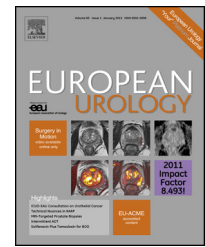


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Platinum Priority – Collaborative Review – Prostate Cancer
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Early Salvage Radiotherapy Following Radical Prostatectomy

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Abstract

Context: Depending on the pathologic tumour stage, up to 60% of prostate cancer patients who undergo radical prostatectomy will develop biochemical relapse and require further local treatment.

Objectives: We reviewed the results of early salvage radiation therapy (RT), defined as prostate-specific antigen (PSA) values prior to RT ≤ 0.5 ng/ml in the setting of lymph node-negative disease.

Evidence acquisition: Ten retrospective studies, including one multicentre analysis, were used for this analysis. Among them, we received previously unpublished patient characteristics and updated outcome data from five retrospective single-centre trials to perform a subgroup analysis for early salvage RT.

Evidence synthesis: Patients treated with early salvage RT have a significantly improved biochemical recurrence-free survival (BRFS) rate compared with those receiving salvage RT initiated after PSA values are >0.5 ng/ml. Similarly, within the cohort of patients with pre-RT PSA values <0.5 ng/ml, improved BRFS rates were noted among those with lower rather higher pre-RT PSA levels. It is possible that higher RT dose levels and the use of adjunctive androgen-deprivation therapy improve biochemical control outcomes in the salvage setting.

Conclusions: Based on a literature review, improved 5-yr BRFS rates are observed for patients who receive early salvage RT compared with patients treated with salvage RT with a pre-RT PSA value >0.5 ng/ml. Whether the routine application of early salvage RT in patients with initially undetectable PSA levels will be associated with demonstrable clinical benefit awaits the results of ongoing prospective trials.

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1. Introduction

There is an increasing trend towards using surgical therapy to address locally advanced prostate cancer (PCa) as local control and oncologic outcome improve [1]. Nevertheless,

the risk of recurrent disease after radical prostatectomy (RP), in particular for advanced stages and in patients with positive surgical margins (PSM), can range from 30% to 60% [2,3]. Recent studies have shown that about 50% of patients in the observation arm do not relapse [4–7]. Only in one prospective

Table 1 – Ongoing prospective trials on salvage radiation therapy (RT), early salvage RT, and adjuvant RT and hormone treatment

Trial	Design	Arms	Pts	Intention	Dosage, Gy	Primary end points	Secondary end points
RADICALS RT	International, multicentre, open-labelled, randomised, controlled	Adjuvant vs Deferred RT (PSA failure)	1150	RT	66 Gy in 33 fractions 52.5 in 20 fractions	Freedom from distant disease PCa mortality	PCa-specific survival Freedom from treatment failure Clinical PFS OS Nonprotocol hormone therapy Treatment toxicity Patient-reported outcomes
RADICALS HD	International, multicentre, open-labelled, randomised, controlled	No hormones, short-term ADT (6 mo) vs long-term ADT (24 mo)	2000	Hormones	66 Gy in 33 fractions	PCa-specific survival	Freedom from distant metastases (any distant metastases or PCa-specific death) Freedom from treatment failure Clinical PFS OS Nonprotocol hormone therapy Treatment toxicity Patient-reported outcomes
GETUG-17	Multicentre, open-labelled, randomised, controlled	Adjuvant RT vs early salvage RT (PSA >0.2 ng/ml)	718	RT and hormones (6 mo)	66 Gy in 33 fractions	PFS (clinical or biochemical)	OS Metastasis-free survival Toxicity QoL Functional results in patients >75 yr of age
RAVES	Multicentre, open-labelled, randomised, controlled	Adjuvant RT vs early salvage RT (PSA >0.2 ng/ml)	470	RT Noninferiority of early salvage RT	64 Gy in 32 fractions	PFS QoL	Toxicity OS PCa-specific survival Time to local failure Time to distant failure Time to ADT
EORTC 22043-30041	Multicentre, open-labelled, randomised, controlled	Adjuvant RT vs early salvage RT (0.1 < PSA <0.5 ng/ml) plus ADT	600	RT and hormones	64–74 Gy	bRFS	Toxicity, early/late Clinical PFS OS Distant metastasis-free survival QoL

