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Radiotherapy after radical prostatectomy: immediate or early delayed?

Radical prostatectomy (RP) and radiation therapy (RT) are the two first-line therapeutic options for patients with prostate cancer, with best results achieved in patients with organ-confined disease. Recurrence after RP is associated with a high Gleason score, a high level of prostate-specific antigen (PSA) before surgery, advanced tumor stage, infiltration of the seminal vesicles, or positive surgical margins [13, 35, 42, 56]. However, even in patients with favorable prognostic factors, biochemical recurrence is a common event.

Following RP, PSA should become undetectable within 4–6 weeks [52]. Persistent serum PSA levels after RP indicate residual prostate tissue, either malignant or benign. In the former case, the marker precedes clinical evidence and correlates well with disease progression.

A PSA increase above 0.2 ng/ml, a common definition of progression of disease following RP [23], occurs in up to 50% of patients with pT3/4 tumors and up to 70% of those with pT3 tumors with positive surgical margins and/or positive pelvic lymph nodes [39, 55]. The 7-year rate of biochemical progression in patients with organ-confined tumors (pT2) and positive surgical margins is about 25% [55]. Residual tumor tissue was biopically confirmed in 35–55% of patients with rising PSA after RP without clinical correlates [46].

Here, we compare post-PR treatment approaches for high-risk patients: Adjuvant radiation therapy (ART) for men with an undetectable post-RP PSA vs. observation and salvage radiation therapy (SRT) for men with postoperatively persisting PSA or values re-rising from initial nondetectability.

Clinical target volume

The most common sites of biopsy-proven local relapse are the vesicourethral anastomosis (VUA, 66%), followed by the bladder neck (16%) and the retrotrigone area (13%) [16]. Based on the relapse patterns as determined by magnetic resonance imaging, a cylindrical shape for the clinical target volume (CTV), centered 5 mm posterior and 3 mm inferior to the VUA, has been recommended [29].

To address uncertainties in CTV definition, the Radiation Therapy Oncology Group (RTOG) [28], the EORTC Radiation Oncology Group [37], and other cooperative groups [66] have created consensus guidelines for delineation of target volumes for postprostatectomy patients. The RTOG results are available as a CT image atlas under http://www.RTOG.org. They allow for a uniform CTV definition for clinical trials that include postprostatectomy RT.

Adjuvant radiotherapy

Three randomized trials demonstrated an almost 20% benefit for biochemical progression-free survival (bNED) after ART (60–64 Gy) compared with a "wait and see" policy, mostly for pT3 cN0 or pN0 tumors (**Tab. 1**). The greatest advantage (30% bNED after 5 years) was seen in patients with pT3 tumors and positive margins [5, 57, 62, 64]. In fact, after central pathological review of the EORTC data, the benefit was exclusively confirmed in patients with positive margins [6, 62]. In the trial of the German Cancer Society, bNED was improved after ART: 72% vs. 54% (p<0.03). In the subgroup of pT3 R1 tumors, bNED was still 28% vs. 18% [64]. In the study of the South Western Oncology Group (SWOG), overall survival improved from 13.5 years without ART to 15.2 years with ART [58]. The seemingly poorer results of the German trial are probably due to the reduced PSA detection threshold (**Tab. 1**).

The location and extent of positive surgical margins after RPy are significant risk parameters of biochemical progression after RP [5]. According to the above-mentioned trials, patients with positive margins and pT3 tumors have the largest benefit from postoperative RT.

Among EORTC patients with pT2 tumors and positive surgical margins, there was a significant benefit of 5-year bNED in the irradiated group (76.4% vs. 52.2% in the wait-and-see group) [5]. However, biochemical progression was not a primary endpoint of this study. Therefore, the results must be interpreted cautiously. The benefit of radiotherapy is restricted by potential late effects such as erectile dysfunction.

