Salvage Versus Adjuvant Radiation Therapy Following Radical Prostatectomy in Localised Prostate Cancer: A War Without a Winner

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Abstract

Objective To review current literature regarding the efficacy of adjuvant radiation therapy (ART) and salvage radiation therapy (SRT) following radical prostatectomy (RP) in patients with undetectable postoperative prostate-specific antigen (PSA) levels and high-risk features of prostate cancer (PCa) recurrence.

Methods Seven randomized controlled trials focused on the use of ART compared with either observation or SRT after RP that had been published in PubMed up to May 2022 were reviewed.

Results The use of ART following RP has been the treatment of choice over the past decade. Three RCTs comparing ART with early SRT show that SRT given as soon as biochemical recurrence (BCR) is detected is not inferior to ART while it offers the opportunity to avoid overtreatment and potential RT-related side effects. A meta-analysis summarizing the results from these trials supports these findings.

Conclusions Early SRT may be suggested as the standard of care for patients with PCa and high-risk features for disease recurrence following RP. Nevertheless, further investigations are needed to identify those patients who will benefit from ART, particularly, in case of lymph node involvement. Moreover, some patients might avoid SRT despite reaching detectable postoperative serum PSA levels.

Introduction

Because of its complexity and heterogeneity, prostate cancer (PCa) management at any disease stage is under constant debate[1–3], and the use of adjuvant radiation therapy (ART) following radical prostatectomy (RP) to address risk factors for disease recurrence has been questioned in recent years[4].

While earlier randomized controlled trials (RCTs) showed a biochemical recurrence (BCR)-free survival benefit with ART, a meta-analysis published in 2020 has shown no event-free survival benefit compared with salvage RT [5–9]. Nevertheless, the impact of each of the risk factors and their combination on recurrence remain under debate[10].

In this respect, the last European Association of Urology (EAU) guidelines, published in 2022, propose ART be offered to a select group of patients: (a) patients without lymph node involvement but adverse pathology such as International Society of Urologic Pathologists (ISUP) grade group 4–5 and pT3 with or without positive margins and,

Key Words

Prostatic neoplasms, prostatectomy, risk factors, adjuvant radiotherapy, salvage therapy

Competing Interests

None declared.

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Abbreviations

ADT androgen-deprivation therapy
ART adjuvant radiation therapy
BCR biochemical recurrence
CT computed tomography
MFS metastasis-free survival
OS overall survival
PCa prostate cancer
PET positron emission tomography
PFS progression-free survival
PSADT PSA doubling time
RCT randomized controlled trial
RP radical prostatectomy
SRT salvage radiation therapy

(b) patients with lymph node metastasized PCa with > 2 nodes involved[11].

In this review, we discuss the RCTs evaluating ART and salvage radiation therapy (SRT) for patients treated with RP who had high-risk features for disease recurrence.

Methods

We searched RCTs and meta-analyses published up to May 2022, using the following terms: "adjuvant radiotherapy, prostatectomy," salvage radiotherapy, prostatectomy," and "postoperative radiotherapy, prostatic neoplasm." Articles not written in English were excluded. Conference abstracts that did not provide enough information, case reports, review articles, and editorial comments were also excluded from review. Seven RCTs focused on the use of ART compared with either observation or SRT after RP were included in our review.

Results

Available evidence

Approximately 25% of men will experience recurrence of their cancer following RP for localised PCa[10]. ART has been the treatment of choice since the publication of 3 RCTs over the past decade: the SWOG 8794[6], the European Organisation for Research and Treatment of Cancer (EORTC 22911)[7], and the German Cancer Society (ARO 96–02/AUO AP 09/95)[8] trials, with their last results published in 2009, 2012, and 2014, respectively.

The SWOG 8794 trial[6] (**Table 1**) was the first randomized study to support the use of ART in patients with unfavourable pathologic features (pT3 disease or positive surgical margins). Thomson et al. proved that the use of ART leads to better oncologic outcomes in terms of metastasis-free survival (MFS) and overall survival (OS). Nevertheless, it is important to note that the patients enrolled were randomized to ART or observation instead of SRT. Hence, not every patient with BCR received timely SRT. Accordingly, the median serum PSA level at the time of SRT in the case of PSA-only relapse was 0.75 ng/dL, and 37% of patients receiving SRT had already experienced objective cancer recurrence. In addition, 33% of patients included in this trial did not have undetectable postoperative PSA levels.

Similarly, Bolla et al.[7] (**Table 1**) randomized 1005 patients with pT3 disease or positive surgical margins following RP to ART or a wait-and-see/observation policy. According to the SWOG 8794 trial, ART improved biochemical progression-free survival (PFS) and local control compared with observation. Unfortunately, half of the patients in the wait-and-see arm experienced only BCR (defined as an increase in PSA concentration > 0.2 ng/dL after the lowest postoperative value was measured), but only 14.5% of them received SRT. Thus, at least 30% of patients with BCR after surgery did not receive SRT as the first active salvage therapy. In addition, although pre-SRT PSA values were not reported, the median PSA value before any type of active salvage treatment was 1.7 ng/dL, and 14 patients received SRT despite a PSA level that had not reached a nadir below 0.2 ng/mL after RP.

The ARO 96–02/AUO AP 09/95[8] study (**Table 1**) included only patients with undetectable postoperative serum PSA levels. The results of this study also favoured ART. ART reduced the risk of progression (biochemical progression, local or distant clinical recurrence, or death from any cause) by 49%. In any case, no patient enrolled in the wait-and-see arm received additional treatment, so we cannot deduce whether the use of SRT could have decreased the differences between study arms.

