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

Lee JW *et al.* 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 α/βratio; 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; Radiation dose; Radiation technique; Radiation volume

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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 radiotherapy 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) × 10], Nguyen formula, or even the Yale formula, which reflects the T stage[3,6-9]. 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 LNs 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/βratios exhibit more linear curves. However, lower α/βratio 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/βratio is affected. Most tumor cells are classified as cells with a higher α/βratio owing to their rapid proliferation. Prostate cancer cells are classified as cells with a lower α/βratio that present a late response and slow proliferation. Prostate cancer has a very low α/βratio; 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*[22] reported a 7.5-year freedom from biochemical relapse (FFBR) rate of 53% and 34% with the hypofractionated and conventional RT groups, respectively.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*[23] 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 EBRT: INTENSITY-MODULATED RADIOTHERAPY, STEREOTACTIC BODY RADIOTHERAPY, AND IMAGE-GUIDED RADIOTHERAPY**

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 stereotactic body radiotherapy (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 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[28-31]. Compared to 3D-CRT, IMRT can reduce the dose to normal tissues and improve target coverage[32]. IMRT has the main advantage of reducing possible late side effects by decreasing the dose to the rectum and bladder[33]. Most studies comparing the toxicity outcomes of IMRT with those of 3D-CRT in patients with prostate cancer are retrospective. Zelefsky *et al*[34] 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/βratio in patients with prostate cancer. The NCCN guidelines[3] 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[35]. The PACE-B trial[36] 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 (Gy3) 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 image-guided radiotherapy (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[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[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[17,56]. The long-term clinical outcomes of the POP-RT randomized trial were published, with a median follow-up time of 68 mo[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, N0pNx, and M0 prostate cancer to receive either WPRT or PORT[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 α/β 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.

**REFERENCES**

1 **Wolff RF**, Ryder S, Bossi A, Briganti A, Crook J, Henry A, Karnes J, Potters L, de Reijke T, Stone N, Burckhardt M, Duffy S, Worthy G, Kleijnen J. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. *Eur J Cancer* 2015; **51**: 2345-2367 [PMID: 26254809 DOI: 10.1016/j.ejca.2015.07.019]

2 **Potosky AL**, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, Harlan LC. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst* 2004; **96**: 1358-1367 [PMID: 15367568 DOI: 10.1093/jnci/djh259]

3 **NCC.** NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer [Internet]. Fort Washington, PA: National Comprehensive Cancer Network; c2022 [cited 10 May 2022]. Available from: https://www.nccn.org/professionals/physician\_gls/pdf/prostate.pdf

4 **Joslyn SA**, Konety BR. Impact of extent of lymphadenectomy on survival after radical prostatectomy for prostate cancer. *Urology* 2006; **68**: 121-125 [PMID: 16806432 DOI: 10.1016/j.urology.2006.01.055]

5 **Edward C.Halperin DEW,** Carlos A.Perez, Luther W.Brady. Perez and Brady's principles and practice of radiation oncology 6th ed. Philadelphia: Lippincott Williams & Wilkins. 2013: 1318-1319 [DOI: 10.1093/jnci/90.19.1485]

6 **Cagiannos I**, Karakiewicz P, Eastham JA, Ohori M, Rabbani F, Gerigk C, Reuter V, Graefen M, Hammerer PG, Erbersdobler A, Huland H, Kupelian P, Klein E, Quinn DI, Henshall SM, Grygiel JJ, Sutherland RL, Stricker PD, Morash CG, Scardino PT, Kattan MW. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. *J Urol* 2003; **170**: 1798-1803 [PMID: 14532779 DOI: 10.1097/01.ju.0000091805.98960.13]

7 **Roach M,** 3rd, Marquez C, Yuo HS, Narayan P, Coleman L, Nseyo UO, Navvab Z, Carroll PR. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. *Int J Radiat Oncol* 1994: **33** [DOI: 10.1016/0360-3016(94)90138-4]

8 **Nguyen PL**, Chen MH, Hoffman KE, Katz MS, D'Amico AV. Predicting the risk of pelvic node involvement among men with prostate cancer in the contemporary era. *Int J Radiat Oncol Biol Phys* 2009; **74**: 104-109 [PMID: 19286330 DOI: 10.1016/j.ijrobp.2008.07.053]

9 **Yu JB**, Makarov DV, Gross C. A new formula for prostate cancer lymph node risk. *Int J Radiat Oncol Biol Phys* 2011; **80**: 69-75 [PMID: 20594769 DOI: 10.1016/j.ijrobp.2010.01.068]

