fraction) on alternate days. Gross total volume (GTV) consisted of prostate gland and proximal 5.0-7.0 mm of seminal vesicles. Clinical target volume (CTV) was dilated 2.0 mm anteriorly and posteriorly and 4.0 mm in all other dimension.

Patients were monitored on the day of stereotactic body radiation therapy completion and subsequently 3 monthly. Drop in the PSA (biochemical marker) was assessed at baseline, at 3 months, and 6 months follow-up.

Statistical package for social sciences (SPSS) version 24 was used for the purpose of statistical analysis. Median and interquartile ranges were calculated for variables like age, PSA at baseline, at 3 month and 6 months. Frequency and percentages were calculated for variables like gender, co-morbidities, urinary complications, TNM stages, and risk group. Friedman test was applied to see the median difference of PSA at different time intervals. p-value ≤0.05 considered as significant.

Table 1. Baseline characteristics of the patients (N=84)

Characteristics	N	%
Age, years [median (IQR)]	65 (60-71)*	
≤65	31	57.4
>65	23	42.6
Comorbidities		
CVD	6	11.1
Diabetes	28	51.9
Hyperthyroidism	1	1.9
Urinary complications		
Nocturia	30	55.6
Difficult urination	2	3.7
Dysuria	4	7.4
Hematuria	5	9.3
Increased urinary frequency	45	83.3
Altered bowel habits	22	40.7

Abbreviations: CVD: Cardiovascular Disease, IQR: Interquartile Range

RESULTS

Total of 54 patients were enrolled. Median age was 65 (60-71) years. There were 37 patients with comorbidities. Diabetes was the most common comorbidity observed in 28 (51.9%), followed by cardiovascular disease in 6 (11.1%). One patient (1.9%) had hyperthyroidism. There were 50 (92.6%) patients with urinary complications. Increased urinary frequency, nocturia and altered bowel habits were the most common urinary complications observed in 45 (83.3%), 30 (55.6%) and 22 (40.7%) patients, respectively (Table 1). Majority, 49 (90.7%) patients were presented with T2 N0 M0 TNM status while only 5 (9.3%) patients presented with T1 N0 M0 TNM status. There were 5 (9.3%) with high risk, 26 (48.1%) with intermediate risk, and 23 (42.6%) with low risk. ADT was received by 5 (9.3 %) high risk patients for 9 months.

Overall median PSA level was 2.7 (0.86-7.3) ng/ml. Median PSA at baseline was 10.1 (6.9-18.1) ng/ml which significantly drops to 1.6 (0.8-3.6) ng/ml at 3rd months, and 0.4 (0.2-1.2) at 6th months (p-value <0.01) (Figure 1). A significant median difference of PSA at different time interval was also observed when stratified on the basis of baseline characteristics (p-value <0.05) (Table 2).

DISCUSSION

The finding of the current study reveal that the overall median PSA level was 2.7 ng/ml. The median PSA at baseline was 10.1 ng/ml which significantly drops at

Table 2. Median difference of PSA at different time interval with respect to baseline characteristics

Characteristics	Frequency *n*	Baseline median (IQR)	3 months median (IQR)	6 months median (IQR)	p-value
Age, years					
≤65	31	11.3 (7-20)	2.3 (1.0-4.0)	0.5 (0.2-1.4)	<0.001
>65	23	9.4 (6.9-12.3)	1.0 (0.3-2.4)	0.2 (0.1-0.9)	<0.001
Comorbidities					
Yes	32	10.1 (5.5-17.9)	1.6 (0.8-3.9)	0.2 (0.1-1.2)	<0.001
No	22	10.1 (7.5-18.6)	1.6 (0.7-3.2)	0.5 (0.3-1.4)	<0.001
Urinary Complications					
Yes	50	9.8 (7.0-18.0)	1.6 (0.8-3.5)	0.4 (0.1-1.2)	<0.001
No	4	9.0 (4.8-17.1)	0.8 (0.1-1.5)	0.2 (0.1-0.5)	<0.001
TNM Staging					
T1 N0 M0	5	17.4 (7.3-18.6)	1.6 (0.6-4.0)	0.6 (0.0-1.1)	<0.001
T2 N0 M0	49	9.6 (6.9-18.2)	1.6 (0.8-3.5)	0.4 (0.2-1.2)	
Risk Group					
High	5	5.0 (4.5-10.9)	0.3 (0.2-5.1)	0.2 (0.1-0.9)	<0.001
Moderate	26	11.1 (7.3-19.3)	1.5 (0.9-3.6)	0.4 (0.1-1.3)	<0.001
Low	23	9.8 (7.3-18.0)	1.6 (0.7-2.7)	0.5 (0.2-1.4)	<0.001
Gleason Score					
6	29	12.3 (8.0-19.8)	1.6 (0.7-3.8)	0.5 (0.1-1.4)	<0.001
7	25	9.4 (5.1-11.4)	1.5 (0.6-2.9)	0.4 (0.2-0.9)	<0.001
ADT Given					
Yes	4	7.3 (4.2-10.9)	1.3 (0.2-6.4)	0.5 (0.1-1.1)	<0.001
No	50	10.4 (7.2-18.4)	1.6 (0.8-3.6)	0.4 (0.2-1.2)	<0.001