Following this, many retrospective studies were reported that focused on the effect of SRT given to those patients with unfavourable clinical and pathologic features[10]. Aiming to shed light on this topic, Tao et al.[10] published a systematic review and meta-analysis that included 15 studies published between 2002 and 2018 comparing the prognosis of ART and SRT. It must be noted that this review did not include the above 3 RCTs as those RCTs compared ART with observation, while the review focused on ART versus SRT. Therefore, all studies considered for analysis were retrospective. According to this meta-analysis, the use of ART following RP reduces the risk of BCR and 5-year overall mortality, although no benefit from ART was demonstrated in terms of patient survival at 10 years from RP. Importantly, (a) all patients considered had received either ART or SRT, which means that all patients included in the SRT group had developed BCR, which

in turn may imply a greater predisposition to unfavourable disease, and (b) no improvement in BCR in the ART arm was observed when only early SRT (defined as SRT given at PSA levels < 0.5 ng/dL) was considered.

Finally, a Finnish trial published in July 2019 (**Table 1**) randomized 250 patients with pT2 disease and positive margins or pT3a disease (irrespective of margin status) to ART or observation[9]. ART prolonged BCR-free survival compared with RP alone, but (a) the increase in PSA levels before receiving SRT was counted as an event, while nearly three-quarters of patients achieved PSA remission after SRT; (b) 29% of patients in the observation group whose disease progressed locally did not receive SRT; and (c) the median PSA level at SRT was 0.7 ng/mL (range, 0.42 to 8.2).

In short, the above-mentioned studies support the use of ART when it is compared with observation or salvage radiotherapy, but they do not provide adequate outcome information about early SRT.

In this vein, several retrospective studies have suggested that early initiation of SRT will not compromise cancer control but rather reduce the overtreatment that is associated with ART[12–15]. In 2020, a meta-analysis showed that SRT results may not differ from ART results if the postoperative serum PSA value is below 0.2 ng/mL at the time of treatment[5]. Consequently, it has recently been disputed whether the use of SRT as soon as PSA values reach a detectable level may have an important impact when SRT is compared with ART.

New investigations and findings

At present, SRT is recommended when the postoperative serum PSA value is ≤ 0.5 ng/mL[13,16]. It has been observed, however, that 5-year freedom from BCR after SRT was 71% for those patients with a pre-SRT PSA level ≤ 0.2 ng/mL, 63% for those with a PSA of 0.21 to 0.50 ng/mL, 54% for those with a PSA value between 0.51 and 1.0 ng/mL, and 37% for those with a PSA value ≥ 2.0 ng/mL[17]. Hence, the timing of SRT may alter its effectiveness[18].

Three RCTs — RADICALS-RT, RAVES, and GETUG-AFU-17 — were aimed at answering a hitherto unresolved dilemma: "What is the best timing for postoperative RT?"[19–21] (**Table 1**). In this case, patients were randomized to ART or observation followed by SRT when the PSA level was ≥ 0.2 ng/dL[19,20] or even ≥ 0.1 ng/dL[21]. A collaborative and prospectively designed systematic review and meta-analysis that included these 3 trials suggested that ART does not improve event-free survival in men with localised or locally advanced PCa compared with SRT. Five-year event-free survival in ART and SRT were 89% and 88%, respectively[5]. Of interest, more than half of the patients included in the SRT group did not meet the BCR criteria avoiding overtreatment and potential RT-related-side effects, including sexual, urinary, and bowel dysfunctions[5,22]. The RADICALS-RT, RAVES, and GETUG-AFU-17 trials[19–21] revealed that RT toxicity was more common among patients randomized to ART compared with SRT. Grade 1 to 2 events were about twice as prevalent in the ART group; grade 3 to 4 events were uncommon in both groups.

Data from these RCTs support the notion that early SRT avoids overtreatment without compromising the oncologic outcome. Therefore, it seems reasonable to adopt this approach as the standard of care following RP for localised prostate cancer. Nevertheless, can we generalise it to all patients? Should we give special consideration to the different risk factors for recurrence and their combination? Will the development of biomarkers and imaging techniques allow us to identify the best timing for RT after surgery?

Discussion

Accurate risk of recurrence estimation

Extracapsular extension, seminal vesicle invasion, positive surgical margins, high Gleason score, and lymph node involvement are the main independent predictors of BCR[10,23,24]. However, the increasing use of genomic biomarkers to identify both germline and somatic variations may provide a more precise assessment of patients at risk of recurrence[25,26].

The heterogeneity of PCa, with variable responses to treatment, is probably related to the molecular heterogeneity of this disease, which in turn is closely related to its genetic profile. Thus, germline testing together with molecular profiling or tumour genomic profiling may lead us to understand more about the biology of the tumour, and distinguish PCa with indolent behaviour from those cases with a lethal course[27]. Approximately 5% of patients with localised PCa harbour germline variations[28,29], such as BRCA2, and ATM variations that are associated with both PCa susceptibility and higher risk of aggressive disease[28]. In this regard, BRCA1/2 carriers with localised PCa have a 16% increased absolute risk of developing metastases[30]. Therefore, the identification of these variations may have a role in the management of patients at risk of BCR after RP.

Somatic changes in DNA repair genes are found in nearly 10% of PCa tumours confined to the prostate gland[31]. Spratt et al. evaluated a 22-marker genomic classifier (GC; DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources [DECIPHER], Sanger Institute) to predict metastasis through a metanalysis of 5 studies. The authors proved that GC was an independent predictor of metastases. Likewise, the 5-year cumulative incidence of metastasis was 2.4% for patients with a low GC score but 15.2% for patients

TABLE 1.