Pelvic lymph nodes

The effect of ART in node-positive prostate cancer has not yet been prospectively assessed. One retrospective study reported a significant positive impact of RT combined with hormone therapy (HT) in

Tab. 1 Overview of all three randomized trials for adjuvant radiation therapy after radical prostatectomy

Reference	*n*	Inclusion criteria	Randomization	Definition of biochemical recurrence, PSA (ng/ml)	Median follow-up	Biochemical progression free survival (bNED)	Overall survival
Thompson et al. [56]	431	pT3 cN0 ±involved SM	60–64 Gy vs. "wait and see"	>0.4	152 mo.	10 years: 53% vs. 30%	10 years: 74% vs. 66%
SWOG 8794						(p<0.05)	Median time: 15.2 vs. 13.3 years
						5-year data not given	p=0.023
Bolla et al. [4]	1,005	pT3 ±involved SM cN0 pT2 involved SM	60 Gy vs. "wait and see"	>0.2	60 mo.	5 years: 79% vs. 56%	91.5 vs. 90.8
EORTC 22911							n. s.
Wiegel et al. [63]	388	pT3 (±involved SM) pN0 PSA post RP undetectable		>0.05 +confirmation	54 mo.	5 years: 72% vs. 54%	not given
ARO 96–02							

n.s. not significant, **mo.** months, **PSA** prostate-specific antigen, **SM** surgical margins

Tab. 2 Results for salvage radiotherapy after biochemical recurrence from selected studies

Investigator	Patients (n)	Median PSA (ng/ml)	Median dose (Gy)	bNED
Anscher et al. [1]	89	1.4	66	50% at 4 years
Buskirk et al. [11]	368	0.7	64.8	35% at 8 years
Cadeddu et al. [12]	82	4.1	64	10% at 5 years
Garg et al. [20]	78	1.2	66	65% at 3 years
Hagan et al. [21]	88	4.5	64	55% at 5 years
Neuhof et al. [28]	171	1.1	60–66	35% at 5 years
Pazona et al. [31]	307	0.8	64	40% at 5 years; 25% at 10 years
Pisansky et al. [34]	166	0.9	64	46% at 5 years
Siegmann et al. [46]	301	0.28	66.6	74% at 2 years
Stephenson et al. [50]	1,540	1.1	65	32% at 6 years
Tsien et al. [59]	57	1.2	65	30% at 8 years
Ward et al. [61]	211	0.6	64	34% at 10 years
Wiegel et al. [64]	162	0.33	66.6	54% at 3.5 years

Tab. 3 Recommended procedures for patients with undetectable PSA after radical prostatectomy [23]

For patients with pT3 pN0 tumors with a high risk of local failure due to positive margins, and/or seminal vesicle invasion and negative PSA, two options can be offered within the frame of an informed consent
Either an immediate radiotherapy with 60–64 Gy to the surgical bed upon recovery of urinary function
Or clinical and biologic monitoring followed by salvage radiotherapy with at least 66 Gy ideally when the PSA rises but does not exceed 0.5 ng/ml

pre-RP node-positive patients [17]. ART patients in this study were those affected by more aggressive disease. However, including ART in the multivariable models of bNED and cancer-specific survival improved the predictive accuracy significantly.

A retrospective study of 703 matched node-positive patients compared post-RP adjuvant HT plus ART with HT alone. Better survival rates were associated with combined ART/HT when patients were stratified according to nodal invasion (≤2 vs. >2 positive nodes). The overall survival advantage was 19% in favor of HT plus ART [8]. Without standardized target volumes, radiation dose, and duration of HT, these data should be interpreted cautiously. However, this treatment may be indicated in selected cases, and should be validated in prospective clinical trials.

In a study of 160 patients who underwent ART or SRT, 114 were considered at high risk of lymph node involvement despite cN0 classification. Seventy-two had whole pelvic radiation and 42 had prostate bed radiation therapy. The bNED after whole pelvic radiation therapy was higher (5-year rate 47% vs. 21%, p<0.05). While these data have to be confirmed in a prospective trial, whole pelvic radiation preferably with IMRT can be considered in high-risk patients [23, 51].

Hormone therapy and adjuvant radiotherapy

The standard nonoperative management of patients with locally advanced prostate adenocarcinoma includes long-term androgen deprivation therapy (ADT) [4, 24]. By contrast, for men who had RP and pelvic lymph node dissection for high-risk, node-negative prostate adenocarcinoma, the benefit from adjuvant ADT was not clearly established. The primary rationales for post-RP ADT is to eradicate potentially radioresistant cells in a hypoxic scar, address micrometastatic disease, and delay PSA progress in patients who will eventually relapse [22, 25, 41].

In the ongoing EORTC trial 22043, in patients with a Gleason score of 5–10, undetectable PSA, and pathological stage pT2R1 or pT3a-b, the primary trial endpoint is 5-year bNED.

