Review

DOI: 10.4274/uob.galenos.2019.1418

Bull Urooncol 2020;19:49-55

Current Approach in Radiation Therapy for Prostate Cancer

İlknur Alsan Çetin

Marmara University Faculty of Medicine, Department of Radiation Oncology, İstanbul, Turkey

Abstract

Prostate cancer is one of the most common malignancies in men. Radiotherapy is one of the main treatment modalities in the treatment of prostate cancer. The reflection of technological advances in the field of radiation oncology enables the safe application of higher doses of radiotherapy in the treatment of prostate cancer. In addition, improvements in normal tissue preservation are reflected in patients' quality of life. Radiotherapy can be applied in all stages of prostate cancer and postoperative radiotherapy can be applied in appropriate indication. Side effects are expected to be observed more in patients undergoing postoperative radiotherapy. The treatment decision should be based on personal preference after informing the patient about the advantages and disadvantages of each treatment approach.

Keywords: Prostate cancer, radiotherapy, treatment

Introduction

Prostate cancer (PC) is one of the most common malignancies in men. Radical prostatectomy (RP), external beam radiotherapy (EBRT), brachytherapy (BCT) are different options that can be applied in patients with limited disease. Surgery and radiotherapy (RT) are considered standard in the treatment of localized PC. Treatment decision should be made with the patient after a multidisciplinary evaluation of the patient's age, performance status, accompanying diseases, life expectancy and possible side effects of the treatment. In addition to life expectancy, quality of life is also important in patients. The patient should also be informed that RT may be needed after surgery and that side effects may increase.

The reflection of technological developments in Radiation Oncology has enabled increased sensitivity in determining tumor sites, to reflect these identified areas to treatment at high accuracy rate [Image-guided Radiotherapy (IGRT)], to decrease margins given to tumors (Intensity-Modulated Radiotherapy-IMRT), and thus to preserve more normal tissue (1). As a result of the increase in sensitivity and accuracy, the increase in doses administered and the application of high doses within a short period of time [Stereotactic Body Radiotherapy (SBRT)] is possible and the treatment times are shortened. Thanks to all these developments, both high tumor control and increased life expectancy, as well as a decrease in normal tissue toxicity of patients and the resulting increase in quality of life have been achieved.

The RT used in PC is EBRT and BCT. Current approaches in RT techniques are IMRT and SBRT. The form of treatment, dose and hormone therapy (HT) vary according to the risks and stages of PC. Curative RT of localized PC is administered in doses between 74-81 Gy for 7-9 weeks with conventional fractions (1.8-2 Gy/day) as standard and 5 days per week. It is possible to apply higher doses to the tumor with fewer side effects in parallel with technological developments in imaging methods and computer software.

Very Low Risk PC; T1c, grade group 1 (GS 6), prostate specific antigen (PSA) <10, 1 or 2 quadrant positivities and ≤50% for each quadrant positivity and PSA density ≤0.15 ng/mL. Magnetic resonance imaging and genomic tests may be performed to rule out high-grade disease in patients younger than 62 years. Active follow-up is often recommended except this group of patients.

Low Risk PC; T1c/T2a, grade group 1 (GS 6), PSA <10. Treatment options are ERT and BCT. EBRT can be applied as standard fractionation (2 Gy per day) with 78-80 Gy, as Hypofractionated RT (HRT); 70 Gy (2.5 Gy per day), 60 Gy (3 Gy per day) or as SBRT; 36-40 Gy (7.25-8 Gy per day). BCT can be applied as Low-dose-rate (LDR): I-125, Pd-103, Cs-131 (with permanent source placement) or High-dose-rate (HDR) (with Ir-192 catheters, 4 times). D'Amico et al. (2) showed that the results of treatment with RP, EBRT and BCT were similar in patients with low-risk PC. BCT studies showed results ranging from 95% to 85% in 5-10-year PSA controls in different series (3,4,5,6). In the Spirit trial, BCT and RP were compared in

