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Stereotactic Hypofractionated Accurate Radiotherapy of the Prostate (SHARP), 36.25 Gy in Five Fractions for Localized Prostate Cancer

M.W. Hegazy\textsuperscript{1,2}, R Mahmood\textsuperscript{1}

\textsuperscript{1}Department of Radiation Oncology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia.
\textsuperscript{2}Department of Clinical Oncology and Nuclear Medicine, Zagazig Faculty of Medicine, Egypt

Abstract

Purpose

To evaluate the feasibility, efficacy and toxicity of stereotactic hypofractionated accurate radiotherapy (SHARP) for localized prostate cancer.

Methods and Materials

The current series of SHARP included six patients with localized prostate cancer treated with 36.25 Gy in 5 fractions by Cyber-knife. Non-coplanar conformal fields and daily stereotactic localization of implanted fiducials were used for treatment. Acute and Late Genitourinary (GU) and gastrointestinal (GI) toxicity were evaluated by Common Toxicity Criteria (CTC). Prostate–specific antigen (PSA) values and self–reported sexual function were recorded at 3 months interval at first two years then every 6 months thereafter.

Results

The median follow–up is 32 months. Acute toxicity Grade 1 (GU) noted in four cases and two cases were Grade II; Grade I (GI) was in five cases and one patient in Grade II; also with regards to late toxicity, Grade 1 (GU) and (GI) was present in all cases. No patient has experienced grade 3 or greater acute or late toxicity. Regarding sexual activity, three patients reported impotency before and after therapy and all of them have insulin dependent diabetes mellitus and ischemic heart disease; fourth patient has developed impotence and the other two patients developed no changes as before radiation. The mean basal PSA was 8 ng/ml and became 0.658 ng/ml.

Conclusions

SHARP for localized prostate cancer is feasible with minimal acute or late toxicity. Dose escalation should be possible. MRI guided target volume delineation and intrafraction prostate motion tracking with real–time beam adjustment are critical for safe high dose per fraction prostate SBRT.

Keywords

Prostate cancer, Stereotactic radiotherapy, Hypofractionation

Introduction

The long term effectiveness and safety of hypofractionated external beam radiotherapy in the definitive treatment of prostate cancer was first suggested by a landmark program which ran in the UK during the 1980s that delivered 6 fractions of 6 Gy each over a two week period\textsuperscript{(1)}. Over the ensuing two decades the evolution of radiotherapy technology to integrate 3D anatomy, conformal dose coverage and image guidance combined with a deeper understanding of the radiobiology of prostate cancer led to the proliferation of various fractionated radiotherapy schedules. Consequently, substantial clinical data now exist from several studies including randomized trials using various moderately hypofractionated regimens, with dose–per–fraction ranging from 2.5 Gy per fraction to 70 and 3.1 Gy per fraction to 62 Gy 2–10 and more recently, extreme hypofractionation schemes of 7.25 Gy per fraction for 36.25–10 Gy for 50 Gy \textsuperscript{(11–18)} using stereotactic body radiotherapy (SBRT) approaches. The basis for the successful clinical results from these hypofractionation schemes stems from the unique radiobiology of prostate cancer that favors large dose
per fraction over conventionally fractionated schedules. Moreover, hypofractionation for prostate results in a means of radiobiological dose-escalation and probably represents a therapeutic gain. It also affords a more economical course of definitive radiotherapy, improves patient access to care, and enhances patient convenience. At present only a handful of smaller studies using SBRT for prostate cancer have been published which have shown successful outcomes with low toxicity profiles. (11–19)

Methods and materials

Patient Characteristics

Between Nov 2010 and Dec 2013, 6 patients with clinically localized prostate cancer were treated with SBRT as primary therapy in King Faisal Specialist Hospital, Saudi Arabia. Eligible patients have newly diagnosed, biopsy–proven adenocarcinoma of the prostate documented by 12–quadrant, transrectal ultrasound–guided biopsies, non–metastatic and untreated prostate cancer presenting with low–risk features. The criteria for low–risk classification included a pre–treatment PSA of 10 ng/mL or less, Gleason score of 3+3 or lower and clinical stage T1 or T2a. One patient with a Gleason score of 3+4 was included as the cancer was present in 2 cores and involved less than 5 mm aggregate tumor length and received neoadjuvant hormonal therapy. Patient, disease and treatment characteristics are listed in Table I. Staging work–up included a bone scan, MRI pelvis and CT scan of the chest, abdomen and pelvis to rule out regional or distant metastases. The mean age was 70 years (range 60–78 years), all patients were T1 stage, Gleason score was 6 in 5 patients & 7 in one patient, the mean for PSA was 8 (range 3.8–10) and 12 cores were taken as biopsy where 2 cores were positive in 3 patients (50%), 3 cores were positive in 2 patients (33%) and 4 cores were positive in one patient (17%).