Salvage radiotherapy

The best treatment in patients with positive PSA but no clinical evidence of disease is still controversial. However, only RT offers the chance of cure to patients with real local relapse. There are indicators suggesting purely local recurrence, such as a PSA doubling time of 12 months or more, more than 1-year latency in a positive post-PR PSA, a Gleason score under 7, and negative surgical margins [36].

On the other hand, a PSA doubling time of less than 12 months or a Gleason score of 8–10 at RP [33] hint instead at metastatic disease. Recently, a predictive model for the outcome of SRT after post-RP PSA progression has been established [53]. Assuming local disease, SRT of the prostate bed has been widely used to treat patients in the absence of biopsy-proven local recurrence. An established standard is conformal radiotherapy with 66 Gy to lower the risk of a "second wave of metastasis" [15, 23].

Diagnostic tools

Bioptic sensitivity for post-RP local recurrence ranges from 29–50% when based on digital rectal examination. With transrectal ultrasound (TRUS) guiding, it increases to 66–77%, depending on the PSA level [18, 44, 46], and with MRI even 87% can be achieved [45]. Among the new PET/CT tracers, radiolabeled choline plays a major role [14, 43], but it can only be recommended at a PSA level over 1 ng/ml [34, 38].

Results of salvage radiotherapy

The PSA level at the time of SRT is the most important predictor for response. In a multicenter study (1,540 patients), the 6-year bNED was 48% with a pre-RT PSA vs. 18% with a PSA level under 0.5 ng/ml, while the overall progression-free survival rate was 32% [53]. A Gleason score of 8–10, pre-SRT PSA over 2 ng/ml, negative surgical margins, postoperative PSA doubling time of less than 10 months, and seminal vesicle invasion were negative prognostic factors. Patients without these features had a 6-year progression-free survival of 69%. Despite a Gleason score of 8–10, patients would benefit from SRT if the pretreatment PSA was less than 2.0 ng/ml, surgical margins were positive, and PSA doubling time was more than 10 months. In this situation, the 6-year bNED was 33% [53]. An earlier treatment start, e.g., with a PSA lower than 0.3 ng/ml, can significantly improve the outcome [48, 49]. Importantly, achieving an undetectable PSA after SRT offers a second chance of cure: In a multivariate analysis of a homogeneously treated group of 162 patients (all pN0, median dose 66 Gy 1.8 Gy fractions), this was the most important predictor for bNED [65]. This is in agreement with earlier data [30].

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Radiotherapy after radical prostatectomy: immediate or early delayed?

Abstract

Background. Biochemical recurrence after radical prostatectomy (RP) is associated with risk indicators, including Gleason score, preoperative PSA level, tumor stage, seminal vesicle invasion, and positive surgical margins. The 5-year biochemical progression rate among predisposed patients is as high as 50–70%. Post-RP treatment options include adjuvant radiotherapy (ART, for men with undetectable PSA) or salvage radiotherapy (SRT, for PSA persisting or re-rising above detection threshold). Presently, there are no published randomized trials evaluating ART vs. SRT directly.

Methods. Published data on ART and SRT were reviewed to allow a comparison of the two treatment approaches.

Results. Three randomized phase III trials demonstrated an almost 20% absolute benefit for biochemical progression-free survival after ART (60–64 Gy) compared to a "wait and see" policy. The greatest benefit was achieved in patients with positive margins and pT3 tumors. SRT can be offered to patients with elevated PSA after RP. In 30–70% of SRT patients, PSA will decrease to an undetectable level, thus giving a second curative chance. The rate of side effects for both treatments is comparably low.The role of irradiation of pelvic lymph nodes and the additional use of hormone therapy and radiation dose are discussed.

Conclusion. It remains unclear whether early SRT initiated after PSA failure is equivalent to ART. Where SRT is indicated, it should be started as early as possible.

Keywords

Prostate cancer · Radical prostatectomy · Adjuvant radiotherapy · Salvage radiotherapy · Progression-free survival

Strahlentherapie nach radikaler Prostatektomie: Sofort oder verzögert?

Zusammenfassung

Hintergrund. Zu den Risikoindikatoren eines biochemischen Rezidivs nach radikaler Prostatektomie (RP) gehören Gleason-Score, präoperativer PSA-Wert, Tumorstadium, Status der Samenblase und der Operationsränder. Prädisponierte Patienten haben eine biochemische 5-Jahres-Progressionsrate von 50–70%. Postoperative Behandlungsoptionen sind die adjuvante Strahlentherapie (ART, bei nicht detektierbarem PSA) oder die Salvage-Radiotherapie (SRT, bei persistierendem oder überschwellig werdendem PSA). Bisher liegen keine Publikationen randomisierter Studien vor, die ART und SRT direkt gegenüberstellen.

