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Acute toxicity and quality of life in prostate cancer patients treated with definitive hypofractionated pelvic radiation therapy: a single-center report

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ABSTRACT

Background: The objective was to report acute toxicity and quality of life in prostate cancer patients treated with definitive hypofractionated pelvic radiation therapy.

Materials and methods: Patients were designated candidates for hypofractionated pelvic radiation therapy if biopsy or imaging studies evidenced unfavorable intermediate-risk, high-risk or node-positive disease. Patients were treated using a regimen of 44 Gy to the nodal areas and simultaneous integrated boost of 60 Gy to the prostate in 20 fractions with CBCT-based imaging and volumetric arc therapy (VMAT). Patient data was obtained retrospectively; acute gastrointestinal (GI) and genitourinary (GU) toxicity was classified per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and obtained from clinical records. Quality of life was surveyed via phone call using the European Organization for Research and Treatment of Cancer (EORTC) questionnaire QLQ-PR25.

Results: 78 patients were treated between May and December 2021. 83.33% of patients had high-risk disease, 16.67% had intermediate-risk disease, and 34.62% patients had node-positive disease. Median follow-up was 10.6 months. No patients presented acute grade >3 GI toxicity, and one patient presented grade 3 GU toxicity. 25.64% patients presented acute G2 GI toxicity and 17.95% patients presented acute G2 GU toxicity. 60.26% of patients responded to the EORTC-PR25 questionnaire. Mean scores for symptom scales were 11.26, 4.96 and 9.57 for Urinary Symptoms, Bowel Symptoms and Hormonal Treatment-Related Symptoms; mean scores for Sexual Activity and Functioning were 19.86 and 31.08, respectively.

Conclusion: Definitive hypofractionated pelvic radiation therapy has an acceptable acute toxicity and QoL profile in this series of patients, although longer follow-up is needed to properly evaluate short and long-term toxicity. Further follow-up and patient recruitment is ongoing.

Key words: prostatic neoplasms; pelvic neoplasms; radiotherapy, intensity-modulated; radiation dose hypofractionation

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Introduction

Prostate cancer is the second most commonly occurring cancer and the fifth leading cause of cancer death in men in the world. In Chile, it is currently the most commonly diagnosed cancer in the male population, with an incidence of 56.7 cases per 100,000 people and 8,157 new cases in 2020 [1].

Unfavorable intermediate and high-risk prostate cancer patients are considered to have increased risk of lymph-node metastasis, justifying elective radiotherapy to pelvic lymph nodes with the objective of

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eradicating regional microscopic disease [2]. Although the data is conflicting in regard to the benefit of pelvic elective nodal irradiation (ENI), there are several trials that have demonstrated favorable outcomes with the use of whole-pelvic radiation therapy (WPRT) in this group of patients [3–5].

In node-positive disease, results from treatment with hypofractionated radiotherapy are scarce, though existing evidence suggests favorable biochemical control rates and acceptable toxicity [6].

From a radiobiological standpoint, the prostate's low alpha/beta ratio supports the use of higher doses per fraction, and prostate-only hypofractionated radiotherapy has been proven to be safe and non-inferior to conventional fractionation in prostate cancer patients [7–9]. Hypofractionated treatment modalities are currently endorsed by National Comprehensive Cancer Network (NCCN) guidelines for all risk groups [10]. In regard to hypofractionated WPRT, although there are several studies that explore its effectiveness and safety [4, 11, 12], there is still a deficiency of high-quality evidence regarding its relative efficacy, toxicity and quality of life [13].

This single-center retrospective study includes both node-positive and node-negative disease and aims to report acute toxicity and quality of life (QoL) in prostate cancer patients treated with definitive hypofractionated pelvic radiation therapy.