10 **Dirix P**, Haustermans K, Junius S, Withers R, Oyen R, Van Poppel H. The role of whole pelvic radiotherapy in locally advanced prostate cancer. *Radiother Oncol* 2006; **79**: 1-14 [PMID: 16631267 DOI: 10.1016/j.radonc.2006.03.011]

11 **Salembier C**, Villeirs G, De Bari B, Hoskin P, Pieters BR, Van Vulpen M, Khoo V, Henry A, Bossi A, De Meerleer G, Fonteyne V. ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer. *Radiother Oncol* 2018; **127**: 49-61 [PMID: 29496279 DOI: 10.1016/j.radonc.2018.01.014]

12 **Harris VA**, Staffurth J, Naismith O, Esmail A, Gulliford S, Khoo V, Lewis R, Littler J, McNair H, Sadoyze A, Scrase C, Sohaib A, Syndikus I, Zarkar A, Hall E, Dearnaley D; PIVOTAL Trialists. Consensus Guidelines and Contouring Atlas for Pelvic Node Delineation in Prostate and Pelvic Node Intensity Modulated Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2015; **92**: 874-883 [PMID: 26104940 DOI: 10.1016/j.ijrobp.2015.03.021]

13 **Sargos P**, Guerif S, Latorzeff I, Hennequin C, Pommier P, Lagrange JL, Créhange G, Chapet O, de Crevoisier R, Azria D, Supiot S, Habibian M, Soulié M, Richaud P. Definition of lymph node areas for radiotherapy of prostate cancer: A critical literature review by the French Genito-Urinary Group and the French Association of Urology (GETUG-AFU). *Cancer Treat Rev* 2015; **41**: 814-820 [PMID: 26508669 DOI: 10.1016/j.ctrv.2015.10.005]

14 **Lawton CA**, DeSilvio M, Roach M 3rd, Uhl V, Kirsch R, Seider M, Rotman M, Jones C, Asbell S, Valicenti R, Hahn S, Thomas CR Jr. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007; **69**: 646-655 [PMID: 17531401 DOI: 10.1016/j.ijrobp.2007.04.003]

15 **Bittner N**, Merrick GS, Wallner KE, Butler WM, Galbreath R, Adamovich E. Whole-pelvis radiotherapy in combination with interstitial brachytherapy: does coverage of the pelvic lymph nodes improve treatment outcome in high-risk prostate cancer? *Int J Radiat Oncol Biol Phys* 2010; **76**: 1078-1084 [PMID: 19553031 DOI: 10.1016/j.ijrobp.2009.02.069]

16 **Pinkawa M**, Piroth MD, Holy R, Fischedick K, Klotz J, Székely-Orbán D, Eble MJ. Quality of life after whole pelvic versus prostate-only external beam radiotherapy for prostate cancer: a matched-pair comparison. *Int J Radiat Oncol Biol Phys* 2011; **81**: 23-28 [PMID: 20832182 DOI: 10.1016/j.ijrobp.2010.05.054]

17 **Pommier P**, Chabaud S, Lagrange JL, Richaud P, Le Prise E, Wagner JP, Azria D, Beckendorf V, Suchaud JP, Bernier V, Perol D, Carrie C. Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Update of the Long-Term Survival Results of the GETUG-01 Randomized Study. *Int J Radiat Oncol Biol Phys* 2016; **96**: 759-769 [PMID: 27788949 DOI: 10.1016/j.ijrobp.2016.06.2455]

18 **Peeters ST**, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, Bonfrer JM, Incrocci L, Lebesque JV. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006; **24**: 1990-1996 [PMID: 16648499 DOI: 10.1200/jco.2005.05.2530]

19 **Michalski JM**, Moughan J, Purdy J, Bosch W, Bruner DW, Bahary JP, Lau H, Duclos M, Parliament M, Morton G, Hamstra D, Seider M, Lock MI, Patel M, Gay H, Vigneault E, Winter K, Sandler H. Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. *JAMA Oncol* 2018; **4**: e180039 [PMID: 29543933 DOI: 10.1001/jamaoncol.2018.0039]

20 **Daşu A**. Is the alpha/beta value for prostate tumours low enough to be safely used in clinical trials? *Clin Oncol (R Coll Radiol)* 2007; **19**: 289-301 [PMID: 17517328 DOI: 10.1016/j.clon.2007.02.007]