Adjuvant radiation therapy randomized controlled trials

	SWOG 8794[6]	EORTC 22911[7]	ARO 9602[8]	FP/FINROG 0301[9]	GETUG-AFU 17[19]	RADICALS-RT[21]	RAVES[20]
Publication	2009	2012	2014	2019	2020	2020	2020
Number of patients	425	1005	307	250	424	1396	333
Randomisation	ART group: 214 Observation group: 211	ART group: 502 Observation group: 503	ART group: 148 Observation group: 159	ART group: 126 Observation group: 124	ART group: 212 SRT group: 212	ART group: 697 SRT group: 699	ART group: 166 SRT group: 167
Inclusion criteria	Extracapsular extension and/or SVI and/or R1 N0M0 Any postoperative PSA	pT2–3 with at least one of the following risk factors: Capsular perforation SVI R1 N0M0 Any postoperative PSA	pT3–4 /R1–0 N0M0 Postoperative PSA <0.1 ng/dL	pT2/R1 or pT3a/ R0-1 N0M0 Postoperative PSA < 0.5 ng/dL	≥ pT3/R1 N0M0 Postoperative PSA ≤ 0.1 ng/dL	≥ pT3 and/or preoperative PSA ≥ 10ng/mL and/or Gleason-score ≥ 7 and/or R1 N0/1M0 (5% pN1) Postoperative PSA ≤ 0.1 ng/dL	pT3 or R1 N0M0 Postoperative PSA ≤ 0.2 ng/dL
Primary outcome	MFS	BCR-free survival	PFS (BCR, clinical recurrence, or death)	BCR-free survival	Event-free survival (disease relapse, BCR or death)	Freedom from distant metastases	Freedom from biochemical progression
Median follow-up (years)	ART group: 12.7 Observation group: 12.5	10.6	ART group: 9.25 Observation group: 9.4	ART group: 9.3 Observation group: 8.6	6.25	4.1	6.1
HT added to SRT/ART	Not defined	Not defined	Not defined	Not defined	6 months of HT together with ART and SRT (All patients included in the trial)	Randomization to 0 vs 6 months vs 24 months of HT together with ART and SRT (Some patients included in the trial)	No
RT dose	60–64Gy	60Gy	60Gy	66.6Gy	66Gy	66Gy or 52.5Gy	64Gy
Use of SRT in the observation group	33%	31%	—	30%	54%	33%	50%

PSA: Prostate specific antigen; HT: hormonotherapy; BCR: biochemical recurrence; SRT: salvage radiotherapy; ART: adjuvant radiotherapy; SVI: seminal vesicle invasion; R1: positive surgical margins; MFS: metastasis-free survival; PFS: progression-free survival; OS: overall survival.
**All patients in the observation group who received SRT*

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TABLE 1.

Adjuvant radiation therapy randomized controlled trials, *Cont'd*

	SWOG 8794[6]	EORTC 22911[7]	ARO 9602[8]	FP/FINROG 0301[9]	GETUG-AFU 17[19]	RADICALS-RT[21]	RAVES[20]
Early or late SRT	Late (median PSA 1 ng/dL*)	Unknown (median PSA unknown)	—	Late (median PSA 0.7 ng/dL*)	Early (median PSA 0.24 ng/dL)	Early (median PSA 0.2 ng/dL)	Early (median PSA 0.2 ng/dL)
5-year event-free survival					ART group: 92% SRT group: 90% HR 0.81 [95% CI 0.48–1.36], *P* = 0.42		
5-year BCR-free survival						ART group: 85% SRT group: 88% HR 1.10 [95% CI 0.81–1.49], *P* = 0.56	ART group: 86% SRT group: 87% HR 1.12 [95% CI 0.65–1.90], *P* = 0.15
10-year PFS			ART group: 56% Observation group: 35% HR: 0.51 [95% CI 0.37–0.70], *P* < 0.0001				
10-year BCR	ART group: 53% Observation group: 30% HR 0.43 [95% CI 0.31–0.58], *P* < 0.001	ART group: 60.6% Observation group: 41.1% HR 0.49 [95% CI 0·41–0·59], *P* < 0.0001		ART group: 82% Observation group: 61% HR 0.26 [95% CI 0.14–0.48], *P* < 0.001			
10-year MFS	ART group: 71% Observation group: 61% HR 0.71 [95% CI 0.54–0.94], *P* = 0.016	ART group: 76.5% Observation group: 71.3%		ART group: 98% Observation group: 96% HR 0.49 [95% CI 0.09-2.68], *P* = 0.4			
10-year OS	ART group: 74% Observation group: 66% HR 0.72 [95% CI 0.55–0.96], *P* = 0.023	ART group: 60.6% Observation group: 41.1% HR 0.49 [95% CI 0·41–0·59], *P* < 0.0001		ART group: 92% Observation group: 87% HR 0.69 [95% CI 0.29–1.60], *P* = 0.4			

PSA: Prostate specific antigen; HT: hormonotherapy; BCR: biochemical recurrence; SRT: salvage radiotherapy; ART: adjuvant radiotherapy; SVI: seminal vesicle invasion; R1: positive surgical margins; MFS: metastasis-free survival; PFS: progression-free survival; OS: overall survival.
**All patients in the observation group who received SRT*

with high-risk GC scores[32]. Later, Marascio et al. explored the clinical benefit of decision-making based on DECIPHER CG testing after RP. This prospective observational study revealed that patients with high GC risk who received ART had a 2-year cumulative incidence of PSA recurrence 8 times lower than those who did not.

