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Adjuvant and Salvage Radiotherapy after Radical Prostatectomy in Prostate Cancer Patients

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Abstract

Context: Prostate cancer (PCa) patients found to have adverse pathologic features following radical prostatectomy (RP) are less likely to be cured with surgery alone.
Objective: To analyze the role of postoperative radiotherapy (RT) in patients with aggressive PCa.
Evidence acquisition: We performed a systematic literature review of the Medline and EMBASE databases. The search strategy included the terms radical prostatectomy, adjuvant radiotherapy, and salvage radiotherapy, alone or in combination. We limited our search to studies published between January 2009 and August 2016.
Evidence synthesis: Three randomized trials demonstrated that immediate RT after RP reduces the risk of recurrence in patients with aggressive PCa. However, immediate postoperative RT is associated with an increased risk of acute and late side effects ranging from 15% to 35% and 2% to 8%, respectively. Retrospective studies support the oncologic efficacy of initial observation followed by salvage RT administered at the first sign of recurrence; however, the impact of this delay on long-term control remains uncertain. Hopefully, ongoing randomized trials will shed light on the role of adjuvant RT versus observation ± salvage RT in individuals with adverse features at RP. Accurate patient selection based on clinical characteristics and molecular profile is crucial. Dose escalation, whole-pelvis RT, novel techniques, and the use of hormonal therapy might improve the outcomes of postoperative RT.
Conclusions: Immediate RT reduces the risk of recurrence after RP in patients with aggressive disease. However, this approach is associated with an increase in the incidence of short- and long-term side effects. Observation followed by salvage RT administered at the first sign of recurrence might be associated with durable cancer control, but prospective randomized comparison with adjuvant RT is still awaited. Dose escalation, refinements in the technique, and the concomitant use of hormonal therapies might improve outcomes of patients undergoing postoperative RT.
Patient summary: Postoperative radiotherapy has an impact on oncologic outcomes in patients with aggressive disease characteristics. Salvage radiotherapy administered at the first sign of recurrence might be associated with durable cancer control in selected patients but might compromise cure in others.

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1. Introduction

Radical prostatectomy (RP) represents one of the treatments of choice for patients with localized prostate cancer (PCa) and is associated with excellent long-term outcomes [1,2]. Nonetheless, more than 30% of contemporary patients treated with RP will harbor aggressive disease characteristics (ie, extracapsular extension, seminal vesicle invasion, or lymph node invasion) at final pathology [3,4]. In some of these individuals, surgery alone might not provide adequate long-term oncologic control [5–8]. Therefore, a multimodal approach that includes radiotherapy (RT) should be considered. Adjuvant RT (aRT) is defined as the administration of RT to the prostatic bed ± the seminal vesicle bed and the pelvic lymph node area delivered typically 1–6 mo after surgery in the absence of signs of recurrence [9]. Prospective randomized trials support a role for aRT in reducing the risk of biochemical recurrence (BCR). Nonetheless, more than 40% of patients managed with initial observation will not recur at 10-yr follow-up [6,7]. Potential short- and long-term side effects associated with aRT, as well as patient inconvenience and expense, significantly limit its adoption [10–12]. Consequently, aRT is administered in approximately 20% of contemporary patients with aggressive pathologic features in the USA [3]. By contrast, initial observation followed by RT in the case of BCR (ie, salvage RT [sRT]) represents an increasingly adopted option even in the absence of strong data from randomized trials [13]. Several improvements in patient selection criteria, radiation dose, techniques of radiation delivery, and use of hormonal therapies have been introduced over the last decades and might impact on patient outcomes. The aim of our review is to analyze the current role and future perspectives of postoperative RT in PCa patients treated with RP.

2. Evidence acquisition

2.1. Search strategy

The literature review was performed in September 2016 according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [14]. The Medline and EMBASE databases were searched for relevant articles between January 2009 and August 2016. The search strategy included the terms prostate cancer, radical prostatectomy, adjuvant radiotherapy, salvage radiotherapy, alone or in combination.

2.2. Inclusion and exclusion criteria

Inclusion criteria were: (1) English language, (2) more than 100 patients enrolled, (3) original articles, (4) cohorts of PCa patients treated with RP ± postoperative RT, (5) studies reporting on oncologic outcomes (BCR, progression-free survival, cancer-specific mortality, and overall mortality) and/or patient-reported side effects, and (6) prospective randomized trials and/or retrospective studies. Exclusion criteria were: (1) other types of articles (ie, reviews, conference abstracts, letters to editor, and editorials), (2) insufficient details provided, and (3) possible data overlap with articles of the same group. If multiple publications evaluating the same cohort were available, the most recent one was selected. After an analysis of the abstracts and recovery of all full texts, additional references were identified. Cited references from selected articles retrieved in our search were also used to identify manuscripts that were not included in the initial search. Two authors (G.G. and M.R.) selected studies for inclusion. Discrepancies between the two authors were resolved via discussion with all coauthors. The articles that provided the highest level of evidence were then evaluated and selected with the consensus of all participating authors (Fig. 1).

2.3. Assessment of risk of bias

The risk of bias in the included randomized controlled trial was assessed using the Cochrane risk of bias assessment tool for randomized controlled trials [15]. Risk of bias in nonrandomized comparative studies was assessed using the modified Cochrane tool. Publication bias for studies comparing progression-free survival after aRT versus sRT was assessed using a funnel plot.

2.4. Data extraction

The following information was abstracted: the number of patients, age, study design, primary treatment, pathologic stage and grade, type of RT after surgery, administration of androgen deprivation therapy (ADT), median follow-up, oncologic outcomes, and short- and long-term side effects.

3. Evidence synthesis

3.1. Characteristics of the studies included in the review process

Overall, three randomized controlled trials comparing immediate postoperative RT and initial observation [6–8], one randomized trial assessing the impact of dose intensification in the salvage setting [16], and two randomized controlled trials comparing the use of RT alone versus RT plus ADT [17,18] were identified. Overall, six nonrandomized comparative studies evaluating the role of postoperative RT in node positive patients [19–24], and seven nonrandomized studies comparing aRT and sRT were included in the review process [13,25–30]. Finally, seven case series reporting predictors of oncologic outcomes after aRT [31–37], 21 case series reporting the outcomes of sRT [38–58], and 20 studies describing postoperative RT side effects have been identified [10–12,28,59–74].

3.2. Risk of bias assessment of the included studies

Fig. 2 presents the risk of bias assessment of six randomized controlled trials included in our systematic review [6–8,16–18]. The risk of selection, detection, and reporting biases was low. The risk of bias related to the blinding of participants and personnel when evaluating patient-reported outcomes (performance bias) was high. When considering nonrandomized comparative studies, we observed a high risk of selection, performance, and detection

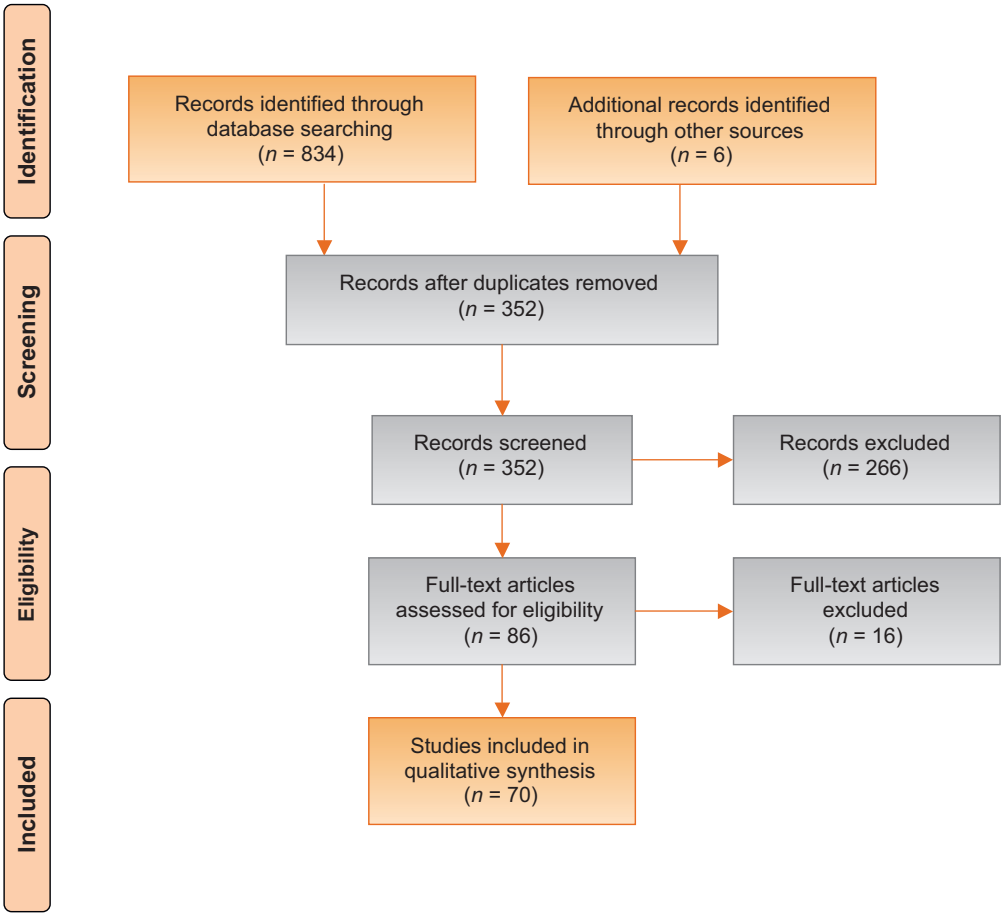

Fig. 1 – Preferred Reporting Items for Systematic Reviews flowchart.

biases. Moreover, the effect of confounders such as pretreatment PSA, pathologic stage, and Gleason score could not be excluded. Case series were at a high risk of bias regarding the selection of consecutive patients and incomplete outcome data (attrition bias). Supplementary Figure 1 depicts the funnel plot that was generated to assess the presence of publication bias in studies comparing the progression-free survival of aRT versus sRT ($n = 4$).

