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Oncologic outcomes of postoperative adjuvant versus salvage radiotherapy in prostate cancer

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Introduction The aim of this study was to compare the long-term oncological results of patients with the diagnosis of prostate cancer who underwent open radical retropubic prostatectomy (RRP) and subsequent adjuvant (ART) or salvage radiotherapy (SRT).

Material and methods A total of 145 patients underwent open RRP for prostate cancer and subsequent ART or SRT postoperatively between 2010 and 2019. ART (n = 56) is defined as the group of patients with prostate-specific antigen (PSA) <0.2 ng/mL or with positive lymph nodes without PSA increase who received radiotherapy within the first 6 months of urinary continence. SRT (n = 89) is defined as the group of patients with PSA >0.2 ng/mL who received RT before PSA amounted to 0.5 ng/mL.

Results Statistically no significant difference was found between groups in terms of age, prostate volume, final pathology Gleason scores, lymphadenectomy, duration of androgen deprivation therapy (ADT), time to relapse after radiotherapy, development of biochemical recurrence and disease progression. Extraprostatic extension, seminal vesicle invasion and surgical margin positivity were significantly higher in the ART group. No difference was found between the groups in terms of biochemical recurrence-free survival, while cancer-specific survival and overall survival rates were significantly higher in the SRT group.

Conclusions It was found that cancer-specific and overall survival was better in the SRT group. It will be more appropriate to follow-up until the recurrence and then to perform SRT after the relapse in the postoperative period.

Key Words: prostate cancer ‹› biochemical recurrence ‹› adjuvant radiotherapy ‹› salvage radiotherapy

INTRODUCTION

Biochemical or radiological recurrence is detected in about a quarter of patients undergoing radical retropubic prostatectomy (RRP) [1]. Biochemical recurrence or radiological progression is more likely, especially in patients with high serum prostate-specific antigen (PSA) or locally advanced pathology or adverse pathological features. Surgical treatment alone does not provide adequate oncological control in these patients in the long term, which requires multimodal treatments, including radiotherapy (RT) [2–6]. The current European guideline specifies the path to be followed in patients with an increased risk of local recurrence, negative lymph node involvement and PSA <0.1 ng/mL in two options. One of them is to perform adjuvant radiotherapy (ART) within the first six months postoperatively, in which the patients have urinary continence while the other option is to perform a close biological and clinical follow-up and then salvage radiotherapy (SRT) before the PSA value exceeds 0.5 ng/mL. Similarly, the guideline recommends androgen deprivation therapy (ADT) or ADT additional RT or follow-up protocol in patients with positive lymph node involvement [7].

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Prospective randomized studies support the role of ART in reducing the risk of biochemical recurrence [3]. However, the fact that the patients who were administered the follow-up protocol, no recurrence was observed more than 40% of the patients in the 10-year follow-up and the long and short-term side effects of RT, the negative effects of RT on patient comfort and treatment costs restricted the adoption of ART [4, 8, 9, 10]. A study evaluating the National Cancer Data Base records on this subject is also supportive. According to the study, it has been found that postoperative ART has decreased from 9.1% to 7.3% in recent years [11]. In this regard, the radiotherapy option performed in the presence of biochemical recurrence after the priority follow-up has become the mainly preferred treatment protocol despite the absence of randomized studies [12].

The absence of prospective randomized studies comparing both methods in the current literature does not provide a clear consensus about which method is more appropriate in these patients. In this respect, we aimed to compare the long-term oncological results of patients with the diagnosis of prostate cancer who underwent open RRP and subsequent adjuvant or salvage radiotherapy.

MATERIAL AND METHODS

Patient selection

One hundred forty-five patients who underwent open RRP for prostate cancer in our clinic between 2010 and 2019, and then underwent adjuvant or salvage RT were included in our study. The demographic, clinical and pathological features of the patients were evaluated retrospectively. ART has been defined as the group of patients with PSA level below 0.2 ng/mL or who had positive lymph node involvement without increased PSA level and received RT as soon as possible within the first 6 months of urinary continence. SRT is defined as the patient group with PSA value above 0.2 ng/mL and receiving RT before reaching 0.5 ng/mL. Patients who had metastatic disease or underwent preoperative hormonotherapy or RT were excluded from the study.