Cite this article as: Çetin İA. Current Approach in Radiation Therapy for Prostate Cancer. Bull Urooncol 2020;19(2):49-55

Address for Correspondence: İlknur Alsan Çetin, Marmara University Faculty of Medicine, Department of Radiation Oncology, İstanbul, Turkey
Phone: +90 532 702 15 92 **E-mail:** ilknurcet@gmail.com **ORCID-ID:** orcid.org/0000-0003-4206-6393
Received: 30.09.2019 **Accepted:** 25.12.2019

terms of quality of life and there were statistically significant less urinary leakage and better sexual outcomes in BCT (7). Donovan et al. (8) compared quality of life results between RP and EBRT in the "Prostate Testing for Cancer and Treatment" (Protect) trial and showed that RP had better results in terms of intestinal functions and nocturia, while EBRT had better results in terms of incontinence and erectile dysfunction.

HRT (daily fraction dose 2.4-4 Gy, total treatment duration 4-6 weeks). The total duration of treatment for PC due to its radiobiological characteristics can be shortened by increasing the fraction dose, i.e. hypofractionation. The results of studies comparing moderate hypofractionation with standard fractionation were found to be similar (Table 1). The meta-analysis showed similar results except for higher acute gastrointestinal (GI) side effects with conventional EBRT (16). Therefore, moderately HRT is recommended in low and moderate risk PC (17). In Ultra HRT (SBRT), fraction doses between 4-10 Gy per day are generally applied in ≤5 fractions with a total dose of 35-50 Gy. The studies are shown in Table 2.

SBRT can cause more side effects than moderately HRT. The Swedish study, a phase III randomized study, compared 42.7 Gy (6.1 Gy per day) SBRT with 78 Gy (2 Gy per day) conventional

Table 1. Trials comparing moderate hypofractionation with external beam radiotherapy

Trial	n	Trial design	Trial arms	Risk groups	HT	Median follow-up	Cancer control	Acute GU SE	Acute GI SE	Late GU SE	Late GI SE
Dearnaley et al. (9)	3216	Multicenter Non-inferiority Biochemical or clinical failure rate	74 Gy (2 Gy) 60 Gy (3 Gy) 57 Gy (3 Gy)	15% Low 73% Intermediate 12% High	97% 3-6 months	5.2 years	60 Gy/74 Gy same 57 Gy was worse than 74 Gy	Similar	Increased risk with hypofractionation 25%/38%	Similar	Similar
Catton et al. (10)	608	Multicenter Non-inferiority Biochemical or clinical failure rate	78 Gy (2 Gy) 60 Gy (3 Gy)	Intermediate	No	6 years	Hypofractionation was non-inferior	Similar	Increased risk with EBRT 10%/16%	Similar	Reduced risk with hypofractionation 11%/7%
Lee et al. (11)	1115	Multicenter Disease-free survival	7380 cGy (1.8 Gy) 70 Gy (2.5 Gy)	Low	No	5.8 years	Hypofractionation was non-inferior	Similar	Similar	Increased risk with EBRT 23%/30%	Increased risk with EBRT 14%/22%
Incrocci et al. (12)	820	Çok merkezli Recurrence-free survival	78 Gy (2Gy) /78 Gy 6460 cGy (3.4Gy) / 87 Gy	26% Intermediate 74% High	67%	5 years	Non-significant difference	Similar	Increased risk with BRT 31%/42%	39%/41%	18%/22%
Shaikh et al. (13)	303	Single center Biochemical failure	76 Gy (2 Gy) /76 Gy 7020 cGy (2.7Gy) / 84 Gy	66% Intermediate 33% High	46%	5.7 years	Non-significant difference			Similar	Similar
Hoffman et al. (14)	206	Single center Disease-free survival	7560 cGy (1.8 Gy) /71 Gy 72 Gy (2.4 Gy) / 84 Gy	28% Low 71% Intermediate	%24	8.4 years	Hypofractionation improved cancer control			Similar	Increased trend 5%/13% p=0.08
Valeriani et al. (15)	168	Single center Late toxicity	80 Gy (2 Gy) 62 Gy (3.1 Gy) /81 Gy	High	All	9 years	Non-significant difference	Similar	Increased trend 21%/35% p=0.07	Similar	Similar