3.3. *Rationale for postoperative RT in men with aggressive PCa*

Historically, approximately 30% of PCa patients treated with RP harbor extracapsular extension, seminal vesicle invasion, high-grade disease, or lymph node invasion at final pathology. With the decline of PSA screening and the popularity of active surveillance, an increase in the proportion of patients with more advanced disease among those treated with RP has been observed [31,75,76]. These individuals are, in turn, at increased risk of recurrence after surgery [77]. Due to local disease aggressiveness, RP alone may not be curative as it does not completely eliminate the local tumor. The persistence of microscopic and advanced disease increases the risk of recurrence and up to 50% of men with post-RP BCR evaluated with molecular imaging have pathologic uptake in the prostatic fossa or the pelvis [5,78–81]. A multimodal approach aimed at maximizing local regional control that includes postoperative RT might reduce the risk of biochemical and clinical recurrence, ultimately improving survival. This hypothesis inspired the design of prospective randomized trials aimed at assessing the role of postoperative RT in men with more aggressive disease characteristics.

3.4. *Prospective randomized trials evaluating the role of aRT*

aRT is defined as the administration of RT after surgery to patients with aggressive disease characteristics in the absence of signs of recurrence [82]. Three randomized trials addressing the role of postoperative RT have been completed (Table 1). The largest investigation is represented by the European Organization for Research and Treatment of Cancer (EORTC) trial 22911, which randomized 1005 patients with pT2R1 or pT3N0 PCa to postoperative RT within 16 wk from surgery versus initial observation. After a median follow-up of 5 yr, aRT significantly improved BCR and metastasis-free survival [83]. At a median follow-up of 127 mo, immediate RT after surgery reduced the risk of BCR [6]. In particular, the 10-yr BCR-free survival rates were 60.6 versus 41.1% for patients treated with aRT or initial observation respectively. This

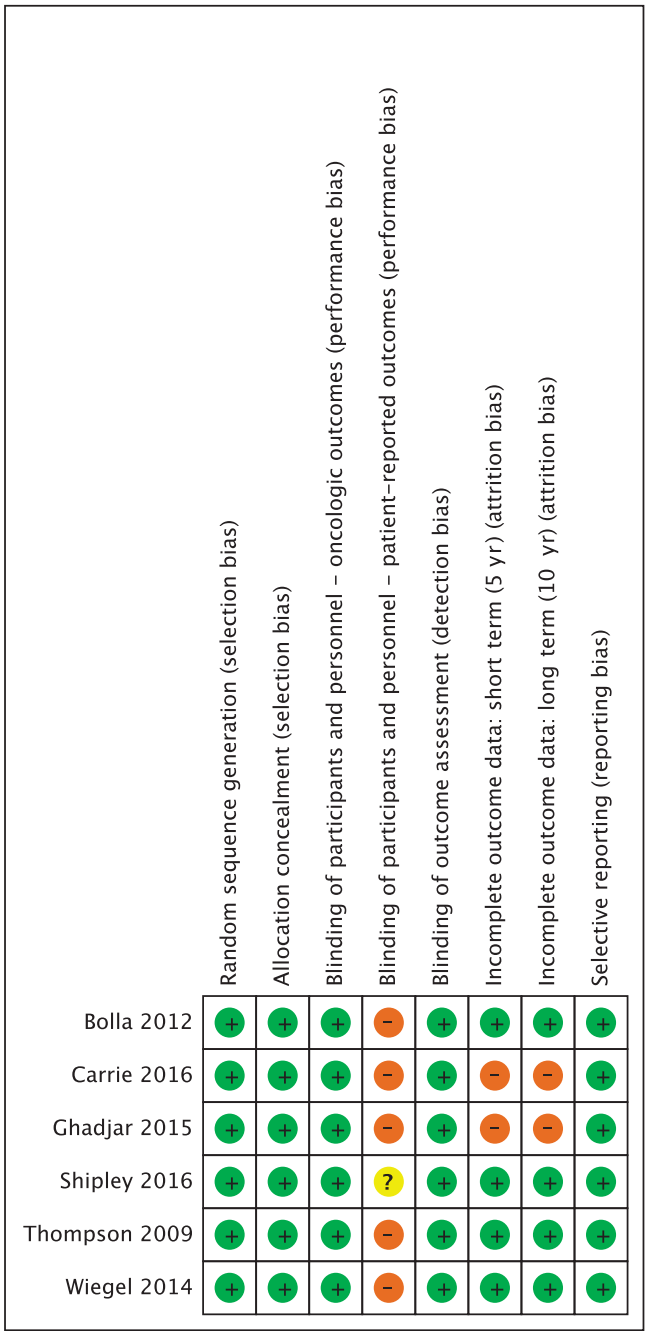

Fig. 2 – Risk of bias for randomized controlled trials included in the systematic review ($n = 6$). Green indicates low risk, red indicates high risk, and yellow indicates unclear.

translated into a number needed to treat (NNT) to prevent a recurrence at 10-yr follow-up of 5. However, no differences were observed in the rate of metastasis-free survival and cancer-specific mortality. The Southwest Oncology Group (SWOG) 8794 trial included 450 patients with pT3N0 PCa randomized to RT within 16 wk of surgery or initial observation [8]. At a median follow-up of 152 mo, the 10-year metastasis-free and overall survival rates were significantly lower for patients treated with immediate RT compared with observation (71% vs 61% and 74% vs 66%, respectively). This translated into a NNT to prevent the development of metastases in one case of 10. Similarly, 13 patients needed to be treated with immediate RT to prevent one death. Although the results of these two trials advocate aRT, approximately one-third of men in the immediate RT group received RT in a salvage setting due to detectable PSA levels immediately after surgery. These individuals have worse metastases-free and overall survival rates compared with their counterparts with complete biochemical response [84]. This issue was partially overcome by the intention-to-treat analysis of the ARO 96–02 trial, which focused exclusively on patients with a PSA <0.5 ng/ml after RP [7]. Overall, 307 men with pT3N0 disease at RP were randomized to aRT or observation. At a median follow-up of 110 mo, individuals in the aRT group had a 20% higher probability of being free from progression compared with those in the observation arm (NNT: 5). These findings support the role of immediate postoperative RT in improving BCR-free survival in men with aggressive disease characteristics, where approximately five patients would need to receive immediate RT to prevent one recurrence at 10-yr follow-up. Although only one study demonstrated an effect of immediate RT after surgery on stronger oncologic endpoints at long-term follow-up [8], a meta-analysis of these prospective randomized trials demonstrated improved overall survival and reduced risk of metastases [85]. Differences in selection criteria, a lack of systematic pathological quality assurance, heterogeneity in radiation technique and dose, as well as the effectiveness of salvage treatment are among the commonly proposed explanations for the discrepancies between these studies [6–8,86].

3.5. How can we identify patients who would benefit from aRT?

Up to 40% of patients eligible for immediate RT according to the inclusion criteria of randomized trials would not experience BCR at 10-yr follow-up and may not thus require additional cancer treatments [6,7]. In a subset of these individuals, the administration of aRT might represent *overtreatment* and be associated with patient inconvenience, expense, and a risk of short- and long-term side effects ranging from 15% to 35% and 2% to 8%, respectively [6–8,85,87,88]. Efforts have been made to improve our ability to identify patients who would benefit from aRT and thereby reduce the risk of overtreatment. In the subset analyses of their randomized controlled trial, Thompson et al [8] demonstrated that the benefit of aRT in terms of cancer-specific survival was greater in patients with higher-grade disease. When considering 552 patients with available pathologic review data included in the EORTC trial 22911, the presence of positive surgical margins represented the strongest predictor of BCR-free survival after aRT [34]. Therefore, aRT should be considered particularly in men with positive margins at RP. Of note, positive margins were an important predictor of recurrence after pathologic review also in the ARO 96-02 trial [37]. Abdollah et al [31] evaluated a cohort of more than 1000 patients treated with RP ± aRT and suggested a benefit

Table 1 – Characteristics of randomized controlled trials assessing the role of adjuvant radiotherapy (aRT) after radical prostatectomy (RP) in prostate cancer patients with aggressive disease characteristics