RADICALS = Radiotherapy and Androgen Deprivation in Combination After Local Surgery; RT = radiation therapy; PSA = prostate-specific antigen; PCa = prostate cancer; PFS = progression-free survival; OS = overall survival; ADT = androgen-deprivation therapy; QoL = quality of life; RAVES = Radiotherapy Adjuvant vs Early Salvage; EORTC = European Organisation for Research and Treatment of Cancer; bRFS = biochemical recurrence-free survival.

randomised trial, Southwest Oncology Group 8794, a significant survival benefit in case of an adjuvant radiation therapy (RT) could be demonstrated [8] compared with the control arm, although this might be partly the result of imbalanced risk factors [9]. In two of these studies, a large number of patients did not reach undetectable prostate-specific antigen (PSA) values after RP; thus, the term *adjuvant RT* must be questioned in this setting. In a recently published meta-analysis, the results of the three prospective randomised trials were further shown to validate improved local control after 5 and 10 yr as well as decreased metastases and overall survival (OS) after >10 yr [10].

Oncologic outcomes are worse in salvage RT compared with adjuvant RT, but in retrospective analysis, there is a hint that results improve in an early salvage RT setting [11]. In the absence of a prospective randomised trial, it is difficult to draw any definitive conclusions. Moreover, it is recognised that several variables influence the outcome of salvage RT, including and perhaps most importantly the PSA level at the time of RT [12–16]. Based on these considerations, salvage RT should start before the PSA level reaches 0.5 ng/ml [16–19].

Currently, four prospective randomised clinical trials—Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS), Radiotherapy Adjuvant Versus Early Salvage (RAVES), GETUG-17, and European Organisation for Research and Treatment of Cancer (EORTC) 22043-30031—are investigating the therapeutic benefit of early salvage RT with or without androgen-deprivation therapy (ADT) compared with adjuvant RT (Table 1). The results of these prospective studies will certainly contribute to guiding clinical practice in terms of indication and timing of postoperative RT. While waiting for these level 1 evidence results, we retrospectively analysed the outcomes of studies on early salvage RT compared with those obtained after adjuvant RT.

2. Evidence acquisition

A search of the PubMed database using the search terms *prostate cancer*, *radiotherapy*, *salvage*, and *toxicity* yielded 437 publications from the past 10 yr. To report on outcomes of patients who received early salvage RT, we applied the

following inclusion and exclusion criteria: Patients with pre-RT PSA values >0.5 ng/ml were excluded, even if the mean or median pre-RT PSA value of the whole cohort was ≤ 0.5 ng/ml. If publications reported on subgroups with pre-RT PSA <0.5 ng/ml, respective data were included. Reports that included early salvage RT for patients with nodal involvement at the time of surgery were excluded. Of 115 potentially eligible publications, only 18 met the above-mentioned criteria. Among these, five reports composed a cohort with a mean pre-RT PSA value ≤ 0.5 ng/ml, which included individual patients with a pre-RT PSA up to 8 ng/ml. In these studies, no subgroup analysis was available; thus, they were excluded. In three additional studies, a subgroup analysis for biochemical recurrence-free survival (BRFS) among patients with a pre-RT <0.5 ng/ml was performed, but the actual patient number was not stated [20–22]. Thus, the final number of studies available for the present analysis was 10 (Table 2), and a summary of the salient characteristics of the study design for each of these studies is shown in Table 3. In five of these studies, data on outcomes of early salvage RT patients have not been published, but we received the original data and were able to calculate the tumour-specific outcome with regard to BRFS [11,23–26] (Table 4). All of these studies are retrospective analyses. Early salvage RT was administered at the discretion of the treating clinician, with known bias to the data.

In all studies, either a lymph node dissection (LND) with pN0 status or cN0 in the preoperative setting was described [4,17,23–26,28–30]. In one analysis, an extended pelvic LND was performed when, according to the Roach formula, a higher risk ($\geq 15\%$) for positive lymph nodes had been calculated [11]. No detailed information about the number of the resected lymph nodes is given in the publications.