21 **Miralbell R**, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: α/β = 1.4 (0.9-2.2) Gy. *Int J Radiat Oncol Biol Phys* 2012; **82**: e17-e24 [PMID: 21324610 DOI: 10.1016/j.ijrobp.2010.10.075]

22 **Yeoh EE**, Botten RJ, Butters J, Di Matteo AC, Holloway RH, Fowler J. Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2011; **81**: 1271-1278 [PMID: 20934277 DOI: 10.1016/j.ijrobp.2010.07.1984]

23 **Arcangeli G**, Saracino B, Gomellini S, Petrongari MG, Arcangeli S, Sentinelli S, Marzi S, Landoni V, Fowler J, Strigari L. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2010; **78**: 11-18 [PMID: 20047800 DOI: 10.1016/j.ijrobp.2009.07.1691]

24 **Daly T**. Evolution of definitive external beam radiation therapy in the treatment of prostate cancer. *World J Urol* 2020; **38**: 565-591 [PMID: 30850855 DOI: 10.1007/s00345-019-02661-6]

25 **Dearnaley DP,** Khoo VS, Norman AR, Meyer L, Nahum A, Tait D, Yarnold J, Horwich A. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999: **267** [DOI: 10.1016/S0140-6736(98)05180-0]

26 **Fenwick JD,** Khoo VS, Nahum AE, Sanchez-Nieto B, Dearnaley DP. Correlations between dose-surface histograms and the incidence of long-term rectal bleeding following conformal or conventional radiotherapy treatment of prostate cancer. *Int J Radiat Oncol* 2001: **473** [DOI: 10.1016/S0360-3016(00)01496-6]

27 **Cahlon O**, Hunt M, Zelefsky MJ. Intensity-modulated radiation therapy: supportive data for prostate cancer. *Semin Radiat Oncol* 2008; **18**: 48-57 [PMID: 18082588 DOI: 10.1016/j.semradonc.2007.09.007]

28 **Vora SA**, Wong WW, Schild SE, Ezzell GA, Halyard MY. Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2007; **68**: 1053-1058 [PMID: 17398023 DOI: 10.1016/j.ijrobp.2007.01.043]

29 **Michalski JM**, Yan Y, Watkins-Bruner D, Bosch WR, Winter K, Galvin JM, Bahary JP, Morton GC, Parliament MB, Sandler HM. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. *Int J Radiat Oncol Biol Phys* 2013; **87**: 932-938 [PMID: 24113055 DOI: 10.1016/j.ijrobp.2013.07.041]

30 **Sujenthiran A**, Nossiter J, Charman SC, Parry M, Dasgupta P, van der Meulen J, Cathcart PJ, Clarke NW, Payne H, Aggarwal A. National Population-Based Study Comparing Treatment-Related Toxicity in Men Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2017; **99**: 1253-1260 [PMID: 28974414 DOI: 10.1016/j.ijrobp.2017.07.040]

31 **Fischer-Valuck BW**, Rao YJ, Michalski JM. Intensity-modulated radiotherapy for prostate cancer. *Transl Androl Urol* 2018; **7**: 297-307 [PMID: 30050791 DOI: 10.21037/tau.2017.12.16]

32 **Nutting CM,** Convery DJ, Cosgrove VP, Rowbottom C, Padhani AR, Webb S, Dearnaley DP. Reduction of small and large bowel irradiation using an optimized intensity-modulated pelvic radiotherapy technique in patients with prostate cancer. *Int J Radiat Oncol Biol Phys* 2000: **649** [DOI: 10.1016/S0360-3016(00)00653-2]

33 **Luxton G**, Hancock SL, Boyer AL. Dosimetry and radiobiologic model comparison of IMRT and 3D conformal radiotherapy in treatment of carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2004; **59**: 267-284 [PMID: 15093924 DOI: 10.1016/j.ijrobp.2004.01.024]

34 **Zelefsky MJ**, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, Amols HI. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1124-1129 [PMID: 18313526 DOI: 10.1016/j.ijrobp.2007.11.044]

35 **Shibamoto Y**, Miyakawa A, Otsuka S, Iwata H. Radiobiology of hypofractionated stereotactic radiotherapy: what are the optimal fractionation schedules? *J Radiat Res* 2016; **57 Suppl 1**: i76-i82 [PMID: 27006380 DOI: 10.1093/jrr/rrw015]