	Inclusion criteria	Patients (*N*)	Timing	Technique	Dose (median)	Study period	Follow-up (median)	Oncologic outcomes
Bolla et al [6] EORTC 22911	pT2 R1 N0 pT3 N0	1005	Within 16 wk from RP	EBRT	50 Gy in 25 fractions + 10 Gy in 5 fractions	1992–2001	127 mo	• Postoperative RT significantly improved biochemical progression-free survival compared with WS (198 vs 311 events); NNT at 10-yr: overall survival was not improved 5
Thompson et al [8] SWOG 8794	pT3 N0	425	Within 16 wk from RP	EBRT	60–64 Gy in 30–32 fractions	1988–1997	152 mo	• RT significantly improved metastasis-free survival (93 vs 114 events); NNT at 10-yr: 10 • RT significantly improved overall survival (88 vs 110 events); NNT at 10-yr: 13
Wiegel et al [7] ARO 96–02/ AUO AP 09/95	pT3 N0 Postoperative PSA <0.5 ng/ml	368	aRT began between 6 wk and 12 wk after RP	3D-CRT	60 Gy in 30 fractions	1997–2004	112 mo vs 113 mo for aRT vs WS	• At 10-yr, progression-free survival was 56% for aRT and 35% for WS; NNT: 5

EBRT = external-beam radiotherapy; EORTC = European Organization for Research and Treatment of Cancer; NNT = number needed to treat; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; SWOG = Southwest Oncology Group; WS = wait-and-see; 3D-CRT = three-dimensional-conformal radiotherapy.

of postoperative RT only in patients with more aggressive PCa. In particular, aRT was associated with a 10.3% improvement in the 10-yr cancer-specific survival rates exclusively in men with at least two of the following characteristics: lymph node invasion, seminal vesicle invasion, and Gleason score 8–10. These retrospective results appeared to be valid in a population-based study, where the NNT to prevent one death at 10-yr follow-up was 10 among men with two or more of the aforementioned features [33].

Patients with lymph node invasion were not included in the randomized trials evaluating aRT. However, recent evidence suggests a potential role of aRT on oncologic outcomes in this setting [19–22,24]. Table 2 reports the characteristics of six retrospective investigations addressing this issue. Five studies concluded that there might be a benefit of aRT in node positive patients [19,20,22–24], while only one population-based analysis reported negative findings [21]. However, the lack of details regarding dose administered, RT technique, PSA levels at RT, and the definition of aRT might preclude its generalizability. The rationale for using aRT in men with lymph node invasion would be to maximize loco-regional disease control, assuming that not all patients with node-positive PCa would be invariably affected by systemic spread [89,90]. Proper patient selection is mandatory in this setting. When considering a large multi-institutional retrospective cohort of node-positive patients, Abdollah et al [19] reported a beneficial impact of aRT only in men with two or less positive lymph nodes with high-grade nonorgan confined PCa and in those with three to four positive lymph nodes, regardless of local disease characteristics. These findings were externally validated in patients included in the Surveillance, Epidemiology, and End Results database [22]. However, as most patients treated by RP do not undergo an extended lymph node dissection, rigorous rules based on such a series may not be applicable [91]. More recently, Tilki et al [23] suggested that aRT might be associated with improved BCR- and metastasis-free survival in a cohort of 773 node positive patients treated with RP and extended nodal dissection. Of note, whole-pelvis RT was beneficial in all node positive patients regardless of the number of positive nodes. Nonetheless, the short follow-up duration (median: 33.8 mo) limits their findings and results of randomized trials assessing strong oncologic outcomes are needed to address the role of aRT in selected patients with pN1 disease [92].

Currently available selection criteria for the administration of aRT are based on clinical characteristics. However, the introduction of novel biomarkers may allow clinicians to individualize postoperative management according to the risk of recurrence. In a retrospective analysis, Ross et al [35] suggested that the genomic classifier score predicted the risk of metastases after RP regardless of postoperative therapies. Moreover, men with higher scores and more aggressive diseases were the ones who benefitted the most from aRT. This was confirmed by Zhao et al [36], who developed a novel genomic classifier based on 24 genes and reported a positive effect of aRT on the risk of metastases only in men with higher scores (10-yr incidence of metastases: 4% vs 35% for RT vs no RT, respectively). Similarly, Den et al [32] showed that patients with a higher genomic classifier score did much better when managed with aRT rather than sRT (5-yr incidence of metastases: 6% vs 23% for aRT and sRT, respectively). Therefore, genomic classifiers might provide important information on RT timing in the postoperative setting. Nonetheless, the rates of metastases in men managed with aRT alone included in these studies raise questions about whether they should have received ADT as well. Genomic classifiers might therefore be useful also in selecting patients for whom ADT might be omitted without compromising oncologic outcomes.

Table 2 – Selected retrospective studies evaluating the role of adjuvant radiotherapy (aRT) in node-positive prostate cancer (PCa) patients

	Patients (*N*)	aRT definition	Technique	Dose (median)	Study period	Follow-up (median)	Outcomes
Briganti et al [20]	171 pts treated with aRT + aHT vs 532 pts with aHT alone	NA	Conventional nonconformal treatment or 3D-CRT	68.4 Gy	1988–2003	95.1 mo	• Patients treated with aRT had higher CSS rates compared with those treated with aHT alone at 10-yr follow-up (86% vs 70%; $p = 0.004$)
Kaplan et al [21]	177 pts treated with aRT vs 400 pts without aRT	RT <1 yr from surgery	NA	NA	1995–2007	NA	• aRT was not associated with an improvement in overall and CSS
Abdollah et al [19]	386 pts treated with aRT + aHT vs 721 pts with aHT alone	RT within 90 d from RP	Conventional nonconformal treatment or 3D-CRT	68.4 Gy	1988–2010	7.1 yr	• aRT associated with improved OS at 8-yr follow-up (87.6% vs 75.1%; $p < 0.001$) • aRT improved survival only in men with 2 or fewer positive nodes and high-grade PCa or nonorgan confined disease and those with 3–4 positive nodes
Rusthoven et al [22]	420 pts treated with aRT vs 1287 pts without aRT	NA	NA	NA	2004–2009	NA	• aRT improved survival only in men with 2 or less positive nodes and high-grade PCa or nonorgan confined disease
Wong et al [24]	3636 pts treated without adjuvant treatments vs 2041 with aHT vs 350 with aRT vs 1198 with aRT + aHT	NA	NA	NA	2004–2011	46 mo	• The 5-yr OS rates were 85.2% for no adjuvant therapy, 82.9% for aHT, 88.3% for aRT, and 88.8% for aRT + aHT ($p < 0.001$)
Tilki et al [23]	213 pts treated with aRT vs 505 pts treated with observation ± sRT vs 55 pts treated with aHT	NA	3D-CRT to the prostatic and seminal vesicle bed + pelvic area	60–70 Gy to the prostatic bed and 50 Gy to the pelvis	2005–2013	33.8 mo	• The 4-yr metastasis-free survival rateswere 82.5% vs 91.8% for observation ± sRT vs aRT ($p = 0.02$) • aRT significantly reduced the risk of BCR and metastases when compared with aHT alone or observation ± sRT

aHT: = adjuvant hormonal treatment; CSS = cancer-specific survival; OS = overall survival; PSA = prostate specific antigen; pts = patients; RP = radical prostatectomy; RT = radiotherapy; sRT = salvage radiotherapy; WS = wait-and-see; 3D-CRT = three-dimensional conformal approach.

3.6. *sRT: rationale, effectiveness, and optimal timing*

sRT is defined as the administration of postoperative RT to the prostatic bed ± the surrounding tissues in patients who experience BCR after surgery [86]. The availability of postoperative PSA levels as a reliable marker of recurrence after RP enables prompt identification of patients with BCR who are at increased risk of developing metastases and dying from PCa [1]. The administration of sRT to these patients is justified primarily because it is the only curative option, although some would argue their preference for its use over aRT in an effort to reduce costs and the risk of treatment-related side effects [86]. Few prospective randomized trials are available evaluating the oncologic benefits of sRT (ie, RTOG 9601 and GETUG-AFU-16) [17,18]. Randomized studies assessing the impact of aRT on survival in patients with adverse characteristics were not initially designed to compare immediate RT versus observation followed by sRT [6–8]. Indeed, the lack of standardized treatment protocols in the case of recurrence, where only less than 50% of patients experiencing recurrence in the control arm of these studies received sRT, precludes an unbiased comparison between the two approaches. In addition, these patients were treated at relatively high PSA levels and with heterogeneous techniques, doses, and protocols [9]. Consequently, the available data is neither complete nor contemporary. It is however the best available currently for sRT decision making in patients with delayed local recurrence after RP.