Among the 10 eligible publications, various definitions of biochemical recurrence (BCR) after RT were used: in two publications, a PSA value >0.2 ng/ml with confirmation by a second value [4,11]; in four studies, a PSA nadir after salvage RT plus 0.2 ng/ml [17,26–28]; in one study, a PSA nadir after salvage RT plus 0.4 ng/ml [23]; and in another study, a PSA value >0.1 ng/ml with confirmed progression [29]. Four studies included systemic treatment as a marker for progressive disease [24–26,29], and in one study two consecutive PSA increases defined a BCR [25]. Time from RP to initiation of early salvage RT varied between the studies (from 11.8 to 28.8 mo), depending on the individual criteria for a relapse and indirectly on the sensitivity of the relapse detection assay (eg, the PSA detection limit for mostly employed BCR).

Radiation regimens were diverse, but the clinical targeted volume (CTV) was focused on the prostatic bed only, because patients were pN0. In three of the studies, the bladder neck and the seminal vesicles were included in the CTV. The nominal dose at the isocentre ranged between 60 and 76 Gy. Patients were treated with energies ranging from 10- to 25-MV photons, with a conventional nonconformal RT ($n = 7$) or three-dimensional conformal RT (3DCRT; $n = 4$) or intensity-modulated RT (IMRT; $n = 3$) technique used. In one study, the technique employed was not documented

[26]. In five studies, different regimens were used: conformal and nonconformal or 3DCRT and IMRT [4,11,24,25,27,28]. In 6 of 10 studies, no ADT before or after RP and RT was given. If ADT was applied (luteinising hormone-releasing hormone agonists), it was usually given for 6 mo but in a minority of patients extended to >12 mo [11,25,27,28].

3. Evidence synthesis

In five of the above-mentioned studies, data for 737 patients receiving early salvage RT were collected. The authors of five additional studies shared their original data, which added a further 475 patients treated with early salvage RT. Therefore, overall clinical data and oncologic follow-up of 1212 patients were available for this review, as indicated in Table 1. Mean follow-up of these studies was 51 mo (range: 30–72).

The 2-yr BRFS in the studies varied between 78% and 92%. In seven studies, the 5-yr BRFS rates were available. We pooled the data on BCR from 886 patients with pre-RT PSA levels ≤ 0.5 ng/ml from these seven trials to calculate the recurrence-free survival. After 5 yr, the probability of BRFS after an early salvage RT was 71.1% (range: 48–81.8%), with 631 patients having no evidence of biochemical progression. In this cohort, only 59 patients (6.7%) had an accompanied hormone treatment to RT, which may have had a further positive influence on biochemical control outcome. There is almost a linear trend of better BRFS with lower PSA values. Stephenson describes 5-yr BRFS with PSA values <0.5 ng/ml, 0.51–1.0 ng/ml, 1.01–1.5 ng/ml, and >1.5 ng/ml in 48%, 40%, 28%, and 18% of patients, respectively [16]. The same trend can be seen in the study group by Ost et al. [11]. The authors state the poor results in PSA values >0.5 ng/ml at the time of salvage RT. The 3-yr BRFS rate is only 46% in patients with PSA values >0.5 ng/ml compared with 86% for patients in the early salvage RT arm. Goenka et al. underlines these results. They compared patients with more favourable parameters (no PSM, no vascular invasion, and PSA <0.4 ng/ml) against patients with poor prognostic markers. They demonstrate a 5-yr BRFS with 70% and 30% [31].

Interestingly, even in the setting of early salvage RT, lower PSA values were associated with improved biochemical control after treatment. Siegmann et al. analysed their patient cohort after stratification with different PSA thresholds and highlighted the importance of the PSA value at the time of RT. In the described retrospective analysis, in a limited follow-up, an improved BRFS was shown with earlier starting points of salvage RT with regard to PSA. By lowering the level to <0.2 ng/ml, the BRFS at 2 yr rises to 83% [17,30].

In addition to clinical outcomes, acute and long-term toxicities associated with RT must be considered. Data on late toxicities of early salvage RT after RP are limited and discordant [31–36]. In most series, most grade 1 and 2 gastrointestinal (GI) and genitourinary (GU) toxicities were successfully treated conservatively. The rate of grade 3 and 4 toxicities was low, ranging from 0.3% to 1.6% for GI toxicities and 1% to 6% for GU toxicities (Table 5).