36 **Brand DH,** Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, Ford D, Tolan S, Jain S, Martin A, Staffurth J, Camilleri P, Kancherla K, Frew J, Chan A, Dayes IS, Henderson D, Brown S, Cruickshank C, Burnett S, Duffton A, Griffin C, Hinder V, Morrison K, Naismith O, Hall E, van As N. Intensity-modulated fractionated radiotherapy vs stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol* 2019: 1531 [DOI: 10.1016/S1470-2045(19)30569-8]

37 **Foerster R**, Zwahlen DR, Buchali A, Tang H, Schroeder C, Windisch P, Vu E, Akbaba S, Bostel T, Sprave T, Zamboglou C, Zilli T, Stelmes JJ, Telkhade T, Murthy V. Stereotactic Body Radiotherapy for High-Risk Prostate Cancer: A Systematic Review. *Cancers (Basel)* 2021; **13** [PMID: 33673077 DOI: 10.3390/cancers13040759]

38 **Koskela K**, Palmgren JE, Heikkilä J, Virsunen H, Sailas L, Auvinen P, Seppälä J, Kataja V. Hypofractionated stereotactic body radiotherapy for localized prostate cancer - first Nordic clinical experience. *Acta Oncol* 2017; **56**: 978-983 [PMID: 28514930 DOI: 10.1080/0284186X.2017.1288923]

39 **Musunuru HB**, D'Alimonte L, Davidson M, Ho L, Cheung P, Vesprini D, Liu S, Chu W, Chung H, Ravi A, Deabreu A, Zhang L, Commisso K, Loblaw A. Phase 1-2 Study of Stereotactic Ablative Radiotherapy Including Regional Lymph Node Irradiation in Patients With High-Risk Prostate Cancer (SATURN): Early Toxicity and Quality of Life. *Int J Radiat Oncol Biol Phys* 2018; **102**: 1438-1447 [PMID: 30071295 DOI: 10.1016/j.ijrobp.2018.07.2005]

40 **Alayed Y**, Cheung P, Vesprini D, Liu S, Chu W, Chung H, Musunuru HB, Davidson M, Ravi A, Ho L, Deabreu A, D'Alimonte L, Bhounr Z, Zhang L, Commisso K, Loblaw A. SABR in High-Risk Prostate Cancer: Outcomes From 2 Prospective Clinical Trials With and Without Elective Nodal Irradiation. *Int J Radiat Oncol Biol Phys* 2019; **104**: 36-41 [PMID: 30445172 DOI: 10.1016/j.ijrobp.2018.11.011]

41 **Callan L**, Bauman G, Chen J, Lock M, Sexton T, D'Souza D, Rodrigues G. A Phase I/II Trial of Fairly Brief Androgen Suppression and Stereotactic Radiation Therapy for High-Risk Prostate Cancer (FASTR-2): Preliminary Results and Toxicity Analysis. *Adv Radiat Oncol* 2019; **4**: 668-673 [PMID: 31681864 DOI: 10.1016/j.adro.2019.07.007]

42 **Lee SW**, Jang HS, Lee JH, Kim SH, Yoon SC. Stereotactic body radiation therapy for prostate cancer patients with old age or medical comorbidity: a 5-year follow-up of an investigational study. *Medicine (Baltimore)* 2014; **93**: e290 [PMID: 25526468 DOI: 10.1097/MD.0000000000000290]

43 **Katz AJ**, Santoro M, Diblasio F, Ashley R. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. *Radiat Oncol* 2013; **8**: 118 [PMID: 23668632 DOI: 10.1186/1748-717X-8-118]

44 **Fransson P,** Nilsson P, Gunnlaugsson A, Beckman L, Tavelin B, Norman D, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, Kindblom J, Ginman C, Johansson B, Björnlinger K, Seke M, Agrup M, Zackrisson B, Kjellén E, Franzén L, Widmark A. Ultra-hypofractionated vs conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. *Lancet Oncol* 2021: 235 [DOI: 10.1016/S1470-2045(20)30581-7]

45 **Zhao X,** Ye Y, Yu H, Jiang L, Cheng C, Guo X, Ju X, Zhu X, Zhang H. Five-year outcomes of stereotactic body radiation therapy (SBRT) for prostate cancer: the largest experience in China. *Int J Radiat Oncol* 2021: 3557 [DOI: 10.21203/rs.3.rs-190455/v1]