How should patients with very high-risk features and a combination of high-risk features and undetectable postoperative serum PSA levels be treated?

Subgroup analysis in the ARTISTIC meta-analysis was limited by the low event rate, while the effect of RT timing could not be properly evaluated in patients with high-risk features for BCR such as seminal vesicle involvement (20% of patient enrolled), Gleason score ≥ 8 (15% of patients enrolled) or node-positive disease (3% of patients enrolled)[5]. Hence, there are still doubts about how to manage those patients with undetectable postoperative PSA levels together with high-risk features, such as node-positive disease, Gleason score > 8, and/or pT3b disease or higher[4]. In addition, investigators in the EORTC 22911 trial determined that patients with 2 risk factors (eg, pT3a-b plus positive surgical margins) tended to have a greater risk of BCR and death if they received ART compared with those who presented with a single risk factor[7]. No combination of adverse pathologic features was evaluated in the ARTISTIC meta-analysis[5], preventing us from knowing which is the best management option for these patients.

Particularly controversial has been the management of pathologically node-positive PCa patients given the prognostic variability according to the number of affected nodes and tumour characteristics. In this regard, Abdollah et al. suggested that patients with high-risk features for BCR (pathological stage > T3a and/or positive surgical margins together with Gleason score 7 to 10) may benefit from ART even when the number of lymph nodes involved is lower than 3[33,34].

In a systematic review of 26 studies published in 2018, only one propensity score-matched study provided information about the effectiveness of initial observation and SRT versus ART in the pN1 PCa setting[34,35]. The study proved a benefit in terms of 4-year MFS for those patients receiving ART regardless of disease characteristic[35].

Recently, Tilki et al., showed that ART may be better when compared to SRT. Moreover, the benefit seems to be directly related to the number of lymph nodes affected. Therefore, ART might be avoided when ≤ 3 positive lymph nodes are found (notably if at least 12 lymph nodes are sampled) but the impact that combination of positive lymph nodes with other risk factors for BCR may have on oncological outcomes was not explored[36].

In summary, RCTs will be needed to determine the benefit of ART in positive lymph node PCa patients. Until then, the use of ART should be always considered in this group of patients, especially if more than 2 lymph nodes are involved and/or other risk factors for BCR are associated.

Impact of novel imaging techniques on treatment

The detection rate of different imaging modalities is determined by PSA level. Thus, the lower the PSA value, the lower the possibility of identifying locoregional or distant disease[37,38]. The decision to initiate ART after RP should be made when serum PSA values are < 0.5 ng /mL (or ideally < 0.2 ng/mL); therefore, the use of sensitive and accurate imaging techniques is of special interest. Choline-based positron emission tomography (PET)/computed tomography (CT) detection rate is 30% when the serum PSA level is ≤ 1 ng/mL after RP, while the corresponding detection rate is 60% for gallium 68 prostate-specific membrane antigen (68Ga-PSMA) PET/CT. Furthermore, when serum PSA is below 0.2 ng/mL the estimated detection rate for 68Ga-PSMA) PET/CT is 40%[38,39]. PET imaging with 68Ga-PSMA ligand was approved on December 1, 2020, by the US Food and Drug Administration to detect PCa recurrence after RP[40].

A meta-analysis of 15 studies showed that 68Ga-PSMA PET results after RP influenced the type and characteristics of treatment. The number of patients who received an increased dose or target volume of SRT rose after 68Ga-PSMA PET[41]. Similar results were presented at ASCO 2022. Armstrong et al. randomized 193 patients who experienced BCR to undergo any conventional imaging or 68Ga-PSMA-11 PET/CT scan prior to SRT (median PSA before SRT of 0.3 ng/mL). Seventy-one percent of major changes, defined as change of androgen-deprivation therapy (ADT) duration ≥ 3 months, change of standard RT volumes, target volume delineation beyond standard RT field, simultaneous-integrated boost beyond standard RT fields, and initiation of advanced systemic therapy, were PSMA-related[42].

Pending final results of the Radiation Therapy Oncology Group (RTOG) 0534 SPPORT trial, which explores the effect of ADT with or without pelvic lymph node treatment added to the prostate bed together with SRT[43], novel imaging techniques may be useful in identifying patients who may benefit from whole-pelvis SRT, although its association with improved oncologic outcomes is not yet known[44].

RT technique

RT techniques in PCa have advanced significantly in the past decades. For example, intensity-modulated RT

(IMRT) is now the gold standard for external beam RT (EBRT)[5]. Although the benefit of dose escalation to 78 Gy or higher for definitive localised PCa RT is well known, its effect in the postoperative setting is still in doubt. A systematic review and meta-analysis of 71 retrospective studies demonstrated a proportional gain in BCR-free survival of 2% per incremental Gy when escalating SRT > 70 Gy was given. A randomized phase 3 study that randomized patients with BCR following RP to either 64-Gy or 70-Gy SRT showed that dose escalation had a minor impact on quality of life but led to significant worsening of urinary symptoms[45]. Thus, neither National Comprehensive Cancer Network (NCCN) nor EAU guidelines specify the appropriate dose to be administered and recommend doses of at least 66 Gy up to 72 Gy[11,46].