A comparison of toxicity rates in 285 patients receiving RT as primary treatment after RP, IMRT, or 3DCRT yielded

Table 2 – Tumour and patient characteristics

	Teraï** [29]	Umezawa** [28]	Siegmann** [17]	Briganti* [4]	Ost* [11]	LiauW* [24]	Hudson** [27]	Stephenson* [26]	Goenka* [25]	Bernhard* [23]
Baseline disease stage	<pT3a	<pT3	<pT3	≥pT3a	<pT3	<pT3a	pT2	<pT3a	<pT3a	<pT3a
No. of patients	26, 70%	43, 42%	168, 56%	390, 100%	24, 50%	13, 38%	13, 46%	34, 19%	46, 32%	38, 45%
	≥pT3a	≥pT3a	≥pT3a		≥pT3a	≥pT3a	pT3	≥pT3a	≥pT3a	≥pT3a
	11, 30%	58, 57%	133, 44%		24, 50%	21, 62%	15, 54%	147, 81%	97, 68%	46, 55%
Grade	GS ≤6	GS ≤6	GS ≤6	GS ≤6	GS ≤6	GS <6	GS ≤6	GS ≤6	GS ≤6	GS ≤6
No. of patients	20, 54%	31, 30%	165, 55%	164, 33%	21, 44%	7, 21%	12, 43%	45, 24%	16, 11%	33, 39%
	GS ≥7	GS ≥7	GS ≥7	GS ≥7	GS ≥7	GS <6	GS ≥7	GS ≥7	GS >6	GS >6
	17, 46%	66, 64%	136, 45%	336, 67%	27, 56%	28, 79%	16, 57%	123, 67%	127, 89%	49, 58%
ECE	No data	No data	No data	100%	23	21	No data	114	89	33
					48%	62%		62%	62%	39%
SVI	No data	No data	No data	116	6	15	4	33	31	15
				30%	13%	44%	14%	18%	22%	18%
PSM	13	No data	168	238	23	16	19	92	72	46
	35%		56%	48%	48%	47%	68%	50%	50%	55%
PSA undetectable	34	No data	177	100%	No data	28	No data	No data	No data	53
	92%		59%			82%				77%
Hormone treatment	None	Partly	None	None	31	None	Partly	None	28	None
					67%				20%	
RT technique	4-field	4-field/3DCRT	CRT	CRT/ 3DCRT	IMRT	CRT	CRT/ 3DCRT	–	3DCRT/ IMRT	CRT/IMRT
CTV	Bladder neck, urethrovesical anastomosis, urethra	Prostate bed, bladder neck, urethral anastomosis, SV (in case of involvement)	Prostate bed, bladder neck, periprostatic clip, SV (in case of T3a)	Prostatic fossa, periprostatic tissue	Prostate bed SV	–	–	–	Prostate bed	Prostate bed
PTV	1.5 cm + CTV	1.0 cm + CTV	1.0 cm + CTV	0.8–1.0 cm + CTV	0.7 cm + CTV	Low pelvis and boost of prostate bed	–	–	No data	–
Median time to RT	11.8 mo	21 mo	23 mo	No data	24.1 mo	23.2 mo	No data	28.7 mo	20 mo	28.8 mo
	3–59 mo	5–99 mo			9–48 mo	6–86 mo		13–44 mo		6–111 mo
Follow-up	31.9 mo	44 mo	30 mo	40.6 mo	53 mo	72.4 mo	34 mo	33 mo	60 mo	8 yr
	34–70 mo	11–103 mo	2–84 mo		18–132 mo	5.2–136 mo	25–47 mo	15–56 mo	4–221 mo	0.6–15 yr

GS = Gleason score; ECE = extracapsular extension; SVI = seminal vesicle invasion; PSM = positive surgical margin; PSA = prostate-specific antigen; RT = radiation therapy; 3DCRT = three-dimensional conformal radiation therapy; CRT = conformal radiation therapy; IMRT = intensity-modulated radiation therapy; CTV = clinical target volume; SV = seminal vesicle; PTV = planning target volume.

* Data from patients with pre-RT PSA ≤0.5 ng/ml.

