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Prostate only radiotherapy using external beam radiotherapy: A clinician’s perspective

Prostate-only radiotherapy for prostate cancer

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Abstract
Prostate-only radiotherapy (PORT) is widely used as the definitive treatment for localized prostate cancer. Prostate cancer has an $a/\beta$ ratio; therefore, radiotherapy (RT) with a large fraction size is biologically effective for tumor control. The current external beam RT technique for PORT has been improved from three-dimensional conformal RT to intensity-modulated, stereotactic body, and image-guided RTs. These methods are associated with reduced radiation exposure to normal tissues, decreasing urinary and bowel toxicity. Several trials have shown improved local control with dose escalation through the aforementioned methods, and the efficacy and safety of intensity-modulated and stereotactic body RTs have been proven. However, the management of RT in patients with prostate cancer has not been fully elucidated. As a clinician, there are several concerns regarding the RT volume and dose considering the patient’s age and comorbidities. Therefore, this review aimed to discuss the radiobiological basis and external beam technical advancements in PORT for localized prostate cancer from a clinician’s perspective.

Key Words: Prostate cancer; Radiotherapy

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Core Tip: The present study discussed the radiobiologic basis and external beam technical advancement of prostate-only radiotherapy (PORT) for localized prostate cancer from a clinician’s perspective. We verified the efficacy and safety of PORT by external beam radiotherapy, and RT techniques are developed to deliver higher doses of radiation to prostate safely. Therefore, PORT is recommended for localized prostate cancer patients, regardless of risk groups of patients.

INTRODUCTION
Radiotherapy (RT) plays an important role in the definitive treatment of prostate cancer. RT is effective for prostate cancer and has outcomes comparable to those of radical prostatectomy [1]. Furthermore, RT shows several advantages over radical prostatectomy. It avoids complications associated with general anesthesia and operation, including bleeding, and has a low risk of urinary incontinence and stricture compared to that of radical prostatectomy [2]. The National Comprehensive Cancer Network (NCCN) guidelines recommend RT combined with or without androgen deprivation therapy (ADT) for localized prostate cancer [3]. Moreover, Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (SEER) data from 1988 to 1991 [4] showed that more extensive lymphadenectomy at radical prostatectomy could increase the accuracy of cancer staging and prostate cancer-specific survival, even in patients with negative lymph node (LN) metastasis. Therefore, whole pelvic radiotherapy (WPRT) at a dose of 40–50 Gy followed by boost RT to the prostate is commonly used for the elective nodal irradiation (ENI) of the prostate cancer with a high risk of >15% of lymph node involvement [5]. Early prostate cancer detection is currently possible, and some efforts have been made for a more accurate estimation of pelvic LN metastasis risk using clinical stage, Gleason score, PSA (prostate specific antigen), Roach formula (RF: 2/3 PSA + [Gleason score-6] x 10), Nguyen formula, or even the Yale formula, which reflects the T stage [3, 6, 7, 8, 9]. The necessity of pelvic ENI has been discussed in the definitive treatment of locally advanced prostate cancer [10].

Prostate-only radiotherapy (PORT) has a target volume that involves the whole prostate above the penile bulb to base, which is continuous with the bladder +/- and sometimes comprises a part of the seminal vesicle depending on the risk of invasion [11]. In contrast, the WPRT target volume includes PORT target volume plus regional pelvic LN area comprising the common (lumbar/sacral junction level), external, internal iliac, and obturator areas [12, 13]. Several studies failed to demonstrate the benefit of WPRT in cancer-related survival outcomes compared to that of PORT. In fact, urinary and intestinal toxicity outcomes were better after PORT than after WPRT [14-17].
This review focused on the background and the efficacy of PORT for localized prostate cancer, as well as the technical advancements in external beam radiotherapy (EBRT) in these patients.

**Radiation dose prescription**

With advances in the RT technique, prescription doses can be more feasibly delivered to the prostate and further improve outcomes. Several randomized trials have confirmed that a minimum dose of >70 Gy can more effectively improve tumor control than that of lower doses of <70 Gy \[^{18}\]. In the Dutch trial, 333 and 331 patients were prescribed doses of 78 Gy, and 68 Gy, respectively, and the five-year freedom from failure rate was 64% and 54%, respectively, implying that the 78 Gy group had significantly better outcomes \[^{18}\]. The patients in the RTOG phase III trial 0126 were randomly assigned to the 70.2 or 79.2 Gy groups \[^{19}\]. The study found that the Phoenix 10-year biochemical failure was higher in the 70.2 Gy group (43%) than in the 79.2 Gy group (26%). These studies found that dose escalation induced dose-dependent improvement in freedom from failure.