HT: Hormone therapy, GU: Genitourinary, SE: Side effect, GI: Gastrointestinal, EBRT: External beam radiotherapy

Table 2. Trials of stereotactic body radiotherapy

Trial	n	Median follow-up (years)	Dose	EQD2	GS 6	Acute G3+		Late G3+			5-year BDFS
						GU	GI	GU	GI	ED	
Pham et al. 2010 (18) (Abstract)	40	5yıl	34 Gy (5 frc)	82 Gy	100%	2%	0%	3%	0%	50%	93%
Kupelian et al. 2013 (19) (Abstract)	135	5	35/40 Gy (4-5 frc)	8650-11060 cGy	80%	NR	NR	NR	NR	NR	97%
Mantz, 2014 (20)	102	>5	40 Gy (5 frc)	11060 cGy	69%	2%	0%	NR	0%	NR	100%
Hannan et al. 2016 (21)	91	4.5	45-50 Gy (5 frc)	13800-16800 cGy	47%	0%	2%	5%	7%	26%	99%
Musunuru et al. 2016 (22)	84	6.2	35 Gy (5 frc)	8650 cGy	100%	1%	0%	0%	1%	43%	97%
Zimmerman et al. 2016 (23)	80	6.9	45 Gy (9 frc)	8470 cGy	100%	NR	NR	4%	13%	NR	96%
Total	532				80%	1.2%	0.6%	3%	2.6%	37%	98%

BDFS: Biochemical disease-free survival, ED: Erectile dysfunction, EQD2: Dose equivalent to 2 Gy fraction, Frc: Fraction, GI: Gastrointestinal, GU: Genitourinary, NR: Not reported

RT in patients with intermediate and high risk PC. Biochemical relapse-free survival rate (83.8% vs. 83.7%), late urinary side effects (3.5% vs. 2.5%) and rectal (2.3% vs. 1.3%) side effects were similar in 5-year follow-up (24). The PACE B randomized study compared 36.5 Gy (7.25 Gy per day) SBRT and 78 Gy (2 Gy per day) EBRT in 858 patients with low and intermediate risk PC. No difference was detected in terms of acute side effects (25). A meta-analysis of 6116 patients showed that SBRT increased biochemical control (p=0.018) but were associated with more grade 3 or above genitourinary (GU) side effects (p=0.014) (26). In light of the studies, SBRT may also be recommended, especially for low-risk patients.

Intermediate Risk PC; Good intermediate risk: <50% biopsy positivity (presence of only 1 moderate risk factor T2b/c or GS (3+4) or PSA:10-20 ng/mL). Good intermediate risk tends to be treated like a low risk group. BCT, EBRT or moderately HRT can be performed. Poor intermediate risk: GS (4+3), contains ≥50% biopsy positivity or many intermediate risk factors. Short term (4-6 months) HT with EBRT, BCT boost with EBRT (and/or short term HT) can be applied. Studies on dose increase in intermediate risk PC are going on. In the GETUG-14 trial, 377 patients with intermediate risk PC were treated with 80 Gy EBRT either alone or in combination with HT for 4 months. Five-year biochemical failure rates were 21% and 10% in the groups (p=0.02) and no difference was detected in terms of toxicity (27). In the ASCENDE-RT trial, medium and high risk patients were either given dose-escalated EBRT boost to 78 Gy (2 Gy per day) or LDR BCT (115 Gy I125) boost. Biochemical failure rates in the BCT arm were found to be statistically significantly 2 times better for medium and high risk patients (28).