Radiation therapy

Radiation treatment was administered to the prostate bed, seminal vesicle bed and if necessary the pelvic lymph nodes area. All patients were treated with linear accelerators with high-energy photon beams (10–16 MV). Three-dimensional conformal RT using individual blocks or multileaf collimation, or intensity-modulated RT with different techniques was used as an alternative. Delineation of the clinical target volume was made on computed tomography (CT) images and included the pelvic lymph nodes area and the prostatic and seminal vesicle bed. Clinical and pathological findings, pre-surgery CT or magnetic resonance imaging (MRI) scans of the pelvis as well as surgical clips were used to guide the clinicians in defining clinical target volume. The planned target volume was defined as clinical target volume plus a margin of 8–10 mm to capture set-up error or organ motion. Doses of 50 Gy were delivered to the pelvic lymph nodes and 60–70 Gy to the prostate bed and seminal vesicle bed with doses per fraction of 1.8–2.0 Gy. Radiotherapy was administered to patients by a single radiation oncologist.

Follow-up

The follow-up of the patients was performed with a detailed history, physical examination and serum PSA value every 3 months in the postoperative period. In addition, imaging methods were used for symptomatic patients or for those with high PSA, according to the clinician's preference. Biochemical recurrence was considered as a PSA increase of ≥0.2 ng/mL evidenced by at least two measurements after RT, or a PSA increase of ≥0.5 ng/mL in a single measurement. Patients with radiologically or pathologically proven metastatic disease after RT were considered as the progression of the disease.

Table 1. *Clinicopathological features of the patients*

Age (years) – mean ±SD (min-max)	63.2 ±6.8 (42–77)
Diagnostic PSA value(ng/mL) – mean ±SD (min-max)	22.4 ±29 (1.1–149)
Prostate volume(mL) – mean ±SD (min-max)	41.3 ±17.8 (11–138)
TRUS biopsy tumor rate (%) – mean ±SD (min-max)	42.5 ±24 (3–100)
RRP – ISUP grade group – n (n/%)	
1	25 (17.2%)
2	29 (20.0%)
3	19 (13.1%)
4	30 (20.7%)
5	42 (29.0%)
Pathological stage – n (n/%)	
pT2a	19 (13.1%)
pT2b	7 (4.8%)
pt2c	25 (17.2%)
pT3a	36 (24.8%)
pT3b	54 (37.2%)
pT4	4 (2.8%)
Surgical margin positivity – n (n/%)	73 (50.3%)
Lymph node positivity – n (n/%)	14 (9.7%)
Follow-up time (months) – mean ±SD (min-max)	55.9 ±41.8 (7–205)

PSA – prostate-specific antigen; TRUS – transrectal ultrasonography; RRP – radical retropubic prostatectomy; ISUP – International Society of Urological Pathology; n – number of patients; SD – standard deviation

Ethics

The present study is approved by the local Ethics Commission is registered with the project number 2020/0513 and is performed in line with the principles of the Declaration of Helsinki.

Statistical analysis

SPSS program was used for statistical analysis. While evaluating the study data, descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as the suitability of quantitative data to normal distribution were tested by Shapiro-Wilk test and graphical examinations. Independent samples t test was used for comparing two groups of normally distributed quantitative variables, while Mann Whitney U test was used for comparing two groups of non-normally distributed quantitative variables. Pearson chi-square test and Fisher's exact test were used to compare qualitative data. Kaplan Meier was used for survival analysis and Log-rank test was used to compare groups. Statistical significance was accepted as $p < 0.05$.