The linear quadratic model describes the curvature of the cell that kills both normal tissue complications and tumor control according to the RT dose. Typically, cells with higher α/β ratios exhibit more linear curves. However, lower α/β ratio cells showed a more curved curve. This plays an important role in the treatment area as the RT resistance according to the tissue’s α/β ratio is affected. Most tumor cells are classified as cells with a higher α/β ratio owing to their rapid proliferation. Prostate cancer cells are classified as cells with a lower α/β ratio that present a late response and slow proliferation. Prostate cancer has a very low α/β ratio; therefore, a higher fraction size can be applied to improve the therapeutic ratio with approximately the same side effects \[^{20, 21}\]. Moreover, hypofractionation reduces the treatment cost and shortens the treatment period for patients compared to that for conventional RT. Several randomized controlled trials have been published on the use of hypofractionated RT in patients with prostate cancer. Yeoh et al reported a 7.5-year freedom from biochemical...
relapse (FFBR) rate of 53% and 34% with the hypofractionated and conventional RT groups, respectively \[^{22}\]. This study was the first randomized trial comparing hypofractionated and conventional RT for prostate cancer to verify the long-term therapeutic benefit of hypofractionated RT. RT planning was performed using two-dimensional radiotherapy (2D-RT) and three-dimensional conformal therapy (3D-CRT). There were more late GU complications with 2D-RT compared to those with 3D-CRT (hazard ratio [HR], 1.58; and 95% CI, 1.01–2.47). Arcangeli et al investigated the effect of hypofractionated RT on oncological outcomes in patients with prostate cancer. This trial showed that there was a statistically significant effect on the FFBR rate. Particularly, in the subgroup analysis of high risk patients, the 3-year FFBR rate of hypofractionated RT (88%) was significantly better than that of conventional RT (76%; \( p=0.014 \)). Moreover, there was no difference in late toxicity between both treatment groups despite a concern regarding toxicity due to the large fraction size \[^{23}\].

**Technical advancements in external beam radiotherapy (EBRT): Intensity-modulated radiotherapy (IMT), stereotactic body radiotherapy (SBRT), and image-guided radiotherapy (IGRT)**

RT can cure prostate cancer and is associated with urinary and bowel discomfort. Particularly, a higher radiation dose with a large fraction size achieves effective tumor control for prostate cancer with or without hormone therapy but may result in more normal tissue damage than that with conventional fractionated RT. In the early stage of RT, 2D-RT was conventionally delivered using simple X-ray images. Subsequently, multiple fields and multileaf collimators (MLC) were utilized for the exposure of OAR to radiation following the conceptualization of 3D-CRT \[^{24}\]. 3D-CRT has the advantage of rectal dose reduction compared to that with 2D techniques \[^{25,26}\], yet PORT has been delivered using more advanced techniques than that of 3D CRT, including IMRT and SBRT.

IMRT has been commonly used in recent years and delivered in five to nine fields with static or dynamic movement MLC types and inverse treatment planning processes \[^{27}\].
Volumetric-modulated arc therapy (VMAT) or helical tomotherapy is affiliated with IMRT as a deformed type of therapy. This technical approach allows the enhancement of conformal and homogeneous radiation dose distribution for the target and minimizes normal tissue exposure. Compared to 3D-CRT, IMRT can reduce the dose to normal tissues and improve target coverage. IMRT has the main advantage of reducing possible late side effects by decreasing the dose to the rectum and bladder. Most studies comparing the toxicity outcomes of IMRT with those of 3D-CRT in patients with prostate cancer are retrospective. Zelefsky et al reported the results of analyzing the late effects of 1571 patients with prostate cancer treated with 3D-CRT and IMRT. In their study, despite higher doses being delivered with IMRT than with 3D CRT, IMRT had reduced late grade 2 or higher gastrointestinal toxicities compared to those with 3D CRT.

SBRT is a radiation technique that delivers a high radiation dose and an ultra-hypofractionated schedule (i.e., >5 Gy per fraction within 5 fractions) to the target with high accuracy and conformity. This therapeutic approach is based on a low α/β ratio in patients with prostate cancer. The NCCN guidelines suggest SBRT as the standard treatment for low- to intermediate-risk patients. The biologic effective dose (BED) using the linear-quadratic model is inappropriate for a very large fraction size and appropriate for fraction sizes up to 6–8 Gy per fraction. The PACE-B trial compared the gastrointestinal and genitourinary toxicities of IMRT with conventional fractionation (78 Gy in 39 fractions) or moderate hypofractionation (62 Gy in 20 fractions) with those of SBRT (36.25 Gy in 5 fractions). The trial included patients with low- to intermediate-risk. Its radiation dose regimens were applicable to the linear-quadratic (LQ) model; therefore, the radiation dose regimen of SBRT and IMRT in this trial were computed using the LQ model. The BED using an α/β ratio of 3 (Gy) for normal tissues was approximately 126.07 and 123.85 in SBRT and IMRT, respectively. This study suggested that these fractionations showed non-inferior outcomes in terms of acute toxicities of SBRT comprising ultra-hypofractionation compared with conventional or moderately hypofractionated IMRT. A longer follow-up is required to
determine the efficacy of SBRT for late toxicity and disease control. Contrary to the approval that SBRT is the main treatment for low- to intermediate- risk patients, the merit of SBRT is controversial in high-risk patients with prostate cancer [37]. As stated by a systematic review by Foerster et al [37], several studies reported biochemical recurrence rates in high-risk patients of >80% within 2 years after SBRT, despite the use of ADT [38-41]. However, favorable results have been reported for SBRT in high-risk patients. Lee et al [42] reported a safe and good result of SBRT using Cyberknife, with a total of 36 Gy in 5 fractions in patients with prostate cancer. Two-thirds of patients belonged to the low- or intermediate-risk group, but approximately one-third of patients belonged to the high-risk group. A 5-year disease free survival (DFS) rate of approximately 90% has been reported. Moreover, there are several studies comprising high-risk patients that reported a 5-year DFS >70% [43-45], and the SHARP consortium supported SBRT efficacy for high risk prostate cancer [46]. According to Zhao et al [45], the 5-year DFS in very high-risk patients with prostate cancer is 61.6%. Therefore, SBRT may be a useful treatment option for patients with prostate cancer who are old or have medical comorbidities.