46 **van Dams R,** Jiang NY, Fuller DB, Loblaw A, Jiang T, Katz AJ, Collins SP, Aghdam N, Suy S, Stephans KL, Yuan Y, Nickols NG, Murthy V, Telkhade TP, Kupelian PA, Steinberg ML, Romero T, Kishan AU. Stereotactic Body Radiotherapy for High-Risk Localized Carcinoma of the Prostate (SHARP) Consortium: Analysis of 344 Prospectively Treated Patients. *Int J Radiat Oncol Biol Phys* 2021: 731 [DOI: 10.1016/j.ijrobp.2020.07.469]

47 **Kim H**, Kim JW, Hong SJ, Rha KH, Lee CG, Yang SC, Choi YD, Suh CO, Cho J. Treatment outcome of localized prostate cancer by 70 Gy hypofractionated intensity-modulated radiotherapy with a customized rectal balloon. *Radiat Oncol J* 2014; **32**: 187-197 [PMID: 25324991 DOI: 10.3857/roj.2014.32.3.187]

48 **Haworth A**, Paneghel A, Bressel M, Herschtal A, Pham D, Tai KH, Oates R, Gawthrop J, Cray A, Foroudi F. Prostate bed radiation therapy: the utility of ultrasound volumetric imaging of the bladder. *Clin Oncol (R Coll Radiol)* 2014; **26**: 789-796 [PMID: 25242000 DOI: 10.1016/j.clon.2014.08.010]

49 **Okamoto H**, Murakami N, Carvajal CC, Miura Y, Wakita A, Nakamura S, Nishioka S, Iijima K, Inaba K, Ito Y, Kato T, Toita T, Itami J. Positional uncertainty of vaginal cuff and feasibility of implementing portable bladder scanner in postoperative cervical cancer patients. *Phys Med* 2018; **45**: 1-5 [PMID: 29472073 DOI: 10.1016/j.ejmp.2017.11.018]

50 **Jeong S**, Lee JH, Chung MJ, Lee SW, Lee JW, Kang DG, Kim SH. Analysis of Geometric Shifts and Proper Setup-Margin in Prostate Cancer Patients Treated With Pelvic Intensity-Modulated Radiotherapy Using Endorectal Ballooning and Daily Enema for Prostate Immobilization. *Medicine (Baltimore)* 2016; **95**: e2387 [PMID: 26765418 DOI: 10.1097/MD.0000000000002387]

51 **Xie Y**, Djajaputra D, King CR, Hossain S, Ma L, Xing L. Intrafractional motion of the prostate during hypofractionated radiotherapy. *Int J Radiat Oncol Biol Phys* 2008; **72**: 236-246 [PMID: 18722274 DOI: 10.1016/j.ijrobp.2008.04.051]

52 **O'Neill AG**, Jain S, Hounsell AR, O'Sullivan JM. Fiducial marker guided prostate radiotherapy: a review. *Br J Radiol* 2016; **89**: 20160296 [PMID: 27585736 DOI: 10.1259/bjr.20160296]

53 **Hewson EA**, Nguyen DT, O'Brien R, Poulsen PR, Booth JT, Greer P, Eade T, Kneebone A, Hruby G, Moodie T, Hayden AJ, Turner SL, Hardcastle N, Siva S, Tai KH, Martin J, Keall PJ. Is multileaf collimator tracking or gating a better intrafraction motion adaptation strategy? An analysis of the TROG 15.01 stereotactic prostate ablative radiotherapy with KIM (SPARK) trial. *Radiother Oncol* 2020; **151**: 234-241 [PMID: 32828839 DOI: 10.1016/j.radonc.2020.08.010]

54 **Sritharan K**, Tree A. MR-guided radiotherapy for prostate cancer: state of the art and future perspectives. *Br J Radiol* 2022; **95**: 20210800 [PMID: 35073158 DOI: 10.1259/bjr.20210800]

55 **Rotman M**, Pajak TF, Choi K, Clery M, Marcial V, Grigsby PW, Cooper J, John M. Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. *JAMA* 1995; **274**: 387-393 [PMID: 7616634 DOI: 10.1001/jama.274.5.387]

56 **Murthy V**, Maitre P, Kannan S, Panigrahi G, Krishnatry R, Bakshi G, Prakash G, Pal M, Menon S, Phurailatpam R, Mokal S, Chaurasiya D, Popat P, Sable N, Agarwal A, Rangarajan V, Joshi A, Noronha V, Prabhash K, Mahantshetty U. Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. *J Clin Oncol* 2021; **39**: 1234-1242 [PMID: 33497252 DOI: 10.1200/JCO.20.03282]

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