Stereotactic body RT (SBRT) that accurately delivers a high radiation dose to an extracranial target in 1 or a few treatment fractions (extreme hypofractionation)[47] has been suggested as a safe procedure for patients with BCR and detectable local recurrence. Although further investigations are needed, this emerging treatment option for isolated relapse may reduce the undesirable side effects of RT without compromising oncologic outcomes[48].

None of the studies included in the ARTISTIC meta-analysis administered RT doses higher than 66 Gy or used hypofractionation techniques. Therefore, new advances in RT may still improve oncologic outcomes following SRT.

Timing and duration of ADT with SRT

The optimal duration of ADT together with SRT is uncertain. The RTOG 9601 trial supports the addition of 2 years of daily bicalutamide 150 mg to SRT because a benefit in OS at 10-year follow-up was observed (16% reduction in risk of death)[49]. Similarly, the results of the GETUG-AFU 16 trial, which randomized 743 patients to SRT alone or SRT plus 6 months of quarterly goserelin, confirmed that the addition of ADT led to a 27% reduced risk of metastasis[50]. Fossati et al. retrospectively explored the impact of ADT duration on oncologic outcomes following SRT and concluded that patients with more than one risk factor (≥ pT3b, ISUP > 3, or PSA level at SRT > 0.5 ng/mL) may benefit from long-term ADT, whereas patients with a single risk factor may receive < 12 months of ADT without compromising oncological outcomes. Patients without any risk factors did not show a significant benefit from concomitant ADT[51]. Irrespective of the study arm, some patients enrolled in the RADICALS trial were randomized to 0 versus 6 versus 12 months of ADT, but results regarding ADT effect are still unknown[21]. Likewise, the ongoing LOBSTER trial investigates whether prolonging the duration of ADT from 6 to 24 months improves oncologic outcomes. Result from these 2 RCTs will allow us to define the most appropriate treatment time for patients receiving SRT.

Several ongoing RCTs are evaluating the role of new androgen receptor pathway targeting agents in combination with SRT. For instance, the SALV-ENZA trial[52] compares SRT plus placebo with SRT plus enzalutamide, while the STEEL trial[53] compares SRT plus standard ADT with SRT plus standard ADT plus enzalutamide. The CARLHA-2 trial is exploring the effect of adding apalutamide to SRT and standard ADT[54]. Finally, the FORMULA-509 trial is studying the addition of apalutamide, abiraterone, and prednisone to SRT plus standard ADT[55].

Benefit of SRT in cases of BCR

Lastly, which patients would truly benefit from SRT in the case of BCR? Beyond reporting the role of ART in the presence of high-risk features for BCR, the SWOG 8794[6],EORTC 22911[7], ARO 96–02/AUO AP 09/95[8], and Finnish[9] trials provided information about the natural history of PCa. They revealed that median MFS and clinical PFS rates were > 10 years even among men included in the observation arm. These findings raise the question of whether all patients with BCR would benefit from SRT and suggest that some patients with BCR following RP who receive SRT may be overtreated. For instance, Pak et al. retrospectively analysed 817 patients with BCR after RP. Patients were categorised into 3 groups according to time from RP to BCR: an early group (median BCR-free survival of 8.5 months), an intermediate group (median BCR-free survival of 17.5 months), and a late group (median BCR-free survival of 70 months). The authors found that 8-year distant MFS and 8-year CSS were significantly better among patients receiving early SRT (with or without ADT) than among those receiving ADT alone in cases of early BCR, but no differences were found in cases of late BCR. Because patients included in the early BCR group had worse clinical and oncologic characteristics, such as higher NCCN risk group, preoperative PSA > 20 ng/mL, Gleason score 9 to 10, and pT3b-stage disease, more challenging tumour biology may explain these results. Nevertheless, not all studies published to date support time from RP to BCR as an independent risk factor for worse oncologic outcomes[56,57].

Although PSA doubling time (PSADT) is not always associated with short BCR-free survival, it has been noted that these variables are interconnected[56]. Thirty-six retrospective studies evaluating prognostic factors in patients with BCR following RP that were included in a systematic review and subsequent meta-analysis showed a significant relationship between shorter PSADT and higher risk of distant metastasis, PCa-specific mortality,

and overall mortality, whereas BCR-free survival was also related to PCa-specific mortality and overall mortality.

In contrast, after PSADT, PCa Gleason score based on prostatectomy histology report was recognized as a second factor more strongly associated with worse oncologic outcomes following RP as a primary treatment. Based on these findings and the hypothesis that not all patients with BCR benefit from salvage treatment, the EAU proposed a new BCR risk stratification that suggested that EAU low-risk BCR patients after RP (PSADT > 1 year and pathologic Gleason score < 8) might avoid salvage treatment[57]. Nevertheless, a recent validation showed that SRT was highly protective, with maximum effect in early delivery[58]. Therefore, risk group stratification after BCR remains inaccurate, and more research is needed to develop a molecular approach.

So far, only retrospective studies have been published regarding this topic. When the ART versus SRT debate comes to an end, selecting those patients who may benefit from SRT seems to be the next step. In this regard, RCTs are of the utmost importance for shedding light on the hypotheses retrospective studies have raised[59,60].

Conclusions

Early SRT may be suggested as the standard of care for patients with PCa with high-risk features and undetectable postoperative PSA. Nevertheless, some aspects, such as the duration of ADT with SRT as well as a more accurate stratification of patients at risk of clinical progression, require further investigation. Therefore, some patients with undetectable PSA following RP may benefit from ART, while other patients can avoid SRT despite reaching serum PSA levels above 0.2 ng/mL. In conclusion, only improving patient selection for ART or SRT will lead to peace.