RESULTS

One hundred forty-five patients who underwent open RRP for prostate cancer and subsequent adjuvant (n = 56) or salvage (n = 89) radiotherapy in our clinic were evaluated retrospectively, according to their clinical, pathological and demographic characteristics (Table 1). Additionally, comparative analysis was performed in terms of biochemical recurrence-free survival, cancer-related survival and overall survival.

In our study, no statistically significant difference was found between patients receiving ART and

Table 2. *Comparative analysis of the adjuvant and salvage radiotherapy*

	Adjuvant (n = 56)	Salvage (n = 89)	p
Age (years) – mean ±SD	62.9 ±7.3	63.4 ±6.6	0.653
Diagnosis PSA (ng/mL) – mean ±SD	32.7 ±38.7	15.9 ±18.3	0.001
Prostate volume (mL) – mean ±SD	40.3 ±13.6	42 ±20.1	0.593
PSA density <0.15 – n (n/%) PSA density ≥0.15 – n (n/%)	4 (7.1%) 52 (92.9%)	22 (24.7%) 67 (75.3%)	0.007
RRP Gleason score – n (n/%) 3 + 3 3 + 4 4 + 3 4 + 4 3 + 5 4 + 5 5 + 5	 7 (12.5%) 10 (17.9%) 8 (14.3%) 11 (19.5%) 0 11 (19.5%) 9 (16.1%)	 18 (20.2%) 20 (22.5%) 10 (11.2%) 14 (15.7%) 5 (5.6%) 16 (18%) 6 (6.7%)	0.224
Pathological stage – n (n/%) pT2a pT2b pt2c pT3a pT3b p T4	 4 (7.1%) 1 (1.8%) 5 (8.9%) 12 (21.4%) 30 (53.6%) 4 (7.1%)	 15 (16.8%) 6 (6.7%) 20 (22.5%) 24 (27%) 24 (27%) 0	0.001
Extraprostatic extension – n (n/%)	41 (73.2%)	38 (42.7%)	0.001
Seminal vesicle invasion – n (n/%)	35 (62.5%)	24 (27%)	0.001
Perineural invasion – n (n/%)	45 (80.4%)	69 (77.5%)	0.686
Surgical margin positivity – n (n/%)	39 (69.9%)	34 (38.6%)	0,002
Lymphadenectomy – n (n/%)	39 (69.6%)	53 (59.6%)	0.219
Lymph node positivity – n (n/%)	12 (30.8%)	2 (3.8%)	0.001
ADT – n (n/%)	48 (85.7%)	55 (61.8%)	0.002
ADT duration (months) – mean ±SD	27.7 ±23.3	28.2 ±24.6	0.929
Time to relapse after RT (month) – mean ±SD	18.07 ±13.6	20.88 ±19.09	0.647
Biochemical recurrence – n (n/%)	14 (25%)	17 (19.1%)	0.399
Progression – n (n/%)	10 (17.9%)	9 (10.1%)	0.178
Follow-up time (months) – mean ±SD	46.6 ±32.6	61.7 ±45.8	0.034

ADT – androgen deprivation therapy; RT – radiotherapy; PSA – prostate-specific antigen; RRP – radical retropubic prostatectomy; n – number of patients; SD – standard deviation