Materials and methods

Medical records of patients with intermediate or high-risk prostate cancer treated between May and December of 2021 were selected from our electronic medical history system. These patients had been referred to our center for definitive radiation therapy after diagnosis, and were designated candidates for hypofractionated pelvic radiation therapy if biopsy or imaging studies evidenced unfavorable intermediate-risk, high risk or node-positive disease. For staging, patients were subjected to computed tomography of thorax, abdomen and pelvis (CT-TAP) scan, as well as either prostate-specific membrane antigen positon emission tomography (PET-PSMA) or Bone Scintigraphy to rule out metastatic disease. Use of multiparametric magnetic resonance imaging (mpMRI) was indicated per discretion of the referring urology team. Patients with extensive metastatic disease, prior pelvic radiotherapy, history of other malignant disease, serious comorbidities and patients unable to complete treatment were excluded from final analysis. Six patients with oligometastatic disease treated with stereotactic body radiation therapy (SBRT) to metastasis site prior to WPRT were included.

Adjuvant treatment with long-term androgen-deprivation therapy (ADT) was prescribed per discretion of the attending physician.

Patients were simulated in planning CT with an empty rectum and comfortably full bladder. Use of intravenous contrast was indicated per discretion of the treating Radiation Oncologist.

Radiotherapy was planned assuming an alpha/beta of 1.5 Gy for prostate cancer, with a regimen of 44 Gy to the nodal areas and a simultaneous integrated boost (SIB) of 60 Gy to the prostate in 20 fractions (4 weeks), in alignment with PROFIT [9] and CHHiP [7] trials. Involved lymph nodes were boosted to 60 Gy when indicated by the treating Radiation Oncologist.

Clinical target volume (CTV) 60 Gy included prostate and seminal vesicles. Proximal seminal vesicles were contoured in intermediate risk disease, and the entirety of the seminal vesicles were included for high risk disease. A margin of 5 mm posteriorly and 7 mm in all other directions was applied to obtain the planning target volume (PTV). Pelvic node contours were realized in accordance with PIVOTAL guidelines [14]; common iliac, internal iliac, external iliac, presacral and obturator nodes were included, using the lower border of the L5 vertebra to limit the superior extent of the nodal CTV.

Organ at risk (OAR) constraints were established according to departmental protocol, based on those used by the Canadian moderately hypofractionated WPRT study [11], calculated with RTOG 0126 constraints corrected to daily fractions of 3 Gy. The constraints used are as follows: for the rectum V60 Gy < 15%; V56 Gy < 25%; V52 Gy < 35%; V48 Gy < 50%; for the bladder V60 Gy < 25%; V56 Gy < 35%; V52 Gy < 50%; for the penile bulb, mean dose < 42 Gy; for femoral heads, maximum dose < 45 Gy; for the bowel bag V45 Gy < 200 cc; D5 cc < 60 Gy. All treatments were delivered with daily CBCT-based imaging and volumetric arc therapy (VMAT).

Acute toxicity was defined as symptoms presenting during treatment or within 90 days of treatment completion. Acute gastrointestinal (GI) and genito-

urinary (GU) toxicity was classified per the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) [15] and was evaluated retrospectively based on clinical records. Quality of life was surveyed via phone call after last follow-up using the Prostate Cancer Module of the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-PR25) [16], consisting of 4 symptom scales and 2 functional scales, measured on a scale of 0 to 100. The official EORTC Spanish translation was used in this cohort and was applied via two medical professionals. A script was drafted to minimize interview variation between surveyors.

Results

A total of 78 patients were treated between May and December of 2021. Details of patient baseline characteristics are summarized in Table 1.

Median age was 70 years, ranging between 49 and 84. Use of mpMRI for staging was carried out in 65.4% of patients. Patients had high risk disease in 83.33% of cases and intermediate-risk disease in 16.67% of cases. Node-positive disease was reported in 34.62% of patients. Oligometastatic disease was present in 7.69% of patients (6/78); metastatic sites were treated with SBRT prior to WPRT. Amongst the six oligometastatic patients, all had 1-2 bone metastases, and SBRT was prescribed to (1) left fifth rib, (2) L2 vertebra and right ilium, (3) sacrum and right ilium, (4) left ilium, (5) T12-L1 vertebrae and (6) T1 and T8 vertebrae, respectively. Boost to positive lymph nodes was prescribed in 11.5% of patients. The Gleason grade group was classified as group 4, 5 and 3 in 30.77%, 25.64% and 24.36% of cases, respectively. Median prostate-specific antigen (PSA) was 11.8 ng/mL at diagnosis, prior to radiotherapy. ADT was prescribed in 92.31% of patients; one patient rejected ADT, and in five patients, no information in their electronic medical history file regarding adjuvant hormone-therapy was found. Median follow-up was 10.6 months.