References

1. Gillessen S, Attard G, Beer TM, Beltran H, Bjartell A, Bossi A, et al. Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. *Eur Urol.*2020;77(4):508–547. doi:10.1016/j.eururo.2020.01.012.

2. Aizawa R, Takayama K, Nakamura K, Inoue T, Yamasaki T, Kobayashi T, et al. Ten-year outcomes of high-dose intensity-modulated radiation therapy for nonmetastatic prostate cancer with unfavorable risk: early initiation of salvage therapy may replace long-term adjuvant androgen deprivation. *Int J Clin Oncol.*2019;24(10):1247-1255. doi:10.1007/s10147–019–01478-y.

3. Tolkach Y, Kristiansen G. The heterogeneity of prostate cancer: a practical approach. *Pathobiology.*2018;85(1-2):108-116. doi:10.1159/000477852.

4. Tilki D, D'Amico AV. Timing of radiotherapy after radical prostatectomy. *Lancet.*2020;396(10260):1374-1375. doi:10.1016/S0140–6736(20)31957–7.

5. Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, et al.; ARTISTIC Meta-analysis Group. 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(10260):1422-1431. doi:10.1016/S0140–6736(20)31952–8.

6. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, 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(3):956-962. doi:10.1016/j.juro.2008.11.032.

7. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. European Organisation for Research and Treatment of Cancer, Radiation Oncology and Genito-Urinary Groups. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet.*2012;380(9858):2018-2027. doi:10.1016/S0140–6736(12)61253–7.

8. Wiegel T, Bartkowiak D, Bottke D, Bronner C, Steiner U, Siegmann A, 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(2):243-450. doi:10.1016/j.eururo.2014.03.011.

9. Hackman G, Taari K, Tammela TL, Matikainen M, Kouri M, Joensuu T, et al; FinnProstate Group. Randomised trial of adjuvant radiotherapy following radical prostatectomy versus radical prostatectomy alone in prostate cancer patients with positive margins or extracapsular extension. *Eur Urol.*2019;76(5):586-595. doi:10.1016/j.eururo.2019.07.001.

10. Tao R, Dai J, Bai Y, Yang J, Sun G, Zhang X, et al. The prognosis benefits of adjuvant versus salvage radiotherapy for patients after radical prostatectomy with adverse pathological features: a systematic review and meta-analysis. *Radiat Oncol.*2019;14(1):197. doi:10.1186/s13014–019–1384-z.

11. Mottet N, Cornford P, van den Bergh RCN, Briers E, De Santis M, Gillesen S, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. 2022. Available at https://uroweb.org/eau-guidelines.

12. Buscariollo DL, Drumm M, Niemierko A, Clayman RH, Galland-Girodet S, Rodin D, et al. Long-term results of adjuvant versus early salvage postprostatectomy radiation: a large single-institutional experience. *Pract Radiat Oncol.*2017;7(2):e125-e133. doi:10.1016/j.prro.2016.10.010.

13. Fossati N, Karnes RJ, Boorjian SA, Moschini M, Morlacco A, Bossi A, 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(6):886-893. doi:10.1016/j.eururo.2016.07.028.

14. Siegmann A, Bottke D, Faehndrich J, Brachert M, Lohm G, Miller K, et al. Salvage radiotherapy after prostatectomy—what is the best time to treat? *Radiother Oncol.*2012;103(2):239-243. doi:10.1016/j.radonc.2011.10.024.

15. Briganti A, Wiegel T, Joniau S, Cozzarini C, Bianchi M, Sun M, et al. Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: results of a match-controlled multi-institutional analysis. *Eur Urol.*2012;62(3):472-487. doi:10.1016/j.eururo.2012.04.056.

16. Fossati N, Karnes RJ, Cozzarini C, Fiorino C, Gandaglia G, Joniau S, et al. Assessing the optimal timing for early salvage radiation therapy in patients with prostate-specific antigen rise after radical prostatectomy. *Eur Urol.*2016;69(4):728-733. doi:10.1016/j.eururo.2015.10.009.

17. Tendulkar RD, Agrawal S, Gao T, Efstathiou JA, Pisansky TM, Michalski JM, et al. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. *J Clin Oncol.*2016;34(30):3648-3654. doi:10.1200/JCO.2016.67.9647.

18. Bottke D, Bartkowiak D, Schrader M, Wiegel T. Radiotherapy after radical prostatectomy: immediate or early delayed? *Strahlenther Onkol.*2012;188(12):1096-1101. doi:10.1007/s00066–012–0234–9.

19. Sargos P, Chabaud S, Latorzeff I, Magné N, Benyoucef A, Supiot S, 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(10):1341-1352. doi:10.1016/S1470–2045(20)30454-X.

20. Kneebone A, Fraser-Browne C, Duchesne GM, Fisher R, Frydenberg M, Herschtal A, 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(10):1331-1340. doi:10.1016/S1470–2045(20)30456–3.

21. Parker CC, Clarke NW, Cook AD, Kynaston HG, Petersen PM, Catton C, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet.*2020;396(10260):1413-1421. doi:10.1016/S0140–6736(20)31553–1.

22. Huelster HL, Laviana AA, Joyce DD, Huang L-C, Zhao Z, Koyama T, Hoffman KE, et al. Radiotherapy after radical prostatectomy: effect of timing of postprostatectomy radiation on functional outcomes. *Urol Oncol.*2020;38(12):930.e23–930.e32. doi:10.1016/j.urolonc.2020.06.022.