Treatment specifics

The CyberKnife (Accuray Inc., Sunnyvale CA) was used to deliver fiducial–based image–guided SBRT. The treatment specifics from different centers have been published previously (11–17). Differences among those centers are primarily related to dose while the remainder of the technical treatment specifications remained remarkably uniform. Anatomical contours of the prostate, seminal vesicles, rectum, bladder, penile bulb, femoral heads and testes were generated.

Treatment Planning and Delivery

Four to five gold fiducial markers were placed in the prostate under transrectal ultrasound guidance for image–guided positioning and motion tracking. Treatment Planning CT scans were performed at a slice thickness of 2 mm one week after fiducial placement. MRI scans were obtained for all with preferred sequences of T2 GRE or T1 post Gd, using a slice thickness of 1–2 mm. Planning CTs were used and fused with MRI images, to differentiate the prostate and the proximal 1 cm of the seminal vesicles (the clinical target volume, or CTV) from the rectum, urogenital diaphragm, bladder, distal seminal vesicles, and other surrounding structures. The planning target volume consisted of a 3 mm anteriorly, laterally and posteriorly expansion to account for errors in target definition and delivery. All patients were treated with the CyberKnife system, composed of a 6 MV linear accelerator mounted on a robotic arm, with two orthogonal kilovoltage X–ray imagers that provide real–time stereoscopic image guidance and automatic correction for movements of the prostate throughout treatment. Typically, 150–200 non–coplanar beams were delivered in each treatment session. Patient positioning and target tracking were

<table>
<thead>
<tr>
<th>Age</th>
<th>70 (60–78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>T1 (6/6)</td>
</tr>
<tr>
<td>G.S.</td>
<td>6 (5 patients)</td>
</tr>
<tr>
<td>PSA</td>
<td>8 (3.8–10)</td>
</tr>
<tr>
<td>Cores of biopsy</td>
<td>3 patients (+2/12)</td>
</tr>
<tr>
<td></td>
<td>2 patients (+3/12)</td>
</tr>
<tr>
<td></td>
<td>1 patients (+4/12)</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>1 (G.S 7)</td>
</tr>
</tbody>
</table>

Table 1. Patient Characteristics

G.S.=Gleason Score; PSA=Prostatic Specific Antigen

Figure 1. Isodose distribution
PSA relapse definition used was the currently adopted standard of care Phoenix definition (i.e., nadir +2).

Toxicity analyses were performed using the Genitourinary (GU) and gastrointestinal (GI) acute and late toxicity data. Acute toxicities were defined as beginning from the start of treatment and lasting until 3 months post-RT, and late toxicities were defined as occurring thereafter. Toxicity grading was based on Common Terminology Criteria (CTC) for Adverse Events version 4.0. A strict definition of the grading system was used for grades 1–4. Grade 1 was defined as minimal side effects not affecting activities of daily living (ADL); grade 2 side effects were those requiring medications for symptom management (or increase in dosage of preexisting medication) with symptoms affecting ADL; grade 3 side effects consisted of severe or medically significant but not life-threatening toxicities or those necessitating procedures (i.e., endoscopy, cauterization, catheterization, blood transfusions); grade 4 side effects were defined as life threatening and urgent treatment/interventions were needed. Median follow-up for this series of patients is 24 months.

**Results**

**Toxicity**

Patients tolerated treatments very well, resuming normal activities within one week of completion. Acute symptoms of dysuria, frequency, nocturia and/or tenesmus typically resolved within three months of treatment completion. Four cases had grade I (67%) and two cases had grade II (33%) acute (GU) toxicities. Five cases had grade I (83%) and one case had grade II (17%) acute (GI) toxicities (Table 2). All late toxicities were grade I only. No patient has experienced grade 3 or greater acute or late toxicity with a median follow up of 32 months (range 13–48).

**Sexual activity**

Regarding to sexual activity, three patients out of six reported impotency before therapy and all of them were insulin dependent diabetes mellitus and ischemic heart disease; fourth patient has developed impotence and the last two patients developed no changes.

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**Follow-up Schedule and Toxicity Analysis**

For each patient the endpoints included early, late genitourinary (GU) and gastrointestinal (GI) toxicities, sexual activity and PSA response. PSAs were obtained at baseline, at 3 months post-treatment intervals during the first 2 years and at 6 month intervals thereafter. The

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Table 2. Acute GI and GU toxicity

<table>
<thead>
<tr>
<th></th>
<th>Grade I</th>
<th>Grade II</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>83%</td>
<td>17%</td>
</tr>
<tr>
<td>GU</td>
<td>67%</td>
<td>33%</td>
</tr>
</tbody>
</table>

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PSA Response

With a median follow up of 32 months (range 13–48):

- First patient PSA nadir was (0.864) ng/mL after 27 months with an initial PSA of 9.5 ng/mL.
- Second patient PSA nadir was (0.22) ng/mL after 32 months with an initial PSA of 10 ng/mL.
- Third patient PSA nadir was (0.3) ng/mL after 8 months with an initial PSA of 7.8 ng/mL.
- Fourth patient PSA nadir was (0.634) ng/mL after 22 months with an initial PSA of 9.3 ng/mL.
- Fifth patient PSA after 15 months of radiation therapy was 1.13 ng/mL & his initial PSA was 7.9 ng/mL where this patient received neoadjuvant hormonal therapy.
- Sixth patient PSA after 9 months of radiation therapy was 0.8 ng/mL & his initial PSA was 3.8 ng/mL.