Table 1. Patient baseline characteristics

Clinical/pathological characteristics	N or median	% or min–max
Median age	70	49 - 84
TNM: T stage		
T2	39	50.00%
T2a	7	8.97%
T2b	8	10.26%
T2c	24	30.77%
T3	35	44.87%
T3a	12	15.38%
T3b	23	29.49%
T4	4	5.13%
TNM: N stage		
N0	51	65.38%
N1	27	34.62%
TNM: M		
M0	72	92.31%
M1	6	7.69%
Gleason Grade Group		
1	4	5.13%
2	11	14.10%
3	19	24.36%
4	24	30.77%
5	20	25.64%
Risk group		
Intermediate risk	13	16.67%
High risk	65	83.33%
PSA Pre-RT	11.8	2.22 - 199
Boost	9	11.5%
ADT	72	92.31%

TNM — tumour–nodules–metastasis; PSA — prostate-specific antigen; RT — radiotherapy; ADT — androgen-deprivation therapy

In regard to toxicity (summarized in Tab. 2), no patients presented CTCAE acute grade ≥ 3 gastrointestinal (GI) toxicity, and only one patient presented with grade 3 genitourinary (GU) toxicity. The patient with grade 3 GU toxicity presented with acute urinary retention, which was resolved in the ER with installation of a urinary catheter. Acute

Table 2. Acute Toxicity per Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Symptom grade	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal toxicity	33 (42.31%)	25 (32.05%)	20 (25.64%)	0 (0%)	0 (0%)
Genitourinary toxicity	32 (41.03%)	31 (39.74%)	14 (17.95%)	1 (1.28%)	0 (0%)

Table 3. European Organization for Research and Treatment of Cancer (EORTC) QLQ-PR25 Questionnaire

Scales	Patients (n)	Mean Score
Symptom scales		
Urinary symptoms (URI)	47	11.26
Incontinence aid (AID)	0	-
Bowel symptoms (BOW)	47	4.96
Functional scales		
Hormonal treatment related symptoms (HTR)	47	9.57
Sexual activity (SAC)	47	19.86
Sexual functioning (SFU)	4	31.08

grade 2 GI toxicity was reported in 25.64% of patients and 17.95% patients presented acute grade 2 GU toxicity.

The EORTC-PR25 questionnaire was answered in 60.26% of the patients, summarized in Table 3. The mean scores for symptom scales were 11.26, 0, 4.96 and 9.57 for Urinary Symptoms, Incontinence Aid, Bowel Symptoms and Hormonal Treatment related symptoms; mean scores for Sexual Activity and Sexual Functioning were 19.86 and 31.08, respectively.

Discussion

Several phase III trials support the use of hypofractionated regimens as a new standard for treatment of localized prostate cancer in patients managed with radiotherapy [7–9], and as mentioned previously, NCCN guidelines currently endorse hypofractionation for all risk groups. The benefit of ENI is still in discussion, although RTOG 9413 did demonstrate a small benefit in progression-free survival in patients with > 15% risk of regional disease [3]. Hypofractionated WPRT also had improved biochemical-failure free survival (bFFS), disease-free survival (DFS) and metastasis-free survival (MFS) compared with prostate-only radiation therapy in the POP-RT trial, although there was an increased grade II or higher late genitourinary toxicity [4]. Additionally, WPRT with adjuvant ADT was the superior arm in the recently published SPPORT trial (RTOG 0534) [5]. The ongoing RTOG 0924 trial will hopefully be able to quantify the overall survival benefit of ENI in unfavorable intermediate and high-risk prostate cancer.

Level 1 evidence for WPRT in node positive disease is still lacking and, traditionally, ADT alone has been the basis of treatment. Currently, WPRT is used in addition to hormone-therapy, with retrospective evidence suggesting favorable bFFS and OS [17]. Additionally, a recent Indian study of moderately fractionated WPRT in node-positive patients reported excellent biochemical control rates at 4 years, and acceptable toxicity [6].