Modern techniques such as IMRT and SBRT have steep radiation dose distributions affected by organ movement. Therefore, they can be supported by a meticulous setup by immobilizing the patient’s position, their pelvic organs using bladder and rectal preparation during simulation, and each treatment, target, and OAR confirmation through IGRT [47]. The volume and position of the bladder and rectum influence the prostate’s position; therefore, it is important to maintain a consistent volume for the bladder and rectum for each duration of RT. Owing to the aforementioned delivery of modern techniques and intrapelvic geometric importance, a bladder scanner before simulation CT and every radiation treatment is useful, and this has been verified in several studies on pelvic RT [48,49]. The efficacy of endorectal ballooning is well known for its immobilizing merit in the prostate and rectum, and reduction in toxicity [50]. IGRT is needed for a more precise RT plan and the delivery of a high radiation dose. The existing set-up process, depending on skin marking and bony landmarks, is insufficient for highly conformal RT techniques. IGRT image registration has been improved from
2D radiography images using bony landmarks to 3D images by cone-beam CT. Nowadays, magnetic resonance imaging-guided radiotherapy or real-time target tracking and gating by IGRT after transrectal ultrasound-guided fiducial marker insertion has been utilized\textsuperscript{[51-54]}. IGRT enables the precise irradiation of the PTV target. Moreover, it can reduce the PTV margin, as well as the irradiated dose to normal organs, further reducing normal organ toxicities.

**Radiation volume**

Prophylactic ENI is not routinely applied in patients with low- and favorable intermediate-risk prostate cancer. In this case, PTV included the prostate +/- seminal vesicles. However, prophylactic ENI should be considered in patients with unfavorable intermediate risk. In such cases, ADT should be performed unless contraindicated. ADT can eliminate the risk of microscopic lymph node metastasis. For other localized advanced solid tumors, prophylactic ENI is the standard of care\textsuperscript{[55]}, yet there is no strong evidence for ENI in patients with high-risk prostate cancer. Therefore, randomized clinical trials have compared PORT and WPRT in patients with high-risk prostate cancer\textsuperscript{[17,56]}. The long-term clinical outcomes of the POP-RT randomized trial were published, with a median follow-up time of 68 mo\textsuperscript{[56]}. The 5-year biochemical failure rates were 95\% and 81.2\% in the WPRT and PORT groups, respectively (95\%CI, 71.6–87.8). The 5-year DFS rates were 89.5 \% and 77.2\% in the WPRT and PORT groups, respectively ($p=0.002$). However, there was no statistically significant difference in ENI for OS. The GETUG-01 trial randomized patients with T1b-T3, N0pN0x, and M0 prostate cancer to receive either WPRT or PORT\textsuperscript{[17]}. Patients were followed-up for a median of 11.4 years. The OS rates of the WPRT and PORT groups at 10 years were 74.9\% and 73.6\%; 87.7\% and 84\%; and 71.2\% and 71\% for the whole population, low risk, and high-risk groups, respectively. The event-free survival rates were not statistically significantly different for the entire series of patients stratified into the high-risk group (57.6\% vs. 55.6\% and 52.0\% vs. 54.2\% at 10 years, respectively).
CONCLUSION

Previous studies have verified the efficacy and safety of PORT by EBRT and discussed the corresponding technical advances, dose, and fractionation of EBRT using its lower $\alpha/\beta$ ratio in prostate cancer, regardless of the risk groups of patients. RT techniques, including IMRT, IGRT and SBRT, have evolved to safely permit higher doses of radiation to be administered to the prostate. Moreover, there were tolerable normal tissue complications and favorable treatment outcomes. Therefore, PORT is recommended for low- to favorable intermediate-risk patients and deserves consideration for unfavorable intermediate- or high-risk patients with old age or medical comorbidities who have difficulties receiving aggressive treatments. Further studies on the optimal dose and fractionation of RT, combination of androgen deprivation therapy by risk group, and prostate disease control are needed to improve prognosis. Finally, new studies are required to assess the exact patient risk group that can benefit from PORT more than that from WPRT.
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