High Risk PC; EBRT and HT (1.5-3 years) or EBRT, BCT boost and HT (1-3 years) are recommended. In 3 randomized studies, biochemical recurrence-free survival was found to be statistically significantly higher with dose-escalating EBRT and BCT (28,29,30).

Table 3. Phase III trials comparing external beam radiotherapy plus hormone therapy with external beam radiotherapy

Trials	Risk groups	Trial arms	5-year results	10-year results
Standard dose EBRT				
D'Amico et al. (31)	Intermediate/high-risk PC	Arm 1= EBRT Arm 2= EBRT + HT (6 months)	CSS= 94/100 OS= 77/88 BPFS= 55/79	OS= 61/74 (8 years) DSS= 84/78 (8 years) OS= 28/35NS (15 years)
Pilepich et al. (32)	High-risk PC	Arm 1= EBRT Arm 2= EBRT + HT	BRFS= 21/55 DM= 29/15 CSS= 87/91 OS= 71/76	DM= 39/24 CSS= 78/84 OS= 39/49 BPFS= 9/31 LF= 38/23 DSS= 78/84
Bolla et al. (33)	High-risk PC	Arm 1= EBRT Arm 2= EBRT+HT (3 years)	CSS= 79/94 BPFS= 45/76 DM= 29/10 OS= 62/78 LF= 1/7	DFS= 23/48 OS= 40/58 CSS= 70/90 DSS= 10/30
Pilepich et al. (34)	High-risk PC	Arm 1= EBRT Arm 2= EBRT+ HT (4 months)	BRFS= 10/28 CSS= 80/85 DM= 39/29 OS= 68/72NS	OS= 34/43NS BRFS= 80/65 DM= 27/35 CSS= 64/77 DSS= 23/36
Jones et al. (35)	Low/intermediate/high-risk PC	Arm 1= EBRT Arm 2= EBRT+ HT (4 months)	LF= 39/21 (2 years)	BRFS= 59/47 OS= 57/62 CSS= 92/96 DM= 8/6
Dose-escalating EBRT				
Bolla et al. (36)	Intermediate/high-risk PC	Arm 1 = EBRT (70, 74, 78 Gy) Arm 2 = EBRT (70, 74, 78 Gy) + HT (6 months)	BRFS= 70/83 DM= 4/8NS OS= 88/91NS	NR
Nabid et al. (37)	Intermediate-risk PC	Arm 1= EBRT (70 Gy) + HT (6 months) Arm 2= EBRT (76 Gy) + HT (6 months) Arm 3 = EBRT (76 Gy)	BF= 7/2/14* DFS= 93/97/86* OS= 90/94/91NS *=NS between arms 1-2	BF= 22/22/33* DFS= 78/78/67* OS= 63/72/75NS *=NS between arms 1-2
Dubray et al. (27)	Intermediate-risk PC	Arm 1= EBRT (80 Gy) Arm 2 = EBRT (80 Gy) + HT (4 years)	BRFS= 76/84 OS= 94/93NS	NR
Dearnaley et al. (38)	Low/intermediate/high-risk PC	Arm 1 = EBRT (64 Gy) + HT (3-6 months) Arm 2 = EBRT (74 Gy) + HT (3-6 months)	-	BPFS= 43/55 OS= 71/71*

EBRT: External beam radiotherapy, HT: Hormone therapy, OS: Overall survival, DM: Distant metastasis, LF: Local failure, NR: Not reported, BRFS: Biochemical recurrence-free survival, CSS: Cause-specific survival, NS: Not significant, DSS: Disease-specific survival, DFS: Disease-free survival, Gy: Gray, BF: Biochemical failure, PC: Prostate cancer, BPFS: Biochemical progression-free survival, *: NS between arms 1-2