23. Chapin BF, Nguyen JN, Achim MF, Navai N, Williams SB, Prokhorova IN, et al. Positive margin length and highest Gleason grade of tumor at the margin predict for biochemical recurrence after radical prostatectomy in patients with organ-confined prostate cancer. *Prostate Cancer Prostatic Dis.*2018;21(2):221-227. doi:10.1038/s41391–017–0019–4.

24. Bernstein AN, Shoag JE, Golan R, Halpern JA, Schaeffer EM, Hsu WC, et al. Contemporary incidence and outcomes of prostate cancer lymph node metastases. *J Urol.*2018 Jun;199(6):1510–1517. doi: 10.1016/j.juro.2017.12.048. Epub 2017 Dec 26. PMID: 29288121; PMCID: PMC6530582.

25. Nguyen PL, Shin H, Yousefi K, Thompson DJ, Hornberger J, Hyatt AS, et al. Impact of a genomic classifier of metastatic risk on postprostatectomy treatment recommendations by radiation oncologists and urologists. *Urology.*2015;86(1):35-40. doi:10.1016/j.urology.2015.04.004.

26. Marascio J, Spratt DE, Zhang J, Trabulsi EJ, Le T, Sedzorme WS, et al. Prospective study to define the clinical utility and benefit of Decipher testing in men following prostatectomy. *Prostate Cancer Prostatic Dis.*2020;23(2):295-302. doi:10.1038/s41391–019–0185–7.

27. Messina C, Cattrini C, Soldato D, Vallome G, Caffo O, Castro E, et al. BRCA mutations in prostate cancer: prognostic and predictive implications. *J Oncol.*2020:4986365. doi:10.1155/2020/4986365.

28. Giri VN, Knudsen KE, Kelly WK, Cheng HH, Cooney KA, Cookson MS, et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol.*2020;38(24):2798-2811. doi:10.1200/JCO.20.00046.

29. Borque-Fernando A, Espílez R, Miramar D, Corbatón D, Rodríguez A, Castro E, et al. Genetic counselling in prostate cancer: how to implement it in daily clinical practice? Asesoramiento genético en cáncer de próstata: ¿cómo implementarlo en la práctica clínica diaria? *Actas Urol Esp.*2021;45(1):8–20. doi:10.1016/j.acuro.2020.08.009.

30. Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol.*2013;31(14):1748-1757. doi:10.1200/JCO.2012.43.1882.

31. Marshall CH, Fu W, Wang H, Baras AS, Lotan TL, Antonarakis ES. Prevalence of DNA repair gene mutations in localized prostate cancer according to clinical and pathologic features: association of Gleason score and tumor stage. *Prostate Cancer Prostatic Dis.*2019;22(1):59-65. doi:10.1038/s41391–018–0086–1.

32. Spratt DE, Yousefi K, Deheshi S, Ross AE, Den RB, Schaeffer EM, et al. Individual patient-level meta-analysis of the performance of the decipher genomic classifier in high-risk men after prostatectomy to predict development of metastatic disease. *J Clin Oncol.*2017 Jun 20;35(18):1991–1998. doi: 10.1200/JCO.2016.70.2811.

33. Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol.*2014 Dec 10;32(35):3939–47. doi: 10.1200/JCO.2013.54.7893.

34. Marra G, Valerio M, Heidegger I, Tsaur I, Mathieu R, Ceci F, et al. Management of patients with node-positive prostate cancer at radical prostatectomy and pelvic lymph node dissection: a systematic review. *Eur Urol Oncol.*2020 Oct;3(5):565–581. doi: 10.1016/j.euo.2020.08.005.

35. Tilki D, Preisser F, Tennstedt P, Tober P, Mandel P, Schlomm T, 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 May;119(5):717–723. doi: 10.1111/bju.13679.

36. Tilki D, Chen MH, Wu J, Huland H, Graefen M, D'Amico AV. Adjuvant versus early salvage radiation therapy after radical prostatectomy for pN1 prostate cancer and the risk of death. *J Clin Oncol.*2022 Jul 10;40(20):2186–2192. doi: 10.1200/JCO.21.02800.

37. Krause BJ, Souvatzoglou M, Tuncel M, Herrmann K, Buck AK, Praus C, et al. The detection rate of [11C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. *Eur J Nucl Med Mol Imaging.*2008;35(1):18–23. doi:10.1007/s00259–007–0581–4.

38. Perera M, Papa N, Christidis D, Wetherell D, Hofman MS, Murphy DG, et al. Sensitivity, specificity, and predictors of positive 68Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. *Eur Urol.*2016;70(6):926–937. doi:10.1016/j.eururo.2016.06.021.

39. Treglia G, Pereira Mestre R, Ferrari M, Bosetti DG, Pascale M, et al. Radiolabelled choline versus PSMA PET/CT in prostate cancer restaging: a meta-analysis. *Am J Nucl Med Mol Imaging.*2019;9(2):127–139.

40. FDA approves first PSMA-targeted PET imaging drug for men with prostate cancer. News release. US Food and Drug Administration. December 1, 2020. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-psma-targeted-pet-imaging-drug-men-prostate-cancer. Accessed June 1, 2022.

41. Han S, Woo S, Kim YJ, Suh CH. Impact of 68Ga-PSMA PET on the management of patients with prostate cancer: a systematic review and meta-analysis. *Eur Urol.*2018;74(2):179-190. doi:10.1016/j.eururo.2018.03.030.

