Revolutionizing localized prostate cancer treatment: Stereotactic radiotherapy “Moroccan experience”

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SUMMARY
Introduction: Prostate cancer is the most common urological cancer, and its incidence is increasing. Radical prostatectomy and radiotherapy are the primary treatments for localized forms. Stereotactic Body RadioTherapy (SBRT), a new and innovative therapy, has been validated for some cancer localizations but not yet for localized prostate cancer. Our study aims to report the efficacy and tolerance results of SBRT for localized prostate cancer.

Materials and methods: This is a retrospective study of 27 patients with localized prostate cancer (CaP) who were treated with SBRT in our department from 2017 to 2021 using transponders for tumor tracking. The dose was 36.25 Gy delivered in five fractions of 7.25 Gy. The delineation and doses of organs at risk were determined based on the recommendations of the SFRO and the TG101 report of medical physics. All patients were treated using a latest-generation linear accelerator (True Beam STXÒ).

Results: Acute toxicities were observed in 33.3% of cases, with 22.2% grade 1 or 2 genitourinary (GU) and no grade 3 while 11.1% gastrointestinal (GI) toxicities were reported as grade 1-2 (7.4%) and one case grade 3 (3.7%). Late grade 1 or 2 GU toxicity was observed in 14.84% of cases, with no reports of late GI toxicity. After a 26-month follow-up period, the biochemical failure-free survival rate was 92.6%.

Conclusions: The results of our study are consistent with the existing literature and support the safety and effectiveness of SBRT as a treatment option for localized prostate cancer (CaP). In the United States, both ASTRO and the NCCN recognize SBRT as a valid treatment option for localized CaP. Ongoing phase III trials are being conducted to further substantiate these long-term results and to establish SBRT as the future standard of care for localized CaP.

KEY WORDS: Localized prostate cancer; Stereotactic radiotherapy; Toxicity; Efficacy.

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INTRODUCTION
Prostate cancer (CaP) is a common cancer, with approximately 1.4 million new cases reported globally in 2020 (1). It accounts for 14.1% of all human cancers and is the fifth leading cause of cancer-related deaths, responsible for 375,000 deaths each year. In the United States, about 80% of CaP cases are localized, and the survival rate for localized cases is over 99% (2). The treatment of localized CaP involves a combination of modalities, and radiation therapy is a standard treatment option recognized as an alternative to radical prostatectomy.

Conventional normo-fractionated radiation therapy is the most commonly used treatment option for localized CaP, but it has a major drawback: it requires a long treatment duration and repetitive patient’s displacement, which can cause fatigue and adding financial burden. Short-term therapies with similar efficacy and toxicity to other radiation therapy techniques are needed. Hypofractionated radiation therapy (2.4 to 3 Gy) in CaP is recommended by several scientific studies (3). Advances in imaging and radiation therapy have led to the development of ultra-fractionated radiation therapy techniques, such as Stereotactic Body Radiation Therapy (SBRT). However, there is a lack of scientific evidence for SBRT in the treatment of localized CaP.

This study aims to present the clinical and biological results in terms of efficacy and tolerance of SBRT in localized CaP, according to the experience of Radiotherapy Department of the Casablanca Cancer Center (CCC) of the International University Hospital Cheikh Khalifa.

MATERIALS AND METHODS
Study and patient characteristics
This is a retrospective, descriptive, observational study conducted at a single center, which included 27 patients with localized prostate adenocarcinoma treated with curative intent using SBRT at the CCC Radiotherapy Department between 2017 and 2021. The median age of patients was 66 years, and the three quarters of the patients had a PSA level less than 10 ng/ml. The Gleason score was 6 in 59.3% of patients, 7 in 40.7%. Regarding the tumor stage, 14.8% were classified as T1 and 85.2% as T2. According to the D’Amico classification, 33.3% of patients were low-risk, 51.9% were intermediate-risk, and 14.8% were high-risk (Table 1).

Protocols and techniques
The decision to treat with SBRT was made during multi-
disciplinary consultation meetings (RCPs) for all patients. The first step in the SBRT treatment process involved the placement of three electromagnetic transponders, by an urologist under general anesthesia, by ultrasound guidance. In fact, the urologist sets up two transponders at the base and one at the apex. These transponders were used to track the tumor during prostate irradiation with the Calypso® repositioning system.

Patients were positioned in a supine position with their hands crossed on their chest and immobilized using restraints such as footrests, headrests, and logs under their knees. A simulation scan was then performed 6 to 15 days after transponder placement with an average of 11 days, with sub-millimeter sections.