In the ASCENDE-RT trial, 398 patients were randomized to a standard arm with 12 months of androgen deprivation therapy, pelvic irradiation to 46 Gy, followed by a dose-escalated EBRT boost to 78 Gy, or an experimental arm that substituted a LDR-BCT boost (28). Nine-year biochemical recurrence-free survival was significantly better in the BCT boost arm (p=0.004). In addition, grade ≥ III urinary toxicity was found lower in the BCT boost arm (19% vs. 5%, p<0.001). In numerous phase III randomized trials, neoadjuvant and adjuvant HT have been proven to be beneficial in combination with EBRT (≥70 Gy) in the treatment of high risk PC (31,32,33,34,35), (Table 3).

Adding HT has significantly reduced the risk of biochemical failure, clinical progress, local recurrence and distant metastasis without increasing the risk of death due to cardiac problems, GU toxicity and GI toxicity. A meta-analysis has shown that adding HT to ERT reduces the risk of death from PC by 24% and the risk of death from other causes by 14% (39). Numerous randomized studies have shown that dose-escalating EBRT (≥74 Gy) improves biochemical outcomes compared with conventional doses (40,41). The EORTC 22991 trial showed that adding short-term HT (ST-HT) to dose-escalating ERT improved 5-year biochemical progression-free survival (BPFS) (36). The results of other phase III dose-escalating-EBRT trials have shown that addition of ST-HT still provides a benefit in intermediate risk patients (27,36). Adding ST-HT to dose-escalating-EBRT in patients with intermediate risk PC improves BPFS and reduces distant metastasis, and PC-specific mortality (PCSM) (37). MRC RT01 showed that dose-escalation from 64 Gy to 74 Gy improved BPFS, even when both arms were given ST-HT (38). Long-term (LT)- HT is used in the treatment of patients with high risk PC (42).

This recommendation is largely based on EORTC 22961 and RTOG 9202 trials (45,46). In both trials, it was shown that cancer-specific survival and overall survival were increased with LT-HT (28-36 months) compared to ST-HT (4-6 months) (Table 4).

DART01/05 trial, a trial comparing the duration of HT with Dose-escalating EBRT, found that LT-HT (28 months) improved biochemical control, distant metastasis-free survival and overall survival compared to ST-HT (4 months) (Table 4) (48). The PCS IV trial compared ST-HT (18 months) and LT-HT (36 months) and concluded that ST-HT was as effective as LT-HT and improved quality of life (49). The use of genomics in the future to find out which patients should be given personalized treatment is the topic on the agenda for high risk PC. Mahal et al. (50) showed

Table 4. Trials comparing different hormone therapy durations with conventional or dose-escalating external beam radiotherapy

Trials	Risk groups	Trial arms	5-year results	10-year results
Conventional dose EBRT				
Denham et al. (43)	Intermediate-risk PC	Arm 1= EBRT Arm 2= EBRT + HT (3 months) Arm 3= EBRT + HT (6 months)	BRFS=32/49/52 DM=19/22/13* CSS=91/92/94 *NS between arms 1-2 LF=28/17/12	BRFS=70/60/53 CSS=78/81/8* OS=57/63/71* *NS between arms 1-2
Pisansky et al. (44)	Intermediate-risk PC	Arm 1= EBRT+HT (9 months) Arm 2= EBRT+HT (4 months)	NR	BRFS= 73/73NS DM= 6/6NS CSS= 96/95NS OS= 67/66NS
Bolla et al. (45)	High-risk PC or Locally advanced disease	Arm 1= EBRT+HT (6 months) Arm 2= EBRT+HT (36 months)	OS=81/85 DSS= 95/97 CSS=91/97 DM=6/14	NR
Horwitz et al. (46)	High-risk PC or Locally advanced disease	Arm 1= EBRT+HT (4 months) Arm 2= EBRT+HT (28 months)	BRFS=44/72 DM=17/12 CSS=95/97 OS=79/80NS	BRFS= 32/48 DM= 23/15 CSS= 84/89 OS= 51/54NS LF= 22/12 DSS= 84/89
Denham et al. (47)	Intermediate/high-risk PC	RT (66,70,74 Gy or 46 Gy +BCT) +HT (12 months) +/- Z RT+ADT (6 months) +/- Z	PCSM (7.8/7.4/4.1/7.8)NS CSS (19.4/13.9/17/18.9)NS PSAP (29.2/26//34.2/39.6) DP (14.2/11.1/14.7/17.3)NS	PCSM 9.7/13.3 DP 20.7/27.5 PSAP 34/45.9
Dose-escalating EBRT				
Zapatero et al. (48)	Intermediate/high-risk PC	Arm 1 = EBRT (70, 74, 78 Gy) + HT (4 months) Arm 2 = EBRT (70, 74, 78 Gy) + HT (28 months)	BRFS= 81/90 DMFS= 83/94 OS= 86/95	NR
Nabid et al. (49)	High-risk PC	Arm 1= EBRT+HT (36 months) Arm 2= EBRT+HT (18 months)	CSS= 97/95NS OS= 91/86NS	CSS= 4/84NS OS= 62/59NS