Table 3 depicts the characteristics of 21 retrospective studies describing the outcomes of sRT [38–58]. Recent investigations report 5-yr BCR- and metastases-free survival rates of 50–58% and 86–92%, respectively. A large study evaluating more than 1100 patients described the long-term outcomes of sRT, where the BCR- and metastasis-free survival rates were 35% and 80% at 10-yr follow-up [54]. The fact that only one out of three patients is free from recurrence at 10-yr after sRT highlights the need for more aggressive salvage strategies and/or earlier treatments. Refinements in patient selection criteria, doses, and techniques might improve the outcomes of postoperative

Table 3 – Contemporary retrospective studies evaluating outcomes and predictors of response in prostate cancer patients undergoing salvage radiotherapy (sRT)

	Patients (*N*)	Pre-RT PSA level (median)	Technique	Concomitant ADT	Dose (median)	Study period	Follow-up (median)	Outcomes	Predictors of response to sRT
Ost et al [30]	136	0.8 ng/ml	IMRT	71% pts received ADT	76 Gy	1999–2008	5 yr	• 5-yr BCR-free survival: 56% • 5-yr CR-free survival: 86%	• Perineural invasion • Pre-RT PSA levels • ADT administration
Cotter et al [41]	519	NA	NA	NA	66 Gy	1988–2008	11.3 yr	• sRT associated with significant reduction in the risk of overall mortality	• NA
Moreira et al [48]	102	0.6 ng/ml	NA	No	66 Gy	1988–2008	50 mo	• 6-yr BCR-free survival: 57%	• Surgical margins • Pre-RT PSA levels
Bernard et al [38]	364	0.6 ng/ml	NA	NA	64.8 Gy	1987–2007	6 yr	• 5-yr BCR-free survival: 50%	• RT dose
Umezawa et al [56]	102	0.24 ng/ml	NA	28% pts received ADT	64 Gy	2000–2009	44 mo	• 4-yr BCR-free survival: 50.9%	• Pathologic stage
Siegmann et al [104]	301	0.28 ng/ml	NA	No	66.6-70.2 Gy	1997–2007	30 mo	• 2-yr BCR-free survival: 74%	• Total dose • Biochemical response • Seminal vesicle invasion
Goenka et al [44]	285	0.4 ng/ml	3D-CRT or IMRT	31% pts received ADT	NA	1988–2007	60 mo	• 7-yr BCR-free survival: 37% • 7-yr CR-free survival: 77%	• Vascular invasion • Surgical margins • Pre-RT PSA levels • ADT
Jackson et al [45]	575	NA	3D-CRT or IMRT	20% pts received ADT	68.4 Gy	1986–2010	56.7 mo	• The median time to BCR was 15.2 vs 21.8 mo for patients with for patients with Gleason pattern 5 vs Gleason 8	• Gleason pattern 5 • Pathologic stage • Surgical margins • Pre-RT PSA levels • ADT
Ploussard et al [51]	201	0.48 ng/ml	NA	No	NA	1998–2011	53.3 mo	• BCR was reported in 42.8% of cases with the need for second-line ADT in 26.9% of cases	• Gleason score • Pathologic stage • PSA velocity • Pre-RT PSA levels
Kwon et al [46]	212	0.46 ng/ml	Pelvic irradiation in 25% of pts	58.2% pts received ADT	66.6 Gy	2003–2012	63.5 mo	• 5-yr BCR-free survival: 58.2%	• Pre-RT PSA levels • PSADT • ADT • Surgical margins
Parekh et al [50]	108	0.24 ng/ml	NA	40% pts received ADT	66.49 Gy	1993–2010	63.09 mo	• 4-yr BCR-free survival 44.6% vs 22.8% for patients who received ADT vs no ADT	• Pre-RT PSA levels • ADT
Ervandian et al [42]	259	NA	NA	50% pts received ADT	NA	2006–2010	NA	• 3-yr BCR-free survival: 57%	• Surgical margins • ADT • Pre-RT PSA levels
Song et al [53]	149	0.54 ng/ml	3D-CRT or IMRT	NA	69.2 Gy	1995–2011	82 mo	• 5-yr BCR-free survival: 53.6%	• Pre-RT PSA levels • Pathologic stage • Gleason score • PSADT • Pre-RT imaging
van der Poel et al [57]	157	0.2 ng/ml	3D-CRT to the prostatic fossa	No	66–70 Gy	2006–2011	36 mo	• 3-yr BCR-free survival: 64%	• pN stage • Pre-RT PSA levels
Lohm et al [47]	151	0.34 ng/ml	3D-CRT	No	66.6 Gy	NA	82 mo	• BCR-free survival: 40% • OS: 87% • CSS: 92%	• Pre-RT PSA levels • Gleason score • PSADT

Table 3 (*Continued*)

	Patients (*N*)	Pre-RT PSA level (median)	Technique	Concomitant ADT	Dose (median)	Study period	Follow-up (median)	Outcomes	Predictors of response to sRT
Blanchard et al [39]	136	0.6 ng/ml	3D-CRT to the prostatic fossa	No	66 Gy	2002–2007	60 mo	• 5-yr BCR-free survival: 57% • 5-yr CR-free survival: 92.5% • 5-yr OS: 96.7%	• PSA decline during RT (PSA at 5 wk after RT/PSA before RT) • Pre-RT PSA levels
Briganti et al [40]	472	0.24 ng/ml	Conventional non-conformal RT or 3D-CRT to the prostatic fossa	No	66.6 Gy	1993–2009	58 mo	• 5-yr BCR-free survival: 73.4%	• Pathologic stage • Gleason score • Surgical margins • Pre-RT PSA levels
Fossati et al [43]	716	0.2 ng/ml	Conventional non-conformal RT or 3D-CRT to the prostatic fossa	No	66.6 Gy	1996–2009	57 mo	• 5-yr BCR-free survival: 82%	• Pathologic stage • Gleason score • Surgical margins • Pre-RT PSA levels
Tendulkar et al [55]	2,460	0.5 ng/ml	Pelvic irradiation in 17% of pts	16% pts received ADT	66 Gy	1987–2013	60 mo	• 5-yr BCR-free survival: 56% • 10-yr CR-free survival: 81%	• Pre-RT PSA levels • Gleason score • Pathologic stage
Stish et al [54]	1,160	0.6 ng/ml	3D-CRT or IMRT; pelvic irradiation in 4% of pts	16.4% pts received ADT	68 Gy	1987–2013	8.9 yr	• 5-yr BCR-free survival: 50.1% • 10-yr BCR-free survival: 35.7% • 10-yr CR-free survival: 80.1% • 10-yr OS: 77.3%	• Pathologic stage • Gleason score • Pre-RT PSA levels • ADT • SRT dose
Fiorino et al	894	<2 ng/ml	3D-CRT	NA	66.6 Gy	1996–2012	72 mo	• 5-yr BCR-free survival: 80%	• Gleason score • Pre-RT PSA levels • Dose
Overall [58]	NA	0.2-0.8 ng/ml	3D-CRT or IMRT in the prostatic fossa or whole pelvis	0–71%	66–76 Gy	NA	3–12 yr	• 5-yr BCR = ~50% (37–82%) • 10-yr CR = ~80% (80.1–81%)	• Pre-RT PSA level • Pathologic characteristics • PSADT • Dose

ADT = androgen-deprivation therapy; BCR = biochemical-recurrence; CR = clinical-recurrence; CSS = cancer-specific survival; IMRT = intensity-modulated radiotherapy; NA = not applicable; OS = overall survival; PSA = prostate specific antigen; PSADT = prostate specific antigen doubling time; pts = patients; RP = radical prostatectomy; RT = radiotherapy; 3D-CRT = three-dimensional conformal approach.

RT in the salvage setting. In particular, the identification of patients with distant metastases at the time of sRT would improve our ability to deliver RT only to individuals who would benefit from local disease control. Standard imaging techniques such as computed tomography and bone scan are limited by their poor sensitivity [93]. Choline and prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography scans play an increasingly important role for assessing recurrence after primary treatment. However, these imaging modalities have poor performance characteristics at very low PSA levels [94,95]. Therefore, clinicians should rely on models based on pathologic parameters, pre-RT PSA, and PSA doubling time to identify patients who would benefit from sRT [40,55,96]. Tendulkar et al [55] recently updated their nomogram in a cohort of 2460 patients treated with sRT. At a median follow-up of 5 yr, pre-RT PSA, Gleason score, surgical margins, pathologic stage, use of ADT, and RT dose were associated with the risk of recurrence after sRT and were included in a predictive model that depicted a concordance index of 0.69 at internal validation.

Besides pathologic variables, the major predictor of response to sRT is PSA at the time of RT. Of note, pre-RT PSA represents a parameter modifiable by the treating physician who can decide the optimal timing for RT delivery according to patient characteristics. When considering exclusively patients who received early sRT (ie, at PSA levels $<$ 0.5 ng/ml), the 5-yr BCR- and metastases-free survival rates increased to 63–80% and 85–90%, respectively [40,43,55]. A systematic review including more than 5500 patients treated with sRT observed a 2.6% loss of BCR-free survival for each incremental of 0.1 ng/ml in the PSA level at the time of sRT [97]. Moreover, a recent tumor control probability model showed that the detrimental effect of increased PSA levels at the time of RT can never be compensated by increasing the dose [58]. Consequently, international guidelines recommend initiating sRT at the first sign of BCR [1]. However, which is the best timing for sRT administration is still debated. Indeed, while the vast majority of studies report improved cancer control when sRT is administered at low PSA levels [40,53–55,86], in a small proportion of patients a slowly growing postoperative PSA might be the expression of residual benign prostatic tissue [86]. A multi-institutional study evaluating more than 700 node-negative patients reported that early sRT conferred better cancer control when administered at the first sign of PSA relapse especially in men with more aggressive features [43]. Conversely, selected individuals with favorable pathologic characteristics might be affected by an *indolent* recurrence (rise in PSA levels that would not increase the risk of metastases) and, therefore, would not benefit from early sRT. A predictive nomogram to identify patients who would benefit from sRT was developed in 472 patients with node-negative PCa treated with early sRT [40]. Pathologic stage, Gleason score, surgical margins, and pre-RT PSA represented independent predictors of treatment failure and were included in the model, which demonstrated a discrimination of 0.74 at internal validation. Of note, PSA doubling time cannot be accurately estimated in men receiving sRT at low PSA levels and, therefore, has not been included in predictive models developed on contemporary patients [40,55].