** Data from patients with pre-RT PSA ≤0.5 ng/ml extracted from the whole study population.

Table 3 – Study design of salvage radiation therapy after radical prostatectomy

First author	No. of patients	Type	PSA pre-RT, ng/ml, mean (range)	Dosage, Gy, mean (range)	Hormone treatment	Definition of BCR after RP	Definition of BCR after salvage RT	End point
Bernard [23]	69	Subgroup analysis	0.32 (0.1–0.49)	66.7 (60–72.4)	None	PSA >0.4 ng/ml	Nadir +0.4	bRFS
Terai [29]	21 of 37	Subgroup analysis	<0.15	60	None	PSA ≥0.1 ng/ml	PSA >0.1 confirmed by a second value, initiation of ADT	PFS
Liauw [24]	34	Subgroup analysis	0.2 (0.05–0.5)	65.7 (61.2–70.2)	None	Persistent or rising PSA	No PSA drop to undetectable values after RT Two rises after undetectable values Initiation of HT	bRFS
Umezawa [27]	52	Subgroup analysis	<0.25 <0.5	64 (60–72)	6 mo (1–18) for 29 patients 18 mo (1–15) for 11 patients	PSA >0.1 ng/ml 2 subsequent increases	PSA >0.2 + nadir a	bRFS
Siegmann [17]	151 of 301	Subgroup analysis	0.28	68.4 (66.6–70.2)	None	No data	PSA nadir +0.2 and further rise	PSA response to dose escalation
Hudson [27]	9 of 40	Subgroup analysis	<0.5	60 (55–74)	31 of 40 with neoadjuvant treatment	Rising PSA >0.2 ng/ml	PSA nadir +0.2	3 yr bRFS
Goenka [25]	143 of 285	Subgroup analysis	<0.5	<66 until >74	–	PSA ≥0.2	Two rises, continuous increase higher than pretreatment initiation of ADT	bRFS/MFS
Briganti [4]	390	Matched control	<0.5 <0.3	66.2	None	No data	PSA >0.2	bRFS
Stephenson [26]	181 of 1540	Subgroup analysis	<0.5	66 (64–69)	None	PSA ≥0.2 ng/ml and rising	PSA nadir +0.2, continuous PSA increase during therapy, initiation of systemic treatment clinical progression	Disease progression in salvage RT
Ost [11]	48	Subgroup analysis	0.3 (0.1–0.5)	75 (72–78)	–	No data	PSA >0.2	Compare adjuvant RT a salvage RT with high-dose IMRT

PSA = prostate = specific antigen; RT = radiation therapy; BCR = biochemical recurrence; RP = radical prostatectomy; bRFS = biochemical recurrence-free survival; ADT = androgen-deprivation therapy; PFS = progression-free survival; HT = hormone therapy; MFS = metastasis-free survival; IMRT = intensity-modulated radiation therapy.

Table 4 – Oncologic outcome

First author	No. of patients	PSA pre-RT, ng/ml, (range)	Follow-up (range)	Fraction bRFS at specific time points	Nodal involvement
Bernard [23]	69	0.32 (0.1–0.49)	8 yr (0.6–15)	5 yr: 79.8%	pN0
Terai [29]	21 of 37	<0.15	31.9 mo (34.3–69.8)	5 yr: 80%	N0
Liauw [24]	34	0.27 (0.05–0.5)	72.4 mo (5.2–136.3)	5 yr: 71%	pN0
Goenka [25]	143	<0.5	60 mo (4–221)	5 yr: 48%	pN0
Briganti [4]	390	<0.5 <0.3	40.6 mo	2 yr: 92.8% 5 yr: 81.8%	pN0
Stephenson [26]	181	0.4 (0.3–0.4)	33 mo (15–56)	6 yr: 48% 5 yr: 61% 3 yr: 69%	pN0
Ost [11]	48	0.3 (0.1–0.5)	53 mo (18–132)	5 yr: 77.1%	pN0/cN0

PSA = prostate-specific antigen; RT = radiation therapy; bRFS = biochemical recurrence-free survival.