EBRT: External beam radiotherapy, HT: Hormone therapy, OS: Overall survival, DM: Distant metastasis, LF: Local failure, TROG: Trans-tasman radiation oncology group, NR: Not reported, DSS: Disease-specific survival, BRFS: Biochemical recurrence-free survival, CSS: Cause-specific survival, NS: Not significant, CSS: Cancer-specific survival, Gy: Gray, Z: Zoledronate, BCT: Brachytherapy, ADT: Androgen deprivation therapy, PCSM: Prostate cancer-specific mortality, PSAP: Prostate specific antigen progression, DP: Distant progression, DMFS: Distant metastasis-free survival, *: NS between arms 1-2

that there was a statistically significant relationship between the rate of metastasis and Decipher score >0.6 (p<0.001). The genomic risk group and the National Comprehensive Cancer Network risk group have been evaluated together and clinical-genomic risk group classification has been established (51). In high risk patients; treatment schemes have been established: LT-HT and RT or ST-HT and RT in patients with low genomic risk and LT-HT and RT or ST-HT and RT with LT abirateron or LT apalutamide arms in patients with high genomic risk (NRG GU 1864 Clinical Trial).

Postoperative RT; Positive surgical margin is recommended in disease at level of pathological T3 or higher (52). In SWOG randomized trial, it was found that the addition of postoperative RT provided a survival advantage in patients with pT3 or positive surgical margin (53). Genomic classification can tell us about the timing of postoperative RT (54). The results of randomized trials (RADICALS-HT for its necessity and duration, RAVES-RT for its timing) on postoperative RT timing (early or early salvage) are expected. The 5-year results of the RAVES randomized trial were reported at ASTRO 2019. Starting adjuvant RT at 4-6 months was compared with early salvage RT when PSA was ≥0.2 ng/mL. Five-year results showed no difference in terms of BPFS and locoregional and distant metastasis free survival rates. In the RTOG 96-01 randomized trial, salvage RT and/or 2-year HT was compared with salvage RT alone in 771 patients who had PSA rising after RP in 13-year follow-up. Salvage RT and/or 2-year HT was associated with lower development of metastasis (11% vs. 19%), lower PCSM (4.5% vs. 10.1%) and longer overall survival (82% vs. 78%), (p<0.01, p=0.036 and p<0.001, respectively). In subgroup analysis; this advantage was increased in those with PSA >1.5 ng/mL and surgical margin positivity (55). In the GETUG/AFU-16 randomized trial, there was statistically significant difference between EBRT in combination with 6-month HT and EBRT alone in terms of 5-year BPFS (62.1% vs. 79.6%, p<0.001 and survival (56). After RP, 1107 patients with lymph node positivity were retrospectively evaluated. Eight-year cancer-specific mortality rates were statistically significantly lower in the postoperative RT and HT group than the HT alone group in patients with lymph node positivity <4 (57).