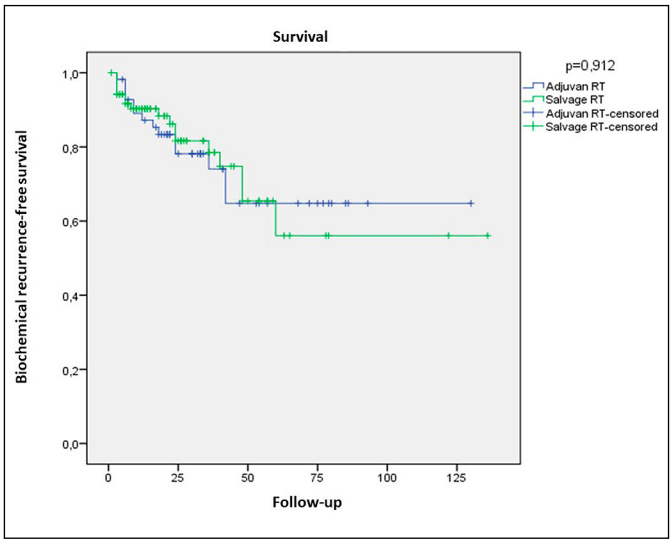

Figure 1. *Kaplan-Meier survival analysis showing the biochemical recurrence-free survival curve after adjuvant and salvage radiotherapy. Biochemical recurrence-free survival was higher in the adjuvant radiotherapy group, but this was not statistically significant (p = 0.912).*

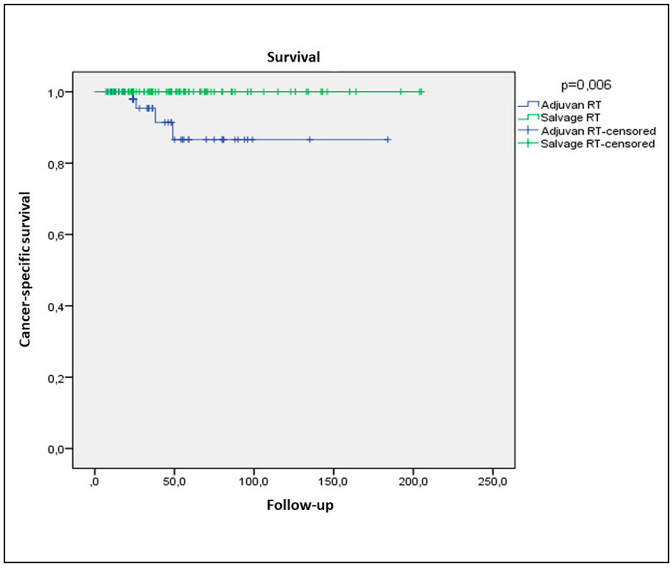

Figure 2. *Kaplan-Meier survival analysis showing the cancer-specific survival curve after adjuvant and salvage radiotherapy. Cancer-specific survival was significantly higher in the salvage radiotherapy group (p = 0.006).*

SRT in terms of age, prostate volume, RRP Gleason scores, lymphadenectomy, duration of ADT, time to relapse after RT, development of biochemical recurrence and disease progression (Table 2) (p >0.05).

Preoperative PSA level and density were higher in the ART group compared to the SRT group, which was found to be statistically significant.

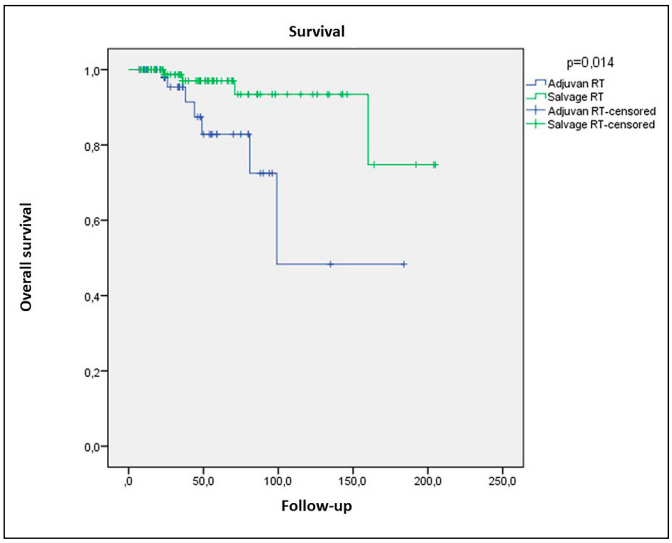

Figure 3. *Kaplan-Meier survival analysis showing the overall survival curve after adjuvant and salvage radiotherapy. Overall survival was significantly higher in the salvage radiotherapy group (p = 0.014).*