10% for early-grade ≥ 2 GI toxicities without significant differences in the radiation technique. In contrast, frequencies of late GI toxicities greater than grade 2 differed considerably: 1.9% in 3DCRT-treated and 10.2% in IMRT-treated patients [31]. Late GU toxicities greater than or equal to grade 2 were seen more frequently in 17% of the patients, half of which were successfully treated conservatively, and were independent of the radiation technique. Recently, long-term toxicity rates after a follow-up of 8 yr were demonstrated by Cozzarini et al. in the salvage setting. They showed slightly increased GU toxicities greater than or equal to grade 2 with 23.7% and greater than or equal to grade 3 in 10% of the cases; 81% of the 186 patients reported being fully continent. In a multivariate analysis, acute grade 2 or greater, age >72 yr of age at RT, and the total applied dosage of >72 Gy had been independent prognostic factors for developing late grade 3 GU toxicities [36].

3.1. Discussion

In this paper, we reviewed oncologic outcomes in patients undergoing RT after RP with pre-RT PSA levels of ≤ 0.5 ng/ml. Although there are differences in the design of studies selected for this review, several important observations can be made.

First and most importantly, when salvage RT is administered early to patients who have BCR after RP, excellent long-term outcomes can be achieved. A pooled analysis consisting of 886 patients from seven trials with ample follow-up shows favourable outcome, with a mean 5-yr BRFS of 71% (range: 48–81.8%) [3,23–26,29,37], but it must be stressed that our analyses could not target either BRFS at longer-term or more clinically significant end points, such as metastases-free survival or OS, because of the relatively limited follow-up invariably reported in all studies addressing the outcome of early salvage RT. Moreover, our review cannot systematically answer the clinically relevant question of whether early salvage RT can be considered comparable to adjuvant RT in terms of cancer control. Our pooled analysis on early salvage RT yielded a BRFS rate of 71%. Similar

results are described with adjuvant RT, where BRFS ranged from 67% to 74% [5–7]. Our analysis comprises data from the only two studies powered to directly compare adjuvant RT and salvage RT, which showed comparable 3-yr [11] and 5-yr [4] BRFS outcomes. However, both studies are limited by their retrospective design. To date, only two retrospective analyses have dealt with salvage RT and survival rates. Boorjian et al. analysed the impact of adjuvant RT and salvage RT on BRFS, metastases-free survival, local control, systemic progression, and OS. In a multivariate analysis, adjuvant RT and salvage RT were independent predictors for biochemical and local control. In addition salvage RT decreased the rate of systemic failures. Patients with salvage RT had a mean PSA at the time of RT of 0.8 ng/ml (range: 0.5–1.7), which is above the recommended PSA threshold [38]. In another retrospective analysis, salvage RT and combined salvage RT with ADT had significant improved PCa-specific survival rates of 96% and 82–86% at 5 and 10 yr of follow-up, respectively, compared with a patient cohort with no salvage treatment. Although there was a higher PSA value at the time of RT (0.7 ng/ml, 0.2–22 ng/ml), salvage RT was a strong independent predictor for disease-specific survival (hazard ratio: 0.32 [range: 0.17–0.57]) [39].

Second, the absolute PSA level may continue to have prognostic significance, especially in the setting of early salvage RT, regarding patients' response to salvage RT, even for values <0.5 ng/ml. For example, PSA at “very low” ranges before initiating RT is associated with improved outcomes. A reanalysis of previously published data shows that PSA values ≤ 0.2 ng/ml before starting RT results in a progression-free survival rate of 83% [30]. Nevertheless, it should be noted that lowering the PSA threshold for starting salvage RT may lead to overtreatment in some cases with slow PSA doubling times (DTs) because it has been demonstrated that not all the patients in whom two consecutive and rising postprostatectomy PSA values >0.20 ng/ml are documented will develop a clinically evident relapse. Yet we believe that when a patient manifests a detectable and rising PSA level, it will likely

