DOI: 10.4081/aiua.2024.12104

ORIGINAL PAPER

Revolutionizing localized prostate cancer treatment: Stereotactic radiotherapy "Moroccan experience"

Asmâa Naim [1, 2, 3], Zineb Lahlou [1, 2], Othmane Kaanouch [3, 4], Abdelajalil Heddat [1, 2, 5], Safae Mansouri [6]

[1] Faculty of Medicine, Mohammed VI University of Sciences and Health, Casablanca, Morocco;
[2] Research Unit, Mohammed VI Center for Research and Innovation, Rabat, Morocco;
[3] Radiotherapy Department of Casablanca Cancer Center, University International Hospital Cheikh Khalifa, Casablanca, Morocco;
[4] Hassan First University of Settat, High Institute of Health Sciences, Laboratory of Sciences and Health Technologies, BP 555, 26000, Settat, Morocco;
[5] Urology Department, University International Hospital Cheikh Khalifa, Casablanca, Morocco;
[6] Faculty of Medicine, University Hassan II, Casablanca, Morocco.

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.

Submitted 17 November 2023; Accepted 23 December 2023

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-

Table 1.
PPLA score system for renal papillae (16).

Median age	66 years (53-76)
Initial PSA data	
Medium	8.9 ng (5-17)
= 5 ng/ml	2 (7.4%)
5-10 ng/ml	18 (66.7%)
10.1- 15 ng/ml	5 (18.5%)
> 15 ng/ml	2 (7.4%)
ISUP Classification	
Group 1 (3+3)	16 (59.3%)
Group 2 (3+4)	6 (22.2%)
Group 3 (4+3)	5 (18.5%)
Group 4 (4+4)	0
Group 5 (4+5 ou 5+4)	0
TNM Classification	
T1cNOM0	4 (14.8%)
T2aNOM0	11(40.8%)
T2bNOM0	8 (29.6%)
T2cNOM0	4 (14.8%)
D'Amico Classification	
Low risk	9 (33.3%)
Intermediate risk	14 (51.9%)
High risk	4 (14.8%)
Androgen deprivation therapy (ADT)	
Yes	12 (44.5%)
Non	15 (55.5%)

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 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 accelerator with real-time automatic correction for target translational and rotational motion thanks to Calypso® system.

Outcomes
Patients were monitored for treatment tolerance and effectiveness following each irradiation session.
Evaluations were done 1 month after treatment, every three months for the first year, every 6 months for the next 3 years, and annually thereafter. Physicians reported any toxicities, which were classified as acute if they occurred within 90 days of treatment and late if they developed after 90 days, using CTCAE v5 (6). The study's primary endpoint was the incidence of biochemical or clinical failure. Biochemical recurrence was defined according to the Phoenix criteria (7). Overall survival was defined as death from any cause.

RESULTS
The *entire tumor volume* (CTV) received 100% of the prescribed dose, while the *planning target volume* (PTV) received 95% coverage. The dose constraints for the *organs at risk* (OARs) were met for all patients (Table 2) and the principals parameters of irradiation are summarized in Table 3.

Table 2.
Dose constraints for the Organs at risk (OAR) in our series.

	Reference constraints		Patients OAR contraints Mean	Min	Max
Bladder	V 18.3 Gy	< 15 cc	13.54	2.14	34
	V 37 Gy	< 10 cc	0,7	0	2.16
	V 35.5 Gy	< 5 cc	1	0	3.45
Rectum	V 25 Gy	< 20 cc	4.7	0.31	14
	V 36.25 Gy	< 1 cc	0.43	0	1.77
	V 36.25 Gy	< 5%	1	0	10
	V 33.625 Gy	< 10%	3	0	11.74
	V 29 Gy	< 20%	5	0.061	17
	V 18.125 Gy	< 50%	17.69	3.48	44
	D max	= 38 Gy	38	32	39.66
Femoral heads	V 30 Gy	< 10 cc	0	0	2
Urethra	V 47 Gy	< 20%	0	0	0
Penile bulb	V 30 Gy	< 3 cc	0	0	0.77
	V 50 Gy	< 0.5 cc	0	0	0
	V 29.5 Gy	< 50%	< 0%	0	56

Table 3.
Irradiation parameters of our patients.

	Mean	Maximum	Minimum
Prostate dose (Gy)	36.25	36.25	36.25
Fractionation (Gy)	7.25	7.25	7.25
Number of fractions	5	5	5
Total Duration of radiotherapy (days)	10	14	9
Maximum Dose (Gy)	43.41	45.3	38.94
Maximum Dose (%)	119.9	125	111.3
Minimum Dose (Gy)	34.47	37.3	30.39
Minimum Dose (%)	95.1%	102%	84%

Table 4.
Results of acute and late toxicities.