Genomic classifiers might play a role also in the salvage setting [98,99]. Freedland et al [99] showed that at a median follow-up of 5.7 yr an increase in the genomic classifier score corresponded to an augmented risk of metastases after sRT. Moreover, the inclusion of the genomic classifier score in a clinical model substantially improved its predictive accuracy from 0.63 to 0.85. As discussed above, individuals with low genomic classifier scores may or may not be able to postpone RT safely. However, molecular markers could identify patients at increased risk of metastases who should be referred for systemic treatments (eg, ADT).

3.7. *Adjuvant versus salvage RT*

Table 4 describes the characteristics of seven retrospective investigations comparing aRT and sRT [13,25–30]. Six studies reported superior oncologic outcomes with aRT compared to sRT [25–30]. At 10-yr follow-up, a reduction in rates of BCR and metastases of 32% and 17% was observed in men undergoing aRT compared with sRT [29]. Of note, these investigations did not include men with aggressive disease managed with observation who never recurred in the salvage arm [86]. Therefore, they compared the efficacy of RT between patients theoretically at risk of recurrence (ie, aRT group) versus individuals who already experienced recurrence (ie, sRT group). Moreover, four studies included men who received sRT at relatively high PSA levels [27–30]. This might impact on the efficacy of RT in the salvage setting. A recent investigation reported the results of the comparison between aRT and observation ± sRT administered at PSA levels $\leq$0.5 ng/ml in a cohort of more than 500 patients with pT3N0 PCa [13]. At 8-yr follow-up the authors did not observe differences in the metastases-free survival and overall survival rates between patients treated with aRT versus observation ± early sRT. These findings are reassuring regarding the oncologic safety of observation ± sRT at low PSA levels in men with aggressive features at RP at intermediate-term follow-up.

Three prospective multi-center open-label trials are currently randomizing patients with adverse pathologic characteristics to aRT versus observation ± sRT (RADICALS, RAVES, and GETUG-17) and their results are badly needed to inform clinicians regarding the role of sRT as compared with aRT in this setting (Table 5). The RADICALS trial is a phase 3 randomized-controlled study taking place in the UK, Canada, Denmark, and Ireland that is divided in two parts: RT timing comparison (RADICALS RT) and hormone duration comparison (RADICALS HT). In the RADICALS RT, patients are randomized to early versus deferred RT, which is administered at the time of PSA failure after surgery. The RADICALS HT trial is randomizing patients to RT alone (early or deferred) versus RT + 6 mo ADT versus RT + 12 months ADT. The primary outcome of both studies is represented by disease-specific mortality. At the latest update, more than 1300 patients were randomized to early versus deferred RT in the RADICALS RT trial [100]. Moreover, more than 2500 patients are expected to be recruited in

Table 4 – Selected retrospective studies comparing adjuvant and salvage radiotherapy (RT) in prostate cancer patients

	Patients (*N*)	Patient characteristics	Pre-sRT PSA (median)	Technique	Concomitant ADT	Dose (median)	Study period	Follow-up (median)	Outcomes
Ost et al [30]	104 aRT vs 134 sRT	GS >3 + 4: 28 vs 28% SVI: 25.8 vs 24.7% PSM: 23.6 vs 33.7%	>0.5 ng/ml in 57% of pts	IMRT to the prostate bed and seminal vesicles	46% vs 37%	74 Gy vs 76 Gy	1999–2009	36 mo	• 3-yr PFS: 95 vs 87% for aRT vs sRT ($p = 0.08$) • 3-yr BCR-free survival: 90 vs 65% for aRT vs sRT ($p = 0.002$)
Budiharto et al [25]	130 aRT vs 89 sRT	GS 8–10: 7.7 vs 14.6% PSM: 35.4 vs 58.4%	0.30 ng/ml	3D-CRT to the prostate bed and seminal vesicles	No	60 Gy vs 66 Gy	NA	103 mo vs 121 mo	• aRT improved PFS
D'Amico et al [26]	65 aRT vs 49 sRT with PSADT <10 mo vs 46 sRT with PSADT ≥10 mo	GS 8–10: 31 vs 10 vs 28% PSM: 97 vs 53 vs 59% SVI: 32 vs 22 vs 20%	NA	3D-CRT to the prostate bed and seminal vesicles	NA	64 Gy vs 66.6 Gy	1989–2008	7.7 yr	• sRT with PSADT <10 mo increased risk of OM • No differences between aRT and sRT with PSADT ≥10 mo in OM
Jereczek-Fossa et al [28]	258 aRT vs 173 sRT	SVI: 26.7 vs 15% PSM: 60.5 vs 33.5%	0.78 ng/ml	The 3D six-field and 3D-ART techniques were used in 25.1% and 74.9% of pts	35% vs 41%	70 Gy	1996–2006	32 mo vs 30 mo	• PFS significantly longer in pts treated with aRT (79.8 vs 60.5% at 4 yr; $p < 0.001$)
Mishra et al [29]	102 aRT vs 74 sRT	GS 8–10: 25.7 vs 29.5% SVI: 31.1 vs 30.4% PSM: 81.1 vs 76.8%	0.6 ng/ml	3D-CRT and IMRT to the bed of the prostate and seminal vesicles	14.9% vs 26.8%	66 Gy vs 66.6 Gy	1990–2009	103 mo	• 10-yr BCR-free survival: 73 vs 41% for aRT and sRT ($p < 0.001$) • 10-yr CR-free survival: 98.6 vs. 80.9% for aRT and sRT ($p = 0.003$)
Detti et al [27]	203 aRT vs 104 sRT	GS 8–10: 40.4 vs 51% SVI: 89.2 vs 77.9% PSM: 49.8 vs 23.1%	1.73 ng/ml[a]	3D-CRT to the prostate bed and seminal vesicles	14.8% vs 26.0%	66.2 Gy vs 66.8 Gy[a]	1995–2010	4.9 yr	• 20.7 vs 31.7% pts experienced BCR in the aRT vs sRT groups ($p = 0.03$)
Fossati et al [43]	243 aRT vs 267 observation ± sRT	GS 8–10: 27 vs 27%	0.2 ng/ml	Conventional nonconformal treatment or 3D-CRT to the bed of the prostate bed and seminal vesicles	No	60 Gy vs 67 Gy	1996–2009	94 mo	• 8-yr CR-free survival: 92 vs 91% for aRT vs sRT ($p = 0.9$) • 8-yr OS: 89 vs 92% ($p = 0.9$)

ADT = androgen deprivation therapy; aRT = adjuvant radiotherapy; GS = Gleason score; IMRT = intensity-modulated radiotherapy; NA = not applicable; OM = overall mortality; PFS = progression-free survival; PSA = prostate specific antigen; PSADT = prostate specific antigen doubling time; PSM = positive surgical margins; pts = patients; sRT = salvage radiotherapy; SVI = seminal vesicle invasion; 3D-CRT = three-dimensional conformal radiation therapy.

[a] Mean.

Table 5 – Ongoing prospective randomized trials comparing adjuvant and salvage radiotherapy (RT) in prostate cancer patients

Trial	Design	Arms	Population	Estimated enrollment	Dose (median)	Type of RT	Primary endpoints	Secondary endpoints
RADICALS RT	Randomized, multicenter, open-label	Immediate RT vs early sRT	pT3/4 and/or pathologic Gleason 7–10 and/or preoperative PSA ≥10 ng/ml and/or positive surgical margins	1350 patients	66 Gy in 33 fractions or 52.5 in 20 fractions	RT to the prostatic bed ± pelvic lymph nodes	Disease-specific survival	• Freedom from recurrence • Progression-free survival • Overall survival • Non-protocol ADT • Toxicity • Patient-reported outcomes
RADICALS HD	Randomized, multicenter, open-label	RT alone vs RT + 6 mo ADT vs RT + 12 mo ADT	Patients due to receive RT	2800 patients	66 Gy in 33 fractions or 52.5 in 20 fractions	RT to the prostatic bed ± pelvic lymph nodes	Disease-specific survival	• Freedom from recurrence • Progression-free survival • Overall survival • Non-protocol ADT • Toxicity • Patient-reported outcomes
RAVES	Randomized, multicenter, open-label	aRT vs early sRT	Positive surgical margins and/or extraprostatic extension and/or seminal vesicle invasion	470 patients	64 Gy in 32 fractions	IMRT or 3D-CRT Target volume and treatment plan centrally reviewed	Biochemical failure	• Toxicity and QoL • BCR-free survival • Overall survival • Disease-specific survival • Distant and local failure • Cost-utility
GETUG-17	Randomized, multicenter, open-label	aRT + ADT vs early sRT + ADT	pT3R1 pN0 or pNx	718 patients	66 Gy in 33 fractions	3D-CRT	Progression-free survival	• Overall survival • Metastases-free survival • Toxicity and QoL
EORTC 22043-30041	Randomized, multicenter, open-label	aRT ± ADT vs eSRT ± ADT	pT2R1 pN0 or pT3 pN0 with undetectable PSA within 3 mo from surgery	600 patients[a]	64–74 Gy	3D-CRT	BCR-free survival	• Clinical progression-free survival • Distant metastases-free survival • Overall survival • QoL • Toxicity

ADT = androgen deprivation therapy; aRT = adjuvant radiotherapy; BCR = biochemical recurrence; IMRT = intensity-modulated radiotherapy; QoL = quality of life; sRT = salvage radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy.