Abbreviations: IQR: Interquartile range
Friedman Test applied, p-value <0.05 was considered as significant

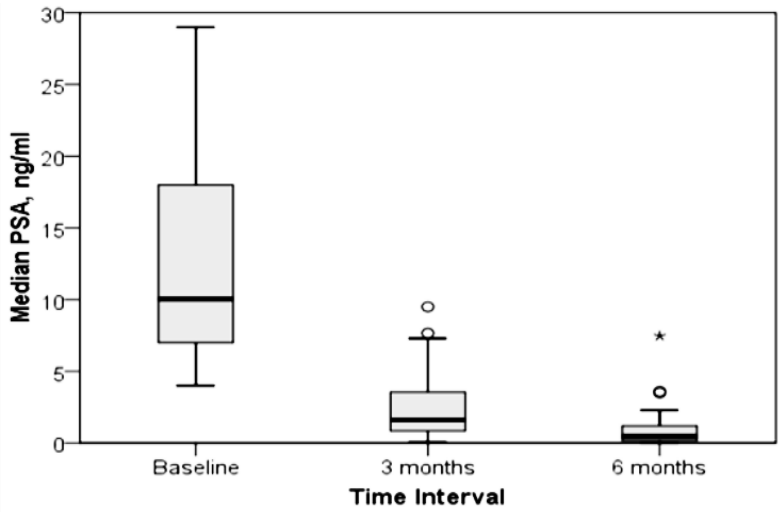

Figure 1. Median PSA level with respect to time interval

each consecutive follow-up of third month, and sixth month. Compared to the current study finding, a lower PSA level at baseline was reported in previous studies.[8,13] Napieralksa and coauthors reported median PSA concentration at the time of metastasis detection as 5.75 ng/ml and 4.66 ng/ml respectively. Furthermore, median PSA at last control in patients without disease progression was 1.67ng/ml and 20 patients had PSA below 1.0ng/ml.[8,13] In one study, median PSA level dropped in majority of the cases and median PSA level was found to be 2.5 ng/ml.[8] However, in the current study, much better PSA level was observed at the last follow-up as PSA level founds to be 0.4. The rapid decline in PSA level as reported in this study is also supported by various studies.[8,13-16]

There were 9.3% with high risk, 48.1% with intermediate risk, and 42.6% with low risk. ADT was received by 9.3 % high risk patients. Majority 90.7% patients presented with T2 N0 M0 TNM status while only 9.3% patients presented with T1 N0 M0 TNM status. ADT is a standard treatment for patients with metastatic or recurrent PC.[17] In case of multiple

metastases as reported in a conducted by Berkovic and coworkers, ADT was introduced after SABR and the PSA concentration level increased, resulting in 1 year of no ADT, in 82% of treated patients.[18] It has been proven that ADT improves radiotherapy effectiveness in patients treated with curative intention and prolongs the overall survival and progression-free survival in this group.[19] In Pakistan, previous studies are available on the outcome stereotactic body radiation therapy in hepatocellular carcinoma.[20] However, reports on prostate cancer are limited. The reason for scarcity on the available data on stereotactic body radiation therapy in Pakistan is that limited services are available, especially in public sector hospitals.[21] Stereotactic body radiation therapy is emerging as an attractive option for treating cancers in the lung, head and neck, prostate, liver and other disease sites outside the central nervous system.[3,9,22] Limitation of this study was that the report is from a single center and includes limited sample size. Moreover, certain important variables like ADT use at the time of follow-up, toxicity, ECOG performance status, and primary treatment detailed were not included. Furthermore, in the current study the maximum follow-up was 6 months. Previous international studies were published with the follow-up of even nine years as well.[13] Lastly, survival rate was also not observed due to the shorter duration of follow-up. Despite these limitations, finding of this study on treatment response of CyberKnife stereotactic radiotherapy of patients with prostatic neoplastic lesions may be considered in future studies.

CONCLUSION

Adequate treatment response of CyberKnife stereotactic radiotherapy of patients with prostatic neoplastic lesions is observed. The therapy has shown a satisfactory outcome in escalating the dose to the target lesion and thus to increase local control while limiting dose to nearby critical organs and normal tissue.

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