42. Armstrong WR, Kishan AU, Booker KM Fendler WP, Hope TA, Nickols NG, et al. Impact of PSMA PET/CT on prostate cancer salvage radiotherapy management: results from the prospective randomized phase 3 trial [PSMA SRT NCT03582774]. *J Clin Oncol.*2022;40(16-suppl):5028–5028. DOI: 10.1200/JCO.2022.40.16_suppl.5028.

43. National Library of Medicine (U.S.). (2007, December). Prostate radiation therapy or short-term androgen deprivation therapy and pelvic lymph node radiation therapy with or without prostate radiation therapy in treating patients with a rising prostate specific antigen (PSA) after surgery for prostate cancer. Identifier NCT00567580. https://clinicaltrials.gov/ct2/show/NCT00567580.

44. Sachdev S, Carroll P, Sandler H, Nguyen PN, Wafford E, Auffenberg G, et al. Assessment of postprostatectomy radiotherapy as adjuvant or salvage therapy in patients with prostate cancer: a systematic review. *JAMA Oncol.*2020 Nov 1;6(11):1793–1800. doi: 10.1001/jamaoncol.2020.2832.

45. Ghadjar P, Hayoz S, Bernhard J, Zwhalen DR, Hölscher T, Gut P, et al. Acute toxicity and quality of life after dose-intensified salvage radiation therapy for biochemically recurrent prostate cancer after prostatectomy: first results of the randomized trial SAKK 09/10. *J Clin Oncol.*2015;33(35):4158–4166. doi:10.1200/JCO.2015.63.3529.

46. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer Version 4.2022 — May 10, 2022. Available at http://www.nccn.org/professionals/physician_gls/pdf/bone.pdf.

47. Guckenberger M, Andratschke N, Alheit H, Holy R, Noustakis C, Nestle U, et al; Deutschen Gesellschaft für Radioonkologie (DEGRO). Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. *Strahlenther Onkol.*2014;190(1):26-33. doi:10.1007/s00066–013–0450-y.

48. Francolini G, Jereczek-Fossa BA, Di Cataldo V, Simontacchi G, Marvaso G, Zerella MA, et al. Stereotactic radiotherapy for prostate bed recurrence after prostatectomy, a multicentric series. *BJU Int.*2020;125(3):417–425. doi:10.1111/bju.14924.

49. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al; NRG Oncology RTOG. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *N Engl J Med.*2017;376(5):417–428. doi:10.1056/NEJMoa1607529.

50. Carrie C, Magné N, Burban-Provost P, Sargos P, Latorzeff I, Lagrange J-L, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. *Lancet Oncol.*2019;20(12):1740–1749. doi:10.1016/S1470–2045(19)30486–3.

51. Fossati N, Robesti D, Karnes RJ, Soligo M, Boorjian SA, Bossi A, et al. Assessing the role and optimal duration of hormonal treatment in association with salvage radiation therapy after radical prostatectomy: results from a multi-institutional study. *Eur Urol.*2019 Oct;76(4):443–449. doi: 10.1016/j.eururo.2019.02.004.

52. Kapoor R, Deek MP, McIntyre R, Raman N, Kummerlowe M, Chen I, et al. A phase II randomized placebo-controlled double-blind study of salvage radiation therapy plus placebo versus SRT plus enzalutamide with high-risk PSA-recurrent prostate cancer after radical prostatectomy (SALV-ENZA). *BMC Cancer.*2019;19(1):572. doi:10.1186/s12885–019–5805-z.

53. Posadas EM, Gay HA, Pugh SL, Morgan TM, Yu JB, Lechpammer S, et al. RTOG 3506 (STEEL): a study of salvage radiotherapy with or without enzalutamide in recurrent prostate cancer following surgery. *J Clin Oncol.* Published online May 25, 2020. doi:10.1200/JCO.2020.38.15_suppl.TPS5601.

54. National Library of Medicine (U.S.) (2019, November). Combined apalutamide, radiotherapy, and LHRH agonist in prostate cancer patients after prostatectomy (CARLHA-2). Identifier NCT04181203. https://clinicaltrials.gov/ct2/show/NCT04181203

55. National Library of Medicine (U.S.) (2017 May). Randomized phase II study of salvage XRT + ADT +/- abiraterone and apalutamide for rising PSA after RP (FORMULA-509). Identifier NCT03141671. https://clinicaltrials.gov/ct2/show/NCT03141671

56. Pak S, You D, Jeong IG, Kim YS, Hong JH, Kim C-S, et al. Time to biochemical relapse after radical prostatectomy and efficacy of salvage radiotherapy in patients with prostate cancer. *Int J Clin Oncol.*2019;24(10):1238–1246. doi:10.1007/s10147–019–01463–5.

57. Van den Broeck T, van den Bergh RCN, Arfi N, Gross T, Moris L, Briers E, et al. Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review. *Eur Urol.*2019;75(6):967–987. doi:10.1016/j.eururo.2018.10.011.

58. Tilki D, Preisser F, Graefen M, Huland H, Pompe RS. External validation of the European Association of Urology biochemical recurrence risk groups to predict metastasis and mortality after radical prostatectomy in a European cohort. *Eur Urol.*2019;75(6):896-900. doi:10.1016/j.eururo.2019.03.016.

59. Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. *New Engl J Med.*2020;382(7):674–678. doi:10.1056/NEJMsb1901642.

60. Trabulsi EJ, Valicenti RK, Hanlon AL, Pisansky TM, Sandler HM, Kuban DA, et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for pT3–4N0 prostate cancer. *Urology.*2008;72(6):1298–1302; discussion 1302–1304. doi:10.1016/j.urology.2008.05.057.