Oligometastasis PC; Ost et al. (58) compared the patients who were treated for metastasis and the patients who were not in a phase II randomized trial. Sixty two patients with ≤3 bone or lymph node metastases were examined. BPFS and cancer-specific mortality were better in the group undergoing treatment for metastasis (p=0.03). In the Stampede phase III randomized trial, 2061 patients with metastatic PC were evaluated. The addition of RT to the treatment of metastatic patients initially was found to increase disease-free survival and overall survival, especially in patients with low metastasis load (p<0.0001 and p=0.007, respectively) (59). In the Horrad randomized trial, 432 patients with bone metastasis (<5) were evaluated and the time to PSA progression was found to be longer (p=0.02) in patients who received RT to prostate and bones, but there was no difference in terms of survival (60). Burdett et al. (61) showed in their meta-analysis that patients who received RT to prostate and HT had 7% longer 3-year survival compared with patients who took only HT in patients with less than 5 bone metastases. Fifty four patients were evaluated in the Oriole phase II trial. The patients with 1-3 bone metastases (≤5 cm lesion) were randomly assigned to SBRT or observation arms. In the early 24 months early results, the time to progression-free survival was longer at the 6th month.

Studies are going on the use of neoadjuvant or adjuvant chemotherapy, immunotherapy and next generation HT agents in combination with EBRT. In the RTOG 0521 randomized study, standard HT (2 years) and RT (72.0-75.6 Gy) arm was compared with RT, HT and docetaxel (adjuvant 6 cures after RT is completed) in 612 patients. In 6-year follow-up, general and disease-free survival rates significantly increased in favor of the docetaxel-added arm (p=0.03 and p=0.05, respectively) (62).

Proton and heavy ion therapy can reduce the amount of radiation used in RT that goes beyond the target. However, more data are needed on this issue. There are ongoing studies.

Conclusion

It is possible to safely perform RT at all stages of PC. With advances in imaging methods and treatment in RT, it has become possible to apply higher doses to the tumor with fewer side effects. In addition, hypofractionation applications increase the fraction dose and decrease the total treatment time. Postoperative RT can also be applied in appropriate indication by looking at clinical and pathological features after surgery. The results of studies in metastatic disease and lymph node positive patients are promising. Studies are ongoing with the use of neoadjuvant or adjuvant chemotherapy, immunotherapy and next-generation hormotherapies in combination with RT.

Acknowledgements

Publication: The results of the study were not published in full or in part in form of abstracts.

Contribution: There is not any other contributors who may not be listed as authors.

Conflict of Interest: The authors have not declared any conflict of Interest.

Financial Disclosure: The authors have declared that they have not been granted any financial support.

Ethics

Informed Consent: All patients read the patient information form and written informed consents were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.A.Ç., Design: İ.A.Ç., Data Collection and Processing: İ.A.Ç., Analysis and Interpretation: İ.A.Ç., Literature Search: İ.A.Ç., Writing: İ.A.Ç.

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Questions

1. What are the treatment options for low risk prostate cancer?

a. Brachytherapy

b. External beam radiotherapy

c. Hypofractionated radiotherapy

d. Stereotactic body radiotherapy

e. All of them

2. Which of the following are not indications of postoperative radiotherapy ?

a. Positive surgical margin

b. pT3 tumor

c. p lymph node positivity

d. pT2 and surgical margin negativity

e. pT4 and seminal vesicle invasion

3. Which of the following is the standard radiotherapy treatment in high risk prostate cancer?

a. External beam radiotherapy +/- brachytherapy+ hormone therapy for 1-3 years

b. Stereotactic body radiotherapy

c. External beam radiotherapy

d. Brachytherapy

e. External beam radiotherapy + hormone therapy for 6 months