		Acute toxicity Grade 1-2	Acute toxicity Grade ≥ 3	Late toxicity Grade 1-2	Late toxicity Grade ≥ 3
GU	Cystitis	22.2% (6)	0% (0)	0% (0)	0% (0)
	Hemorrhage	0% (0)	0% (0)	3.7% (1)	0% (0)
	Urethral stricture	0% (0)	0% (0)	11.1% (3)	0% (0)
GI	Proctitis	7.4% (2)	3,7 (1)	0% (0)	0% (0)

Acute toxicity
During and after the 90 days of radiotherapy, we observed 29.6% 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 *geni-*

Table 5.
Results of trials on the efficacy of SBRT in localized prostate cancer.

Studies	Number of patients	Endpoints	Dose (Gy)	PTV (Gy)	Number of fractions	α/β Ratio (Gy)	Allocated time (days)	Median follow-up (month)	bRFS (%) SBRT	bRFS (%) Conv.
Pace B (2012-2018)	874	Toxicity SSRB	36.25	40	5 *7.25		7 à 14	60	On Going	
HYPO-RT-PT (2005-2015)	1200	Toxicity SSRB QOL	47.7		7 * 6.8	3	16 (15-17)	60	84%	84%
Sharp 2017	40	Toxicity SSRB	33.5		5 *6.7	1.5		41	90%	NC
R.M. Meier	309	Toxicity SSRB	40	36,25	5 * 8		5 à 11	61	97.1%	NC
King and al. 2013	67	Toxicity SSRB		-		-	-	32	94%	NC
Katz and al. 2006-2009	67	Toxicity SSRB QOL	35 36.25	-	5*7.25	-	5	96	94.4% 93.4%	NC
Jackson and al. 2013-2018	6000	Toxicity SSRB	36.25	-	5*7.25	2.5	-	30	95.3%	NC
Our study	27	Toxicity SSRB	36.25	40	5*7.25	1.5	9	26	92.6%	NC

Conv.: Conventional; NC: Not comparative; bRFS: Biological relapse-free survival; QoL: Quality of life.

Table 6.
Study results of acute SBRT toxicity in localized CaP.

Studies of patients	Number	Endpoints	Dose (Gy)	PTV (Gy)	Number of fractions	α/β Ratio (Gy)	Allocated time (days)	Acute GU toxicity SBRT	Acute GU toxicity Conv.	Acute GI toxicity SBRT	Acute GI toxicity Conv.
Pace B (2012-2018)	874	Toxicity SSRB	36.25	40	5 * 7.25		7 à 14	G2: 23.2%	G2: 27.2%	G2: 10.1%	G2: 12.1%
HYPO-RT-PT (2005-2015)	1200	Toxicity SSRB QOL	47.7		7 * 6.8	3	16 (15-17)	G2: 28%	G2: 23%	G2: 10%	G2: 7%
Sharp 2017	40	Toxicity SSRB	33.5		5 * 6.7	1.5		G2: 20.5%	NC	G2: 13%	NC
R.M. Meier (20)	309	Toxicity SSRB	40	36.25	5 * 8		5 à 11	G2: 26%	NC	G2: 8%	NC
Our study	27	Toxicity SSRB	36.25	40	5 * 7.25	1.5	9	G1-2: 22.2	NC	G1-2: 7.4% G3: 3.7%	NC

Conv.: Conventional; NC: Not comparative; SSRB: biological relapse-free survival; QoL: Quality of life.

tourinary (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 Hypo-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 α/β 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.

Acknowledgments

We thank all the staff of *Department of Radiotherapy and Urology Hospital International Cheikh Khalifa, Casablanca, Morocco*.
We thank all the staff of *Medical Physics of Cheikh Khalifa International Hospital, Casablanca, Morocco: Kamal Saidi, Hanae Elgouach*.

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Correspondence
Asmaa Naim, MD
doc.a.naim@gmail.com
Zineb Lahlou, MD
lahlouzineb@outlook.fr
Faculty of Medicine, Mohammed VI University of Sciences and Health, Casablanca, Morocco

Othmane Kaanouch, MD
othmane.kaanouch@gmail.com
Radiotherapy Department of Casablanca Cancer Center, University International Hospital Cheikh Khalifa, Casablanca, Morocco
Hassan First University of Settat, High Institute of Health Sciences, Laboratory of Sciences and Health Technologies, BP 555, 26000, Settat, Morocco

Abdeljalil Heddat, MD
abdeljalilheddat@yahoo.fr
Faculty of Medicine, Mohammed VI University of Sciences and Health, Casablanca, Morocco

Safae Mansouri, MD
m-safae@hotmail.fr
Faculty of Medicine, University Hassan II, Casablanca, Morocco

Conflict of interest: The authors declare no potential conflict of interest.