Methode. Publizierte Daten zu ART und STR wurden analysiert, um die beiden Therapieansätze zu vergleichen.

Ergebnisse. Drei randomisierte Phase-III-Studien zeigen für biochemische Progressionsfreiheit einen fast 20%igen Vorteil durch ART (60–64 Gy) gegenüber einer abwartenden Strategie. Den größten Gewinn haben Patienten mit Tumorstadium pT3 und positiven Schnitträndern. Eine SRT kann Patienten mit postoperativem PSA-Wiederanstieg angeboten werden. Bei 30–70% dieser Patienten wird eine Absenkung des PSA unter die Nachweisgrenze erreicht und ihnen eine zweite Heilungschance eröffnet. Die Nebenwirkungsrate ist bei beiden Therapiemodalitäten vergleichbar gering. Die Rolle der Mitbestrahlung der pelvinen Lymphabflusswege, einer zusätzlichen Hormontherapie und der strahlentherapeutischen Dosis wird diskutiert.

Schlussfolgerung. Es bleibt unklar, ob die SRT nach PSA-Rezidiv einer ART gleichwertig ist. Wenn die SRT indiziert ist, sollte sie möglichst früh beginnen.

Schlüsselwörter

Prostatakarzinom · Radikale Prostatektomie · Adjuvante Strahlentherapie · Salvage-Radiotherapie · Progressionsfreiheit

Total dose of salvage radiotherapy

There is still controversy about the optimal irradiation dose for post-RP SRT/

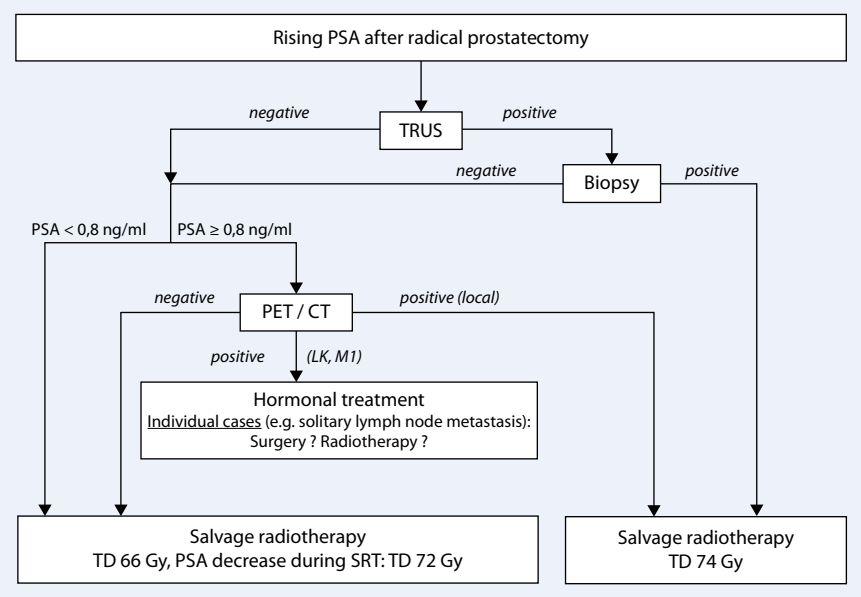

Fig. 1 ▲ Recommended procedures for patients with rising PSA after radical prostatectomy (University Hospital Ulm, Germany). *TRUS* transrectal ultrasonography, *PET* positron emission tomography, *CT* computed tomography

ART. In the guidelines, total doses of "at least 66 Gy" are recommended [23]. However, some recently published series demonstrated a better outcome with higher total doses [3, 26, 40, 49]. In all, 364 prostate cancer patients receiving SRT after RP were followed up for a median 6.0 years. Three dose groups were defined (low: <64.8 Gy; moderate: 64.8–66.6 Gy; high: >66.6 Gy). The high-dose group had an improved bNED compared with the low-dose group (HR 0.60) [3]. Similarly, in a retrospective series with 301 patients receiving 66.6 or 70.2 Gy, dose was a significant predictor (p=0.017 in multivariate analysis) of bNED [49]. Dose escalation seems necessary in patients with histologically confirmed local recurrence.