The target volumes for treatment were determined based on the ICRU 91 report, which involved a systematic fusion of dosimetric scanner images and previously obtained prostate MRI images. The gross tumor volume (GTV) corresponded to the clinical target volume (CTV) GTV=CTV (4), whereas the planning target volume (PTV) was defined by adding a 3 mm posterior safety margin and a 5 mm margin in other directions to the GTV/CTV. Organs at risk (OARs), including the bladder, rectum, urethra, penile bulb, anal canal, and right and left femoral heads, were delineated following the recommendations of the French Society of Oncological Radiotherapy (SFRO) (5).

All patients received the dose of 36.25 Gy in five fractions and were treated using a True Beam STX linear acceler-
Table 4.
Results of acute and late toxicities.

<table>
<thead>
<tr>
<th></th>
<th>Acute toxicity</th>
<th></th>
<th>Late toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade ≥ 3</td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>GU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>22.2% (6)</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Urethral stricture</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>3.7% (1)</td>
</tr>
<tr>
<td>GI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pocstis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.4% (2)</td>
<td>3.7% (1)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

**Acute toxicity**

During and after the 90 days of radiotherapy, we observed 29.6% (n = 29) grade 1-2 genitourinary (GU) and gastrointestinal (GI) toxicity, and one patient (3.7%) presented grade 3 acute GI toxicity exacerbated by an abscess treated surgically (Table 4).

**Late toxicity**

We observed 14.8% (n = 4) grade 2 late urinary toxicity, including urethral stricture resolved by drilling in 11.1% of patients and haematuria related to bladder cancer in one patient. No late GI toxicity was detected (Table 4).

**Biological control**

At 26 months, the biochemical relapse-free survival rate was 92.5% (n = 25), and two patients had a biological recurrence. All patients were alive when we performed our analysis except one who died by pulmonary embolism caused by associated lung cancer.

**DISCUSSION**

**Biological rationale**

The Biologically Equivalent Dose (BED) formula is used to explain cell sensitivity to larger fraction sizes. The formula is BED = nd [1 + d/(α/β)], where n is the number of radiation fractions, and d is the dose size per fraction. The BED formula shows that increasing the dose per fraction, or hypofractionation, has a greater impact on tissues with a low α/β ratio compared to those with a high ratio. If the tumor’s α/β ratio is lower than the surrounding tissues’ α/β ratio (assumed to be between 3 and 5 for bladder and rectum), then increasing the dose per fraction will increase the BED for the tumor more than for the normal tissues, improving the therapeutic ratio. Many publications suggest that the α/β ratio for CaP is around 1.5 Gy (8-11), indicating that hypofractionated radiotherapy may improve the efficacy of treatment. This differential sensitivity to fractionation between the tumor and normal tissue favors the use of hypofractionated radiotherapy for CaP (12-13). Furthermore, higher BED is associated with improved local control (14).

**Benefits of SBRT in CaP**

The radiobiological data indicate that SBRT is a more effective treatment for localized CaP than conventional radiotherapy. Moreover, SBRT provides several other benefits, including a reduction in treatment duration and better quality of life for patients due to fewer treatment sessions (15). SBRT is also more logistically cost-effective for radiation therapy departments and may have financial benefits in systems with fractional reimbursement. Studies have shown that 5-fraction prostate SBRT is a cost-effective and non-invasive treatment with equivalent results to conventional radiotherapy or surgery without compromising patient safety (16).

**Acute toxicity**

Several trials have studied the acute toxicity of SBRT in patients with localized CaP. Our study found that nearly a quarter of patients had grade 1-2 GU acute toxicity and none had grade 3 or higher toxicity. Two patients had grade 1-2 GI toxicity (bleeding, discomfort, or mucosal discharge), and one patient developed grade 3 acute GI toxicity (abscess) probably due to receiving a D100 on 10% of the rectal volume, which was higher than the group average. Our results found the same conclusions reported in the literature (Table 5).