[a] Trial closed in 2013 for poor accrual.

the HD study. The RAVES trial is a phase 3 multicenter trial performed in Australia and New Zealand that randomizes patients to aRT versus sRT administered within 4 mo following the first PSA ≥0.2 ng/ml. Overall, 470 patients will be included and accrual is expected to be completed by the end of the year [101]. Finally, the GETUG-17 trial is a French study that aims at comparing aRT + luteinizing hormone-releasing hormone agonists versus sRT + luteinizing hormone-releasing hormone agonists in men with pT3R1 pN0 or pNx disease at RP.

3.8. How can we optimize postoperative RT? Optimal dose, volume, and technique

The association between RT dose and oncologic outcomes observed in the primary setting led to the hypothesis that higher doses might be beneficial even in men undergoing postoperative RT [102]. Although the median dose delivered to patients undergoing immediate RT included in randomized trials was 60–64 Gy [6–8], retrospective studies proposed a role for dose escalation. Cozzarini et al [103] observed that patients undergoing aRT treated with ≥70 Gy had significantly improved BCR-free and cancer-specific survival rates compared with those receiving <70 Gy at a median follow-up of 108 mo. When considering sRT, clinical guidelines suggest that a minimum dose of 64–65 Gy should be delivered. Nonetheless, the beneficial impact of dose escalation on BCR-free and complete remission-free survival has also been observed in this context [38,44,52,54,104]. Stish et al [54] reported that the delivery of 68 Gy or greater significantly reduced the risk of BCR in a large contemporary cohort of men undergoing sRT. Two systematic reviews addressed this issue, reporting a 2–2.5% improvement in recurrence-free survival for each additional Gy delivered [97,105]. Of note, one prospective trial currently randomizes patients undergoing sRT to 64 Gy or 70 Gy (NCT01272050) [16] and its oncologic results are needed to comprehensively assess the role of dose escalation in patients undergoing sRT.

The use of pelvic radiation in addition to the prostate and seminal vesicle bed RT might be associated with improved oncologic outcomes [106–108]. This approach would allow potentially maximize disease control by *sterilizing* sites of micrometastases in the pelvic lymph nodes. Spiotto et al [108] evaluated 114 patients undergoing aRT or sRT considered at high risk of lymph node involvement according to pathologic characteristics. The authors reported an advantage in BCR-free survival in men treated with whole-pelvis RT (WPRT) compared with prostate bed irradiation only at a median follow-up >5 yr. Similarly, Moghanaki et al [106] evaluated patients receiving sRT without ADT and showed that WPRT was associated with improved BCR-free survival only when administered at pre-RT PSA levels >0.4 ng/ml. Song et al [107] confirmed these findings and reported that the greatest advantage associated with WPRT was in men with more aggressive disease characteristics and higher risk of lymph node invasion. Finally, a comprehensive tumor control probability model recently suggested that recurrence is often related to relapse outside the irradiated volume and supported the role for lymph-node irradiation in patients with Gleason score <7 and PSA levels ≥1 ng/ml or in those with Gleason score ≥7 and PSA >0.3 ng/ml [58]. However, smaller studies have reported conflicting results [45,109]. Further information about the role of WPRT will be provided by the RTOG 05-34 trial (NCT00567580), comparing progression-free survival between patients randomized to prostatic bed RT alone ± short-term ADT or WPRT ± short-term ADT.

Finally, the oncologic benefits associated with novel techniques such as intensity-modulated RT (IMRT) are still debated, where recent studies failed to show an advantage of these approaches over three-dimensional conformal RT in terms of BCR-free and metastases-free survival [44,53,54]. However, IMRT allows a sculpting of high doses around the tumor bed and the pelvic area with deep dose gradients. The potential advantages of this approach might result in a reduced incidence of toxicities associated with postoperative RT [67].

3.9. Concomitant administration of ADT

Although several retrospective studies reported that the addition of ADT to postoperative RT might be beneficial in terms of BCR-free survival [44,50,54,55,110–113], conflicting data exist on the role of hormonal treatment on stronger endpoints such as metastases-free and overall survival [54,112,114]. The rationale for the use of hormonal manipulation during aRT or sRT might be an effect on subclinical metastases. In this context, the greatest oncologic benefit associated with concomitant ADT was observed in men with more aggressive disease characteristics [111,112]. Jackson et al [112] recently evaluated a cohort of more than 600 patients treated with aRT or sRT and reported that concomitant ADT significantly improved BCR-free survival. Moreover, the use of hormonal manipulation for 1 yr or more had an impact on the subsequent risk of BCR and clinical recurrence in men with high-risk features (ie, Gleason score 8–10, seminal vesicle involvement, and/or pre-RT PSA > 1 ng/ml). The RADICALS HT trial is currently randomizing patients to no ADT versus 6-mo ADT versus 24-mo ADT with a gonadotropin-releasing hormone (GnRH) agonist and will help to clarify the role of ADT during postoperative RT.

When considering patients treated exclusively in a salvage setting, the results of two randomized controlled trials addressing this issue were recently published [17,18]. The GETUG-AFU-16 trial (NCT00423475) randomized 743 patients who experienced BCR after RP to RT alone versus RT plus 6-mo goserelin. All patients included in this study had complete biochemical response after surgery. At 5-yr follow-up, patients treated with sRT plus ADT had higher BCR-free and CR-free survival rates as compared to their counterparts receiving sRT alone. No differences were observed in late adverse effects between the two groups. However, a longer follow-up is needed to evaluate the impact of short-term ADT on survival. The RTOG 9601 trial randomized 761 patients with detectable PSA or BCR after surgery to sRT alone versus sRT plus 24-mo bicalutamide [18]. At a median follow-up of 12.6 yr, patients treated with sRT plus ADT had significantly higher clinical recurrence-free and cancer-specific and overall survival rates. Late

Grade 3 and 4 toxicities were similar between the two arms. However, 70% of patients treated with bicalutamide developed gynaecomastia compared to 11% of patients treated with RT alone. When considering the results of the RTOG 9601 trial it should be noted that the use of antiandrogens alone is not a common treatment regimen in contemporary patients and is no longer Food and Drug Administration approved in the USA [112]. This limits the generalizability of these findings to contemporary patients, where GnRH agonists or antagonists should be considered. However, which is the optimal regimen for these molecules is still unknown. The RADICALS HD trial will provide more information regarding the oncologic efficacy of 6-mo versus 12-mo GnRH analogue administration at the time of RT.

3.10. Side effects of postoperative RT

Overall, four randomized controlled studies [6–8,16,87,88] and 20 retrospective investigations reporting adverse events in men undergoing postoperative RT were identified (Table 6) [10–12,28,59–74]. When considering the three available prospective randomized trials comparing immediate RT versus observation ± sRT, patients included in the immediate RT arm had higher rates of Grade 2 or higher genitourinary (GU) and gastrointestinal (GI) toxicity compared with those in the observation arm [6,8,84,87,88]. In the SWOG trial, 47% versus 5% patients had tenderness and urgency with bowel movements at 6 wk (ie, acute side effects) [87]. Urinary frequency at 6 wk was also more common in men undergoing immediate RT (35% vs 20%). Considering late side effects, at 10-yr the Grade 2 or higher GU toxicity reported by the EORTC trial was 8.2% higher (21.3% vs 13.5%) for aRT versus initial observation [6]. No differences were observed in 10-yr GI toxicity (2.5% vs 1.9% for aRT vs observation, respectively, $p > 0.05$). Overall, patients undergoing immediate RT had a cumulative incidence of Grade 3 side effects 2.8% higher than those managed with observation at 10 yr (5.3% vs 2.5%). This was confirmed by a meta-analysis of these trials, concluding that aRT increased the risk of acute GI toxicity, urinary stricture (risk difference: 0.05), and incontinence (risk difference: 0.04) [85]. Conversely, aRT did not impact on erectile function [85]. However, limited data on this issue were available: only one trial reported comprehensive data on sexual function [87]. Moreover, the SWOG trial reported no differences between patients undergoing aRT and observation with regards to quality of life at intermediate term [87].