Evidence regarding toxicity and quality of life in patients treated with hypofractionated WPRT is still scarce, yet important to consider, especially when examining the increased toxicity to the bowel. Fortunately, modern radiation therapy techniques and the use of daily image guidance have allowed for optimized treatment volumes and improved toxicity profiles.

In this retrospective series, treatment was delivered using volumetric arc therapy (VMAT) with daily CBCT-based imaging. Acute grade 2 GI toxicity was reported in 25.64% of patients, and grade 2 GU toxicity was present in 17.95%. There were no grade 3 or higher GI toxicities, and only one grade 3 event was reported for GU toxicity.

The rate of toxicity reported is considered acceptable and is similar to results obtained in other clinical centers. For example, in a recent Canadian study of 105 patients treated with 60 Gy/20 fractions to the prostate volume, and 44 Gy/20 fractions to the nodal areas, the rates reported for acute GI and GU toxicity were 17.2% and GU 15.3%, respectively [11]. Another series that evaluated acute and chronic toxicity using moderate hypofractionation to prostate and pelvic nodes reported grade 2 GI and GU toxicity rates of 22% and 58%, respectively, and grade 3 toxicity in 1% of patients. Although these results are higher than the rates reported by our center and the Canadian series, it is important to note that this study treated patients using a regimen of 50.4 Gy to pelvic lymph nodes, 57.4 Gy to seminal vesicles and 70 Gy to the prostate, all in 28 fractions. Additionally, toxicities were scored using the Radiation Therapy Oncology Group (RTOG) scoring system.

In regard to quality of life, evaluated with EORTC QLQ-PR25, the mean scores for symptom scales were 11.26, 0, 4.96 and 9.57 for Urinary Symptoms, Incontinence Aid, Bowel Symptoms and Hormonal Treatment related symptoms, while mean scores for Sexual Activity and Sexual Functioning were 19.86

and 31.08. It is useful to remember that all items range in score from 0 to 100; a low score for Sexual Activity and Functioning represent a low level of functioning, whereas a low score for Urinary, Bowel and Hormonal Treatment-related symptoms represent a low level of symptomatology [16]. This translates into favorable symptom scores, and acceptable sexual activity and functioning scores in this group of patients.

QoL surveys were applied at last follow-up; although the value of pooling these QoL parameters is questionable, five-year follow-up of the CHHiP quality of life substudy reports little change in patient-reported outcomes between the 6 month and 5 year time point [18]. Since most of our cohort responded the QoL questionnaire at ≥ 6 months of follow-up (97.4%), our results could be a predictor for long-term quality of life parameters.

This study has several limitations; follow-up time is relatively short, limiting outcomes to report only on acute toxicity and quality of life parameters at 10.6 months. Longer follow-up is needed for late toxicity reports. Additionally, the retrospective design of this study and the quality of life survey's reliance on patient self-reporting inevitably generates some degree of Recall Bias. Furthermore, six patients with oligometastatic disease that had previously received SBRT with curative intent were included in this study. The treatment modality in this group of patients could act as a confounding factor for both toxicity and quality of life outcomes, although it is important to note that only 50% (3 patients) received pelvic SBRT (right ilium, left ilium, and sacrum/right ilium, respectively). Only 3 of the 6 patients presented grade 2 toxicity, while none presented grade 3 toxicity. Lastly, baseline quality of life parameters were not evaluated, impeding accurate estimates of treatment (hypofractionated WPRT and ADT) impact on QoL, particularly regarding ADT and sexual function scores.

Conclusions

The results obtained in our center, along with those reported in literature, seem to support that moderately hypofractionated WPRT is practical, well tolerated and convenient. This study is a report of our *initial* experience with moderate hypofractionation for WPRT. Further follow-up and patient recruitment is ongoing, and a future publication, with a larger cohort of patients, will be reported in the near future.

Conflict of interest

None declared.

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None declared.

Data availability

Available upon reasonable request to the corresponding author.

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