Table 5 – Toxicity of early salvage radiation therapy

First author	No. of patients	Toxicity grading	Dosage, Gy	Early complication, no. of patients (%)	Late complication	GU any	GI any	GU 3/4	GI 3/4
Creemers [32]	157	RTOG	60–66	No data	–	45%	40%	6%	0.6%
Brooks [33]	114	RTOG	≥64	13 (11.4%) GU 26 (22.8%) GI	–	11 (9.6%)	9 (8%)	5 (4.4%)	–
Siegmann [17]	234	RTOG	66.6–72	No grade 3/4	–	8 (3.4%)	6 (2%)	4 (1.3%)	–
MacDonald [34]	60	–	61.2–68.4	–	38%	12 (20%)	9 (15%)	2 (3.3%)	1 (1.6%)
Goenka [31]	285	RTOG/CTCAE	<60 >70	7.6–13.2% GI IMRT 3DCRT	GI 1.9–10.2% GU grade ≥2: 17%	Grade ≥2: 17%	9.8%	–	4 (1.4%)
Peterson [35]	308	RTOG/CTCAE	54–72	GU grade ≥2: 16.3%	13%	27 (8.7%)	27 (8.7%)	3 (1%)	1 (0.3%)
Cozzarini [36]	186	CTCAE	59.4–77.4	GU grade ≥2: 17%; grade 3: 6%	GU grade ≥2: 23.7%	–	–	10% (grade 3)	–

GU = genitourinary; GI = gastrointestinal; RTOG = Radiation Therapy Oncology Group; CTCAE = Common Terminology Criteria for Adverse Events; IMRT = intensity-modulated radiation therapy; 3DCRT = three-dimensional conformal radiation therapy.

continue to progress, and such patients are at increased risk for clinical failure. Our data suggest that the administration of RT sooner rather than later would be prudent and associated with an increased BRFs rate after at least 5 yr of follow-up, as one treats a lower tumour volume. Whether this will also be seen in metastases-free survival or OS is the content of ongoing prospective trials. We acknowledge that optimal cut-off of PSA for starting early salvage RT has not been established, yet. From the retrospective available data, it seems to be that salvage treatment should be initiated after a biochemical dynamic with rising PSA values is confirmed. It is likely that other factors in addition to PSA, such as pathologic characteristics and PSA kinetics (eg, PSA DT), might guide the optimal timing of early RT administration.

Outcomes of early salvage RT may be improved further by employing higher radiation dose levels, the use of neoadjuvant or adjuvant ADT, and the use of more conformal and targeted treatment techniques. Two of these parameters are under investigation in ongoing prospective clinical trials: the SAKK09/10 (NCT01272050) trial compares outcomes in salvage RT with 64 and 70 Gy without ADT; the GETUG-17 and the RADICALS trials compare outcomes with and without ADT in the salvage and adjuvant setting; the Radiation Therapy Oncology Group-0534 trial examines the benefit from short-term ADT with salvage RT. In contrast, few comparative studies exist on different treatment techniques (eg, IMRT vs conventional RT). In light of superior outcomes with higher doses in the salvage setting, the risk of severe toxicity can be minimised by using modern radiation techniques, which should be investigated prospectively.

Against the background of heterogeneous treatment schedules employed so far, the beneficial effect of a salvage RT could probably be improved further. First, the starting point of early salvage RT might be the most important parameter for clinical outcome. Even a relatively small shift from 0.28 ng/ml to 0.2 ng/ml for initiation of an RT treatment improved the 2-yr BRFs rate by 5% in one study [30]. In contrast, lowering the PSA cut-off from 0.5 to 0.3 ng/ml for RT did not improve 5-yr BRFs [4], indicating that the optimal threshold for initiating early salvage RT may possibly be well below 0.5 ng/ml. The availability of ultrasensitive PSA assays for close monitoring will allow for further precision of PSA-based thresholds for early salvage RT initiation. Possibly, more complex criteria may be optimal that combine PSA DT and Gleason score and also take preoperational PSA levels into account. Second, radiation dosing must be adequate, and it seems that doses ≥70 Gy may be associated with better local tumour control and metastasis-free survival [25] and higher BRFs [30,40]. Third, it is likely that ADT in the setting of early salvage RT, higher doses, and improvements in molecular imaging to define the region of BCR more precisely may influence outcomes favourably. Further clarification on the use of ADT in the salvage setting and the potential benefit of improved targeted therapies will emerge from results of the ongoing and future clinical trials in the years ahead.