Retrospective studies have described higher adverse GU and GI events associated with immediate RT. However, conflicting results are reported regarding the impact of aRT on urinary incontinence and erectile dysfunction. Suardi et al [11] evaluated a large cohort of patients treated with RP and suggested that individuals undergoing aRT were less likely to recover urinary continence. This was confirmed by Hegarty et al [64] in >6000 patients treated with aRT versus sRT versus RP alone. Conversely, a recent population-based study failed to show a higher rate of urinary incontinence among men treated with aRT [65]. When considering sexual function, Sia et al [59] reported an increase in the rate of erectile dysfunction after RT. Although these results correlate with recent studies showing an association between aRT and erectile dysfunction [12,71], population-based investigations failed to confirm this association [64,65]. These discrepancies might be related to the definition of continence and erectile function, as well as to the follow-up period, baseline characteristics, selection bias, and type of RT [12,115,116].

Considering the side effects associated with sRT, Cremers et al [68] reported that approximately 40% of the patients treated with this approach experience Grade 2 or higher GU toxicity and 1.6% of them experienced GI side effects. Nonetheless, Grade 4 toxicities were not recorded. Hegarty et al [64] suggested that men undergoing sRT are at increased risk of urinary incontinence and GI complications compared to those treated with RP alone. However, it has been hypothesized that the risk of long-term side effects associated with sRT depend on the time elapsed between RP and sRT. Indeed, individuals receiving salvage approaches more than 6–12 mo from surgery experienced better sexual satisfaction and urinary function recovery compared with those treated earlier [10,71]. Therefore, it may be desirable to postpone postoperative RT when oncologically safe to improve long-term functional outcomes.

The role of treatment regimens and RT techniques on the subsequent risk of adverse events during follow-up has also been assessed. Although dose escalation might improve outcomes, its downside is the increased risk of side effects. In particular, doses above 72 Gy have been associated with an increased rate of acute Grade 3 toxicity in some but not all studies [105]. One prospective trial currently randomizes patients undergoing sRT to 64 Gy or 70 Gy (NCT01272050) [16] and reported a relatively low rate of Grade 2 or higher GU and GI acute toxicity at 3 mo, where the only impact of dose-intensified sRT was on urinary symptoms. Hypofractionated RT (ie, daily dose of 2.2–3.0 Gy/fraction in 20–28 fractions) has been proposed to reduce treatment duration and improve patient compliance without impairing outcomes [117]. However, Cozzarini et al [66] reported that the 5-yr risk of late urinary toxicity was significantly higher among patients undergoing dose escalation (median dose 70.4 Gy) and hypofractionation compared with standard fractionation. Therefore, the potential benefits of hypofractionation and radiation dose should be carefully balanced with the detrimental effects. Other studies assessed the impact of RT technique on the risk of acute and late toxicity. A noncomparative study by Ost et al [60] reported no Grade 3 acute GI toxicity in 104 patients treated with IMRT with a median dose of 74 Gy. Moreover, late grade GU 3 toxicity was reported in only four (4%) patients. This is comparable or lower to what reported by other studies using three-dimensional conformal RT and lower doses [6,8]. Similarly, Alongi et al [61] evaluated 172 patients undergoing whole-pelvis three-dimensional conformal versus IMRT and reported a lower risk of acute GI toxicity in the latter group. This was confirmed when considering patients treated with sRT: Goenka et al [67] showed a reduction in the risk of late Grade 2 or higher GI toxicity in men receiving IMRT compared with those treated with three-dimensional conformal. The extent of the radiation field might also play

Table 6 – Contemporary studies reporting the side effects associated with postoperative radiotherapy (RT) after surgery

Prospective randomized trials							
Study	Patients (*N*)	Type of RT	Follow-up (median)	Urinary side effects	Sexual side effects	Bowel side effects	Comments
Bolla et al [6] EORTC 22911	1005	EBRT within 16 wk from RP; 50 Gy in 25 fractions + 10 Gy in 5 fractions	127 mo	• Grade 2 or higher genitourinary toxicity was greater in the immediate irradiation group at 10-yr (21.3% vs 13.5%)	• NA	• Grade 2 or higher GI toxicity was similar at 10-yr (2.5% vs 1.9%)	• No Grade 4 toxicity • The 10-yr cumulative incidence of Grade 3 late toxicity in the immediate RT group (5.3%) was higher than in the wait-and-see group (2.5%) • 10-yr cumulative incidence of late adverse events: 70.8 vs 59.7% for RT vs WS • Quality of life and sexual function not assessed
Thompson et al [8]; Moinpour et al [87] SWOG 8794	425	EBRT within 16 wk from RP; 60–64 Gy in 30–32 fractions	152 mo	• Urinary frequency more common in the RT group within 90-d and at 2-yr • Total urinary incontinence more common in the aRT group (6.5 vs 2.8%)	• No differences in erectile dysfunction rates	• Significantly more tenderness and bowel movements at 6-wk in the adjuvant group (47 vs 5%) • RT associated with worse bowel function within 2 yr from treatment • No late toxicity was observed	• Global health-related quality of life initially worse for the RT arm • At the end of study period no differences in health-related quality of life
Wiegel et al [7] ARO 96–02/AUO AP 09/95	368	3D-CRT between 6 and 12 wk after RP; 60 Gy in 30 fractions	112 vs 113 mo for aRT vs WS	• 3 events of Grade 2 genitourinary adverse effects (2%) in the aRT vs none in WS	• NA	• 2 Grade 2 GI side effects (1.4%) vs none in the aRT vs WS arms	• Sexual function not assessed • 21.9 vs 3.7% of aRT vs WS patients developed adverse effects of the bladder and/or rectum
Ghadjar et al [16] SAKK 09/10	344	3D-CRT or IMRT 175 vs 175 pts with 64 vs 70 Gy	3 mo	• Acute Grade 2 and 3 GU toxicity in 22 (13.0%) and 1 patient (0.6%) with 64 Gy and 29 (16.6%) and three patients (1.7%) with 70 Gy ($p = 0.2$) • Patients receiving 70 Gy had a more pronounced and clinically relevant worsening of urinary symptoms	• Potency rate decreased from 29–24.3% and from 32.6–30.8% in men treated with 64 and 70 Gy	• Acute Grade 2 and 3 GI toxicity in 27 (16.0%) and 1 patient (0.6%), with 64 Gy, and 27 (15.4%) and 4 patients (2.3%) with 70 Gy ($p = 0.8$)	• No difference in acute toxicity in patients treated with 3D-CRT or IMRT

Retrospective studies							
Study	Patients (*N*)	Type of RT	Follow-up (median)	Urinary side effects	Sexual side effects	Bowel side effects	Comments
Sia et al [59]	171	RT administered to the prostate ± pelvic area with a median dose of 66 Gy	56 mo	• The use of one or more incontinence pads daily was reported by 25.6% and was similar to 23% use reported at baseline	• The proportion of patients without erectile dysfunction decreased from 56.7% to 40.4% after RT	• 12.7% patients had bleeding or urgency after RT	• Noncomparative study
Jereczek-Fossa et al [69]	258 pts treated with aRT vs 173 with sRT	3D-CRT within 6 mo from surgery	48 mo	• Higher rate of Grade 3–4 acute urinary toxicity in the aRT group (2.3 vs 0%) • Higher rate of late Grade 3–4 urinary toxicity in the aRT (3.7 vs 0.6%) • 5-yr likelihood of Grade 2 or higher urinary event: 20.5 vs 10.6% for aRT and sRT	• NA	• No differences in acute and late rectal toxicity	• The control group does not include patients treated with observation alone