**Late toxicity**

Several studies have examined the toxicity profiles of different radiotherapy treatments for CaP, with a focus on SBRT. One study found that while SBRT and intensity-modulated radiation therapy (IMRT) had similar rates of gen-

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**Table 5.**

Results of trials on the efficacy of SBRT in localized prostate cancer.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Number of patients</th>
<th>Endpoints</th>
<th>Dose (Gy)</th>
<th>PTV (Gy)</th>
<th>Number of fractions</th>
<th>α/β Ratio (Gy)</th>
<th>Allocated time (days)</th>
<th>Median follow-up (month)</th>
<th>bRFS (%)</th>
<th>SBRT</th>
<th>Comp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pace B (2012-2018)</td>
<td>874</td>
<td>Toxicity SSRB</td>
<td>36.25</td>
<td>40</td>
<td>5*7.25</td>
<td>7±14</td>
<td>60</td>
<td>On Going</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYPO-RT-P (2005-2015)</td>
<td>1200</td>
<td>Toxicity SSRB, QOL</td>
<td>47.7</td>
<td>7 * 6.8</td>
<td>3</td>
<td>16 (15-17)</td>
<td>60</td>
<td>84% 84%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharp 2017</td>
<td>46</td>
<td>Toxicity SSRB</td>
<td>33.5</td>
<td>5 *6.7</td>
<td>1.5</td>
<td>41</td>
<td>90% NC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.M. Meier</td>
<td>309</td>
<td>Toxicity SSRB</td>
<td>36.25</td>
<td>5 * 8</td>
<td>5 ± 11</td>
<td>61</td>
<td>97.1% NC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ring and at. 2013</td>
<td>67</td>
<td>Toxicity SSRB</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>94%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Ratz und at. 2006-2009</td>
<td>67</td>
<td>Toxicity SSRB, QOL</td>
<td>35</td>
<td>5 *7.25</td>
<td>5</td>
<td>96</td>
<td>94.4% NC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jackson and at. 2013-2018</td>
<td>6000</td>
<td>Toxicity SSRB</td>
<td>36.25</td>
<td>-</td>
<td>5*7.25</td>
<td>-</td>
<td>30</td>
<td>95.3% NC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Our study</td>
<td>27</td>
<td>Toxicity SSRB</td>
<td>36.25</td>
<td>40</td>
<td>5 ± 14</td>
<td>9</td>
<td>26</td>
<td>92.6% NC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comp.: Conventional; NC: Not comparative; bRFS: Biological relapse-free survival; QOL: Quality of life.
ourinary (GU) and gastrointestinal (GI) toxicities, SBRT patients had a higher risk of urinary fistula (17). Another meta-analysis estimated rates of late grade 3 GU and GI toxicities over 5 years of follow-up (18). The Hynpo-RT-PC and PACE B trials found no significant differences in late GU and GI toxicities between treatment groups, although the ultra-hypofractionation group in the former had an increase in GU toxicity at 1-year follow-up (19, 20). Another study found that SBRT was associated with a higher rate of GU toxicity, potentially due to the lower $\alpha/\beta$ ratio in urinary tract tissue compared to GI tissue. Ongoing trials are investigating the long-term toxicity and efficacy of SBRT in low and intermediate-risk CaP patients (23).

**Effectiveness of SBRT**

Studies have indicated that ultra-hypofractionated radiotherapy, also known as SBRT, is a secure and efficient treatment option for patients with intermediate and high-risk localized CaP (21-22). The randomized phase III HYPO-RT-PC trial and PACE B trial have reported comparable recurrence-free survival rates with SBRT and conventional radiotherapy, indicating that SBRT may be a viable alternative for these patients (19-20).

Katz et al.'s research has also revealed outstanding long-term control with low toxicity, demonstrating SBRT's potential as a promising treatment option for localized CaP (23). Additionally, the multicenter study by Meier et al. has shown higher rates of overall survival and biological control with SBRT when compared to IMRT, reinforcing the demonstration of the efficacy of SBRT for CaP treatment (17). Although the addition of androgen deprivation therapy (ADT) is recommended for unfavorable intermediate-risk patients, further research is needed to determine if SBRT alone can suffice (24).

Our findings exhibit a high degree of similarity to the results of the main trials, specifically in terms of Biological Relapse-Free Survival (bRFS), as indicated in Table 6.

**Conclusions**

Stereotactic radiotherapy (SBRT) has emerged as a recent treatment option for managing localized CaP and offers a multitude of benefits, including radiobiological, logistical, and financial advantages. Numerous studies have demonstrated that SBRT is comparable to conventionally fractionated radiotherapy for intermediate to high-risk CaP patients. This treatment has the potential to achieve satisfactory levels of acute and late genitourinary and gastrointestinal toxicity, consistent with radiobiological principles. Our findings indicate that ultra-hypofractionation should be regarded as a safe and effective treatment for localized CaP. At present, several phase III trials are ongoing to validate SBRT as the best standard treatment for all localized CaP, such as the SPARC trial and PACE C. However, the potential advantages of combining androgen deprivation therapy with SBRT remain unclear.

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