At median follow up of 32 months the mean for PSA was 0.658 ng/mL while for baseline it was 8 ng/mL.

Discussion

A recent systematic review and analysis (19) combining the clinical outcomes after various hypofractionated schedules for prostate cancer involving over 2800 patients compared to conventionally fractionated regimens among over 11,000 patients confirmed that prostate cancer has a very high sensitivity to dose per fraction (i.e., quantified by the linear quadratic radiobiologic relationship as a low a/b ratio of 1.0–1.7).

Siavash et al. at University of California (20) recently published their experience with SBRT as a monotherapy in low-risk prostate cancer (9.5 Gy X 4 fractions), reporting similarly excellent PSA response and low overall toxicity in a cohort of 20 patients with a median follow–up of 18.3 months (range, 12.6–43.5), with 45% and 5% of the acute Grade 2 GU and GI toxicity, respectively, and no Grade 3 or higher acute toxicity. The majority of patients have no late toxicity, although one patient experienced late Grade 3 GU toxicity, aged 59 years at the time of SBRT required intraurethral injections of steroids and intermittent self–catheterization for urinary irritative symptoms at 16.1 months post–SBRT monotherapy. Regarding PSA response a current median PSA nadir of 0.47 ng/mL (range, 0.2–2.1) with a median follow–up of 18.1 months (range, 12.9–43.5) and a median of five posttreatment PSA measurements (range, 3–10).

Christopher et al at Stanford University (21), published interim results of a prospective phase II clinical trial with SBRT as a monotherapy (36.25 Gy in five fractions of 7.25 Gy) in localized prostate cancer, reporting similarly excellent PSA response and low overall toxicity in a cohort of 41 patients with a median follow–up of 33 months (range, 6–45), with only 2 patients having Grade 3 late GU toxicity and none with Grade 3 GI toxicity. A benign PSA bounce (median, 0.4 ng/mL) was observed in 12 patients (29%) occurring at 18 months (median) after treatment. At last follow–up, no patient has had a PSA failure regardless of biochemical failure definition. Of the 32 patients with 12 months minimum follow–up, 25 patients (78%) achieved a PSA nadir#0.4 ng/mL. A PSA decline to progressively lower nadirs up to 3 years after treatment was observed.

This report describes the preliminary clinical results of hypofractionated stereotactic radiotherapy of the prostate using 5 fractions of 7.25 Gy at our hospital. Our series demonstrates that, with careful treatment planning and delivery, hypofractionated stereotactic radiotherapy of the prostate is associated with minimal acute and late rectal and urinary toxicity as predicted by radiobiologic principles. When we compared our results of toxicity to Siavash et al. at University of California (20) two cases (33%) have G II acute (GU) toxicities; one case (17%) had G II acute (GI) toxicities. All late toxicities were grade I only. No patient has experienced grade 3 or greater acute or late toxicity with a median follow up of 24 months (range 6–39), While in Siavash et al. (25) reported 45% and 5% of the acute Grade 2 GU and GI toxicity and one patient experienced late Grade 3 GU toxicity while in the study of Christopher et al at Stanford University (21), only two patients have Grade 3 late GU toxicity. Regarding PSA response, after a median follow up of 24 months the mean for PSA was 1.17 ng/mL while baseline was at 8 ng/mL. Siavash et al.’s median PSA nadir was 0.47 ng/mL (range, 0.2–2.1) with a median follow–up of 18.1 months while Christopher et al.’s benign PSA bounce (median, 0.4 ng/mL) was observed in 12 patients (29%) occurring at 18 months (median) after treatment. Of the 32 patients with 12 months minimum follow–up, 25 patients (78%) achieved a PSA nadir#0.4 ng/mL with no patient having a PSA failure.

Conclusion

We have been able to demonstrate that it is feasible to deliver hypofractionated radiotherapy to the prostate with careful treatment planning technique and precise daily targeting. Both acute and late GI and GU toxicity are acceptable. The biochemical response seems appropriate; however, it might be possible to achieve a lower PSA nadir and lower rates of biochemical relapse with dose escalation. Dose escalation seems feasible given the low toxicity rates demonstrated in this series.
MRI guided target volume delineation and intrafraction prostate motions tracking with real–time beam adjustment are also critical for safe high dose per fraction prostate SBRT. SBRT is an emerging treatment approach for early–stage prostate cancer, made possible by technological advancements in radiation treatment delivery systems. Additional number of patients and longer follow–up are required to better evaluate potential late toxicity and long–term PSA outcomes. It also affords a more economical course of definitive radiotherapy, improves patient access to care, and enhances patient convenience.

References