In the comparative analysis of the patients based on their pathological stages, the pathological stages of pT3a and below were found to be higher in the SRT group, while the pathological stages of pT3b and above were higher in the ART group, which was found to be statistically significant. Extraprostatic extension (EPE), seminal vesicle invasion (SVI) and surgical margin positivity (CS), which were among the adverse prognostic markers, were statistically found to be significantly higher in the ART group (p = 0.001, p = 0.001 and p = 0.002, respectively). In patients with perineural invasion, there was no significant difference between the groups. Although there was no statistically significant difference in the patients who underwent lymphadenectomy, lymph node positivity was found to be statistically higher in the ART group than in the SRT group (p: 0.001). Again, while the use of androgen deprivation therapy was higher in the ART group (p = 0.002), there was no significant difference between the groups in terms of ADT duration (p = 0.929). There was no significant difference between the groups in view of biochemical recurrence, time to relapse after RT and progression. Considering the survival analysis, biochemical recurrence-free survival was found to be higher in the ART group, but this was not statistically significant (p = 0.912), (Figure 1). However, cancer-specific survival and overall survival rates were statistically found to be significantly higher in the SRT group than in the ART group (p = 0.006, p = 0.014, respectively), (Figure 2 and Figure 3).

DISCUSSION

There are some studies comparing the effectiveness of adjuvant and salvage radiotherapy in the current literature. One of them is a study by Fossati et al. evaluating patients who underwent postoperative RT after RP. Although the purpose of this study was to test the hypothesis that ART is better in cancer control and survival than SRT, the study results revealed no significant difference between patients in view of both metastasis-free survival and overall survival. With this retrospective study, it was concluded that SRT performed after follow-up and biochemical recurrence does not jeopardize cancer control in patients with adverse pathology, and thus, unnecessary excess therapy performed due to ART can be reduced [12]. Another study, conducted by Mishra et al. evaluated the results of 186 patients with adverse pathology [13]. The analysis of this study revealed that there was no difference in view of survival between the two methods in the multivariate analysis of the correction made with the propensity score in the ART group, although the 10-year survival in both metastasis and biochemical recurrence was significantly superior to SRT. In addition, it was stated in the study that the patients who had adverse pathology but did not undergo RT and who did not have biochemical recurrence were not included in the study [13]. Although it was stated in the systematic review that Gandaglia et al. evaluated postoperative RT, the adjuvant RT after RP decreased the risk of recurrence in patients with aggressive disease, but it was stated that these patients had an increased risk in terms of long and short-term side effects related to RT. The study also revealed that observation of these patients and SRT performed at the first sign of relapse can be used as a permanent cancer control method in the selected patients [14]. In another study in which Tilki et al. evaluated 773 lymph node positive prostate cancer patients, the SRT which is administered at a PSA value below 0.5 ng/mL had a significantly lower risk of metastasis than patients with a PSA level above 0.5 ng/mL [15]. Although adverse pathological features, PSA and pathological stage are significantly higher in the ART group, the administration of SRT before PSA exceeds 0.5 ng/mL suggests that cancer-specific survival and overall survival may be higher in the SRT group.

In our study, biochemical recurrence was observed in only 19.1% and progression in 10% of patients who underwent SRT after RRP. Although these rates were lower than the ART group, they were not statistically significant. There is no difference between the two groups in terms of progression and biochemical recurrence after RT, which suggests that waiting for PSA relapse to perform RT in patients with advanced prostate cancer can prevent unnecessary excessive treatment and possible RT toxicity. In the RADICALS-RT study conducted by Parker et al., 1396 patients who underwent ART and post-follow-up SRT were prospectively evaluated. Efficacy and safety of both treatments were analyzed. It was stated that the use of ART and SRT after RRP did not make a difference in terms of progression-free survival, that routine use of ART increased the risk of morbidity and therefore is not recommended [16]. In another randomized phase 3 study, Sargos et al. evaluated 424 patients. It has been shown that there is no difference in event-free survival in a mean follow-up of 75 months, and that ART increases genitourinary toxicity and erectile dysfunction [17]. Another randomized controlled, non-inferiority study recommends SRT because it has similar results with ART in terms of biochemical control at the end of the study, although SRT does not match the non-inferiority criteria of the study at a mean follow-up of 6.1 years [18]. Vale et al. evaluated 2153 men in their meta-analysis. It is recommended that ART should not increase event-free survival in an average follow-up of 60-78 months, and early SRT should be preferred because it protects many patients from RT and RT-related side effects [19].