Acute and especially long-term toxicities have been of special concern, with increased radiation dosages becoming

treatment standard for clinically localised PCa in both adjuvant and salvage settings. Acute GI and GU toxicity rates were comparable in the EORTC trial 22863 [41]. In contrast, late GU toxicities grade 2 or higher occurred more frequently (15.9%) than late GI toxicities (9.8%), yielding an overall toxicity incidence of 22.8% [42]. The toxicity rates in salvage RT are comparable to those in adjuvant RT. With longer follow-up, it seems that late GU toxicities have a trend of increasing. Goenka et al. [31] showed late GU toxicities greater than or equal to grade 2 in 17% of the cases. In another retrospective analysis, after 8 yr, 23% of the patients suffered from GU toxicities ≥ 2 [36]. In this study, the patients with salvage RT were compared with patients receiving adjuvant RT. Although there were no differences in the proportion of patients being fully incontinent (adjuvant RT: 7%; salvage RT: 6%), there was a trend towards better continence in the patients with salvage RT (adjuvant RT: 74%; salvage RT: 81%). At this point, neither adjuvant RT nor salvage RT seem to be preferable with regard to toxicity. Again, this is because of the heterogeneity in study designs with respect to dosage, radiation technique, concomitant hormone treatment, in addition to the few systematic assessments of RT-induced toxicities available to date.

It is important to note that the current study has several limitations that preclude drawing broad conclusions from the comparison of studies assessing differences in outcome of adjuvant and early salvage RT. Most importantly, patients differed with respect to the postoperative PSA levels prior to study entry. End points and definitions therefore varied considerably among all studies, whether on adjuvant or salvage RT. The same is true for definitions of a relapse after RP, which is a critical parameter when assessing outcomes in the salvage setting, as discussed above. As the latest update on EORTC 22911 shows, a long-term follow-up assessing “hard” end points such as PCa death and other-cause mortality might result in adjusted and tailored treatment recommendations [43]. Radiation doses employed in trials evaluating adjuvant RT were what is now considered an inadequate dose (≤ 64 Gy) (60 Gy [5,6], 60–64 Gy [7]). In contrast, most studies on salvage RT and the majority of studies included in our pooled analysis utilised higher doses (66–74 Gy [31], 66.2 Gy [4], subgroup analysis of [26] 64–69 Gy). In addition, hormone treatment was diverse among studies on salvage RT. Finally, we limited our analysis to salvage studies consisting of patients with a maximum pre-RT PSA of 0.5 ng/ml. Therefore, we disregarded studies even if they contained only a few patients with a pre-RT >0.5 ng/ml unless we had access to the original data to perform a subgroup analysis. This introduced a selection bias into our study.

4. Conclusions

Outcomes after RP in preoperatively diagnosed high-risk patients are excellent. Because of a high proportion of overstaging, only 60% [44] of the patients are possible candidates for adjuvant or salvage treatment. Early salvage RT after RP is an effective treatment, with favourable outcomes for patients with pre-RT PSA levels <0.5 ng/ml,

but only retrospective data from heterogeneously designed studies are available to support our notion at this point. Until the outcomes of ongoing prospective trials for early salvage RT are available, we favour a tailored approach. As demonstrated earlier in these high-risk patients, a multidisciplinary approach of the involved parties—patient general practitioner, urologist, and radiation oncologist—should be the aim [45]. In a retrospective analysis of early salvage RT, BRFS rates are promising. In high-risk patients, post-RP PSA levels must be monitored frequently, and treatment should be initiated at the lowest possible PSA value, well under 0.5 ng/ml, by applying 64–70 Gy in 33–35 fractions to the prostatic bed using IMRT. The medical community has to wait for the results of the ongoing trials comparing adjuvant RT and early salvage RT before addressing the value of short-term ADT, dose escalation, and prophylactic nodal irradiation.

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Study concept and design: Zelefsky.

Acquisition of data: Pfister, Zelefsky, Stephenson.

Analysis and interpretation of data: Pfister, Zelefsky, Bolla, Joinau, Briganti.

Drafting of the manuscript: Pfister, Zelefsky.

Critical revision of the manuscript for important intellectual content: Briganti, Bolla, van Poppel, Roach, Correll, Wiegel, Stephenson, Cozzarini.

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