Ost et al [110]	104 pts undergoing aRT	IMRT within 7 mo from surgery with a median dose of 74 Gy	36 mo	• 8% reported Grade 3 acute GU toxicity • 4% developed late Grade 3 GU toxicity • Urethral stricture observed in 6 pts • 2 patients had worsening of incontinence	• NA	• No patients experienced Grade 3 acute GI toxicity • No patients developed Grade 3 late GI toxicity	• Noncomparative study
Alongi et al [61]	172	81 vs 91 pts received 3DCRT vs IMRT	NA	• No Grade 3 or higher GU toxicity	• NA	• No Grade 3 or higher lower GI toxicity • Acute upper GI toxicity: 22.2 vs 6.6% ($p = 0.004$)	• Lack of comparison between aRT and sRT • Treatment interruption due to toxicity higher in the 3DCRT group (11 vs 2 pts, respectively; $p = 0.006$)
Goenka et al [67]	285 pts treated with sRT	109 vs 176 pts received 3DCRT vs IMRT	60 mo	• IMRT was not associated with a reduction in risk of Grade 2 or higher GU toxicity and incontinence	• No differences in the rates of erectile dysfunction	• IMRT was independently associated with a reduction in Grade 2 or higher GI toxicity compared with 3D-CRT (5-yr 1.9 vs 10.2%; p = 0.02)	• All pts treated with sRT
Cremers et al [68]	197 pts treated with sRT	3D-CRT for detectable PSA levels after surgery or BCR	40 mo	• 37% pts experienced Grade 2 or higher late GU toxicity • 50% of pts reported some degree of incontinence	• NA	• 1.6% pts experienced Grade 2 or higher late GI toxicity	• No Grade 4 side effects were reported
Cozzarini et al [62]	556 vs 186 pts treated with aRT vs sRT	RT within 6 mo from surgery irrespective of PSA	99 mo	• Similar risk of Grade 2 or 3 late urinary toxicity (23.9 vs 23.7% and 12 vs 10%)	• NA	• NA	• The control group does not include patients treated with observation alone
Suardi et al [11]	208 pts treated with no aRT vs 153 pts receiving aRT	3DCRT within 6 mo from surgery in the presence of undetectable postoperative PSA	30 mo	• The 1- and 3-yr urinary continence recovery was 51% and 59% for patients submitted to aRT vs 81% and 87% for patients not receiving aRT ($p < 0.001$)	• NA	• NA	• UC defined as the use of no pads over the 24-h period • Lack of use of validated questionnaires
Cozzarini et al [66]	929 vs 247 pts treated with conventionally fractionated vs hypofractionated RT	Patients treated with both aRT and sRT included	98 mo	• 5-yr late GU toxicity 6.9 vs 18.1% • Dose fraction independently associated with the risk of GU toxicity	• NA	• NA	• Heterogeneity in the type of RT administered
Sowerbi et al [63]	162 vs 490 pts treated with aRT vs sRT	RT delivered within 6 mo from surgery	Minimum follow-up: 36 mo	• The rate of incontinence was similar between aRT and sRT at 3-yr: 24.5 vs 23.3%	• NA	• NA	• Urinary incontinence was defined as the presence of any reported leakage • Lack of use of validated questionnaires
Hegarty et al [64]	4509 vs 894 vs 734 pts treated with RP only vs aRT vs sRT	RT within 9 mo from surgery	64 vs 62.9 vs 84.2 mo	• Higher risk of incontinence for aRT and sRT vs RP alone	• Lower risk of erectile dysfunction for aRT vs RP alone and sRT	• Higher risk of GI complications for aRT and sRT vs RP alone	• Population-based study • Urinary, sexual, and bowel complications defined according to administrative codes • Lack of details on type of RT administered
van Praet et al [70]	48 vs 239 pts treated with WPRT vs prostatic bed only	IMRT; 75 Gy to the prostatic bed ± 54 Gy to the pelvic area	12 vs 45 mo	• After WPRT, 35% developed Grade 2 and 4% Grade 3 acute GU toxicity • GU toxicity was similar between WPRT and prostatic bed only	• NA	• Incidence of acute and late GI toxicity was higher following WPRT compared to PBRT ($p = 0.04$)	• All pts received ADT • All pts receiving WPRT had N1 disease at final pathology

Table 6 (*Continued*)

Retrospective studies							
Study	Patients (*N*)	Type of RT	Follow-up (median)	Urinary side effects	Sexual side effects	Bowel side effects	Comments
Showalter et al [65]	2176 vs 7700 pts who received postoperative RT vs RP alone	NA	49.8 vs 50.7 mo	• RT was associated with higher risk of GU non-incontinence events • No differences in GU incontinence events	• RT did not increase the risk of ED	• RT associated with significantly higher risk of GI events	• Population-based study • Urinary, sexual, and bowel complications defined according to administrative codes • Lack of details on type of RT administered • Lack of discrimination between aRT and sRT
Gandaglia et al [12]	74 vs 642 pts treated with aRT vs nerve-sparing RP alone	RT within 6 mo from RP with undetectable PSA levels	48 mo	• NA	• Patients who did not receive aRT had higher 3-yr erectile function recovery compared with those treated with aRT (59.8 vs 40.7%; $p < 0.001$)	• NA	• EF defined according to the IIEF-EF score
van Stam et al [10]	241 vs 1,005 pts treated with sRT vs RP alone	NA	NA	• Pts receiving sRT had worse recovery of urinary continence	• Pts receiving sRT had worse recovery of erectile function	• sRT associated with a higher rate of diarrhea	• Patients with a longer interval (>6 mo) between RP and SRT reported significantly better sexual satisfaction after SRT ($p = 0.02$) and better urinary function recovery
Jereczek-Fossa et al [69]	208 pts treated with aRT or sRT	IMRT to the prostatic bed vs whole pelvis RT	27 mo	• No differences in acute and late toxicities	• NA	• No differences in acute and late toxicities	• No patients treated with CRT
Zaffuto et al [71]	199 vs 128 vs 1863 pts treated with aRT vs sRT vs RP only	aRT within 6 mo from RP with undetectable PSA levels	48 mo	• The 3-yr UC 17 recovery rates were 70.7, 59.0 and 42.2% in no RT, sRT 18 and aRT ($p < 0.001$)	• The 3-yr EF recovery rates were 35.0, 29.0 and 11.6% in no RT, sRT and aRT ($p < 0.001$)	• NA	• EF defined according to the IIEF-EF score • UC defined as the use of no pads over the 24-h period

ADT = androgen-deprivation therapy; aRT = adjuvant radiotherapy; BCR = biochemical recurrence; ED = erectile dysfunction; EF = erectile function; GI = gastro-intestinal; IIEF-EF = international index of erectile function-erectile function domain; IMRT = intensity-modulated radiotherapy; NA = not available; PSA = prostate specific antigen; pts = patients; RP = radical prostatectomy; sRT = salvage radiotherapy; WPRT = whole-pelvis RT; WS = wait-and-see; 3DCRT: three-dimensional conformal radiotherapy.

a role in the development of side effects. Van Praet et al [70] reported that the incidence of acute and late GI toxicity was higher among patients undergoing whole pelvis IMRT. However, Jereczek-Fossa et al [69] showed no differences in toxicity among men treated with IMRT delivered to the prostatic bed only versus the whole pelvis.

The association between the type of RT (ie, aRT vs sRT) and the risk of adverse events has also been investigated. Jereczek-Fossa et al [28] reported that patients undergoing aRT are at higher risk of acute and late Grade 3–4 GU toxicity compared with their counterparts receiving sRT. However, no differences in GI toxicity were observed. Similarly, a retrospective study by Zaffuto et al [71] suggested that men undergoing aRT had lower 3-yr continence and erectile function recovery rates compared with those treated with sRT. Conversely, Cozzarini et al [62] reported similar rates of Grade 2 and 3 late urinary toxicity among patients treated with aRT and sRT. Sowerbi et al [63] also failed to show differences in the rates of incontinence among men treated with aRT and sRT. However, these studies might be limited by the relatively small number of patients included and by the short follow-up interval.

Finally, an association between postoperative RT and the risk of secondary malignancies has been proposed [72–74]. Abdel-Wahab et al [72] reported an increased risk of secondary cancers within the irradiated field (eg, rectum and bladder cancers) in PCa patients receiving postoperative RT included in the Surveillance, Epidemiology, and End Results registry. Singh et al [74] evaluated the same cohort and showed an increased risk of bladder cancer among men treated with RP and postoperative RT. Ciezki et al [73] reported an increased incidence of secondary bladder and rectal cancers among patients treated with RP and postoperative RT compared with those treated with surgery alone at 20-yr follow-up (0.74% vs 1.06% and 1.7% vs 2.7%, respectively). More recently, Wallis et al [118] performed a systematic review and meta-analysis of second malignancies after RT for PCa. The authors concluded that there was an increased risk of cancers of the bladder, colorectum, and rectum with hazard ratios of 1.70, 1.80, and 1.8 compared with those unexposed to RT. They also noted that the absolute risk varied from 0.1% to 4.2% for studies reporting the lowest risk compared with those reporting the highest risk. However, almost all of these studies suffer from a methodological flaw, namely the use of patients treated by RP as a control group to estimate the risk of second cancers after RT. An example of this point is provided in an analysis of more than 18 000 men treated by RP reported by Eifler et al [119]. The authors showed that the rate of deaths from second cancers was lower in men treated with RP than in the general American population (standardized mortality ratio: 0.47). Thus, if men in the general population have twice the risk of deaths from second cancers compared to RP, then most if not all of the estimates from studies supporting an association between postoperative RT and secondary malignancies could be explained by this selection bias. Thus, although radiation can result in second cancers, the true risk is still unknown and is likely to be substantially lower that many studies have suggested.

4. Conclusions

Immediate RT reduces the risk of recurrence after RP in patients with aggressive pathologic characteristics. However, this approach is associated with an increase in the 10-yr cumulative risk of Grade 2 or higher GU toxicity of 8% and of Grade 2 or higher GI and GU toxicity of 3%. Therefore, accurate patient selection is mandatory and genomic classifiers might provide information on RT timing in the postoperative setting and on the need for systemic therapies. Although evidence from randomized trials is lacking, observation followed by sRT administered at the first sign of recurrence might be associated with durable cancer control in selected patients. Dose escalation, WPRT, novel RT techniques, and the concomitant use of ADT might improve the long-term outcomes of postoperative RT.

Author contributions: Giorgio Gandaglia had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Gandaglia, Briganti, Clarke, Karnes, Graefen, Ost, Zietman, Roach.
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Appendix A. Supplementary data

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