In the article published by Tilki et al., it was emphasized that the follow-up period in these prospective studies was short in order to assess metastasis-free survival, and the rate of high-risk patients in these studies was relatively low at 10–20%. It has been stated that there may be results in favor of ART in long-term follow-up [20]. Ghadjar et al. emphasized that RT was started in only 33–54% of the patients in the SRT group and that biochemical progression was not observed in 88–90% of the patients, therefore longer follow-up was required [21].

In the current European urology guideline, ART is recommended in the presence of two of three high-risk features (ISUP grade 4–5, pT3, and positive surgical margin) [7]. In our study, surgical margin positivity, pT3b and above was higher in the group receiving ART.

In the literature, three randomized controlled trials have investigated the effectiveness of adjuvant radiotherapy (ART). These are Arbeitsgemeinschaft Radiologische Onkologie und Urologische Onkologie of the German Cancer Society (ARO/AUO) study, European Organization for Research and Treatment of Cancer (EORTC) study and Southwest Oncology Group (SWOG) study. In these studies, with more than ten years follow-up, it was concluded that ART should be considered more prominently in patients with adverse pathol-

ogy compared to follow-up protocol alone [3, 4, 5, 22, 23, 24]. In all three studies, it was concluded that ART was better than progression-free survival compared to the follow-up protocol. It was stated only in the SWOG 8794 study that it had a positive effect on overall survival [5, 22]. In our study, 145 patients who underwent radical prostatectomy and who received adjuvant or salvage RT were evaluated. When the survival analyses of both groups were evaluated, cancer-related and overall survival was found to be statistically significantly higher in the SRT group. There was no significant difference in biochemical recurrence survival rates between the two groups. These results are not similar to the randomized studies mentioned before. The reason for this is that despite the positive results of these studies, there are some potential limitations. Firstly, the primary result of the studies is that there is no survival analysis, which caused the strength of the end point of the studies to be low. Secondly, less than half of those who developed recurrence in the follow-up stage received SRT. In addition, approximately 40% of the patients in the follow-up protocol never developed recurrence [3, 5, 25]. The third is that only about one-third of those receiving ART presented with undetectable PSA values, and the protocol performed to the remaining patients is not adjuvant, but technically early salvage radiotherapy [22, 23]. In consideration of the above-mentioned prospective studies, the most important point in RT performed after RP is the right patient selection. In this regard, postoperative RT administration in locally advanced prostate cancer patients was performed as recommended by current guidelines in our study, and patients with proven metastasis who received hormonal therapy or RT before RRP, who had proven metastasis and could not be followed up were excluded from our study and thus the biases were minimized.

The main limitation of the study is its retrospective nature. However, the limited number of randomized comparative studies in the current literature suggests that our study may be used as reference in future prospective studies. Another limitation of the study is that postoperative RT is performed at a different center by a single radio-oncologist. In this respect, close follow-up of the patients could not be performed after RT and side effects related to RT could not be evaluated. Another limitation is that analysis cannot be repeated with intergroup propensity score. Although significant differences were found between the groups in view of adverse pathological features, PSA and pathological stage; we believe that obtaining undetectable PSA values for ART and PSA below 0.5 ng/mL for SRT in RT protocol minimized the biases and represent a strength of our study.

CONCLUSIONS

Although there was no difference in terms of biochemical recurrence-free survival, salvage RT group showed longer survival in both overall and cancer-specific survival analyses. Close follow-up until disease recurrence in the post-operative period followed by RT did not affect long-term survival. Therefore, salvage RT should be considered in the foreground in patients who will adapt to regular follow-up.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study, or from their parents.

References

1. Stephenson AJ, Bolla M, Briganti A, et al. Postoperative radiation therapy for pathologically advanced prostate cancer after radical prostatectomy. Eur Urol. 2012; 61: 443-451.
2. Mullins JK, Feng Z, Trock BJ, Epstein JI, Walsh PC, Loeb S. The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. J Urol. 2012; 188: 2219-2224.
3. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomized controlled trial (EORTC trial 22911). Lancet. 2012; 380: 2018-2027.
4. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96–02/ AUO AP 09/95 trial. Eur Urol. 2014; 66: 243-250.
5. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol. 2009; 181: 956-962.
6. Gandaglia G, Cozzarini C, Mottrie A, et al. The role of radiotherapy after radical prostatectomy in patients with prostate cancer. Curr Oncol Rep. 2015; 17: 53.
7. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. ISBN 978-94-92671-16-5.
8. van Stam M-A, Aaronson NK, Pos FJ, et al. The effect of salvage radiotherapy and its timing on the health-related quality of life of prostate cancer patients. Eur Urol. 2016; 70: 751-757.
9. Suardi N, Gallina A, Lista G, et al. Impact of adjuvant radiation therapy on urinary

continence recovery after radical prostatectomy. Eur Urol 2014; 65: 546-551.

10. Gandaglia G, Lista G, Fossati N, et al. Non-surgically related causes of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Prostate Cancer Prostatic Dis. 2016; 19: 185-190.

11. Sineshaw HM, Gray PJ, Efstathiou JA, Jemal A. Declining use of radiotherapy for adverse features after radical prostatectomy: results from the National Cancer Data Base. Eur Urol. 2015; 68: 768-774.

12. Fossati N, Karnes RJ, Boorjian SA, et al. Long-term impact of adjuvant versus early salvage radiation therapy in pT3N0 prostate cancer patients treated with radical prostatectomy: results from a multi-institutional series. Eur Urol. 2017; 71: 886-893.

13. Mishra MV, Scher ED, Andrel J, et al. Adjuvant versus salvage radiation therapy for prostate cancer patients with adverse pathologic features: comparative analysis of long-term outcomes. Am J Clin Oncol. 2015; 38: 55-60.

14. Gandaglia G, Briganti A, Clarke N, et al. Adjuvant and salvage radiotherapy after radical prostatectomy in prostate cancer patients. Eur Urol. 2017; 72: 689-709.

15. Tilki D, Preisser F, Tennstedt P, et al. Adjuvant radiation therapy is associated with better oncological outcome compared with salvage radiation therapy in patients with pN1 prostate cancer treated with radical prostatectomy. BJU Int. 2017; 119, 717-723.

16. Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. Lancet. 2020; 396: 1413-1421.

17. Sargos P, Chabaud S, Latorzeff I, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. Lancet Oncol. 2020; 21: 1341-1352.

18. Kneebone A, Fraser-Browne C, Duchesne GM, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. Lancet Oncol. 2020; 21: 1331-1340.

19. Vale CL, Fisher D, Kneebone A, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet. 2020; 396: 1422-1431.

20. Tilki D, D'Amico AV. Timing of radiotherapy after radical prostatectomy. Lancet. 2020; 396: 1374-1375.

21. Ghadjar P, Höcht S, Wiegel T. Postoperative radiotherapy in prostate cancer. Lancet. 2021; 397:1623.

22. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA. 2006; 296: 2329-2335.

23. Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomized controlled trial (EORTC trial 22911). Lancet. 2005; 366: 572-578.

24. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol. 2009; 27: 2924-2930.

25. Efstathiou JA. Postoperative radiation for prostate cancer. Lancet. 2012; 380: 1974-1976. ■