Salvage radiotherapy plus hormone therapy

In a prospective pilot study, 75 patients were treated with salvage radiation therapy +2-year ADT. All patients achieved an initially complete PSA response (<0.2 ng/ml). The relapse-free survival rate at 7 years was 78% [12]. Another study [50] comprised 630 patients (including 66% with high-risk factors) receiving SRT. Twenty-four percent of the patients had concurrent ADT. In high-risk patients, ADT was an independent predictor of progression-free survival.

RTOG 96–01, a randomized phase III trial compared SRT plus ADT with SRT plus placebo in 770 men with pT3/pT2 R1 N0 M0 prostate cancer and an elevated post-RP PSA [47]. Twenty-four months of peripheral androgen blockade during and after RT significantly improved bNED (57% versus 40%; p<0.0001) and reduced the incidence of metastatic disease 7.4% versus 12.6%, p<0.04) without adding significantly to radiation toxicity. Hence, high-risk patients possibly profit from additional ADT. A current RTOG trial (0534) is investigating the benefit of short-term ADT as well as pelvic nodal irradiation in the SRT setting.

Side effects

The three randomized clinical trials discussed above prospectively collected data on gastrointestinal or genitourinary toxicity. In the EORTC and SWOG trials, 2D treatment planning was used. In the SWOG 8,794 study, 3.3% of the irradiated patients had grade 3 or higher adverse events compared to 0% in the observation group (p=0.002). The incidence of urethral strictures was higher in the RT group (17.8% vs. 9.5%; p=0.02) [57].

In the EORTC trial, there was no significant difference in grade 3 or higher toxicity between the ART and observation groups. In the ART cohort, late grade 2 and 3 toxicity prevailed (p=0.0005) [5].

In the German study, after 3D-planned RT the incidence of late grade 3 or higher events was only 0.3% [64]. One patient developed a urethral stricture in the observation arm, compared with 2 patients in the ART arm. Urinary incontinence was not assessed in this trial.

In the EORTC study, there was no difference between treatment arms in the number of fully continent men after 24 months [5].

SRT with a dose of 66 Gy is generally associated with a low rate of severe acute and late side effects. Urinary incontinence in 0–5% of the cases, moderate proctitis in 0–10%, and mild to moderate cystitis in up to 10% may result from this procedure [19, 30, 54, 65]. Comparable rates of severe complications were found in an SEER database analysis of 11,522 patients after sole RP [2]. A low rate of side effects is of particular importance for a therapy without histologic confirmation, but it may be difficult to differentiate side effects of RT from preexisting disabilities and sequelae of RP.

Adjuvant radiotherapy vs. salvage radiotherapy

Multiple prospective and retrospective studies analyzed whether ART or SRT is preferable in terms of local control and bNED [3, 5, 26, 27, 30, 49, 53, 57, 60, 64, 65]. A consistently better local control and bNED were observed in ART compared with SRT patients. The 5-year bNED rates are approximately 69–89% after adjuvant radiation therapy. Local control is 96–100% after adjuvant radiation therapy and 79–93% after salvage radiation therapy [7]. In a multicenter study including 449 prostate cancer patients with pT3–4 N0, the 5-year bNED was 73% after ART compared with 50% after SRT (p=0.007). A Gleason score of 8 was a significant predictor of bNED [59]. These results were confirmed by others [9]; however, the inverse, i.e., an advantage of SRT over ART, has also been reported [31]. For all these reasons, the best choice of treatment (ART vs. SRT) has to be discussed with each patient individually, also considering the risk of over-

treatment by immediate postoperative irradiation. Treatment options for patients with undetectable PSA after RP according to the EAU guidelines are summarized in Tab. 3. Our recommendations on the procedures for patients with rising PSA levels after RP are presented in Fig. 1.

In 2007, a prospective randomized study was initiated to address this question as well as the potential role of concomitant androgen deprivation [32]. The RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery) trial is an effort to evaluate ART versus SRT. Patients are randomized after surgery to early or delayed radiation. Delayed radiation will be given when there are either three consecutive PSA rises or two consecutive rises and a final PSA over 0.1 ng/ml. The planned accrual is 2,600 patients, with cause-specific survival being the primary outcome. There is a second randomization regarding androgen deprivation therapy.

Conclusion

After RP, ART with 60–64 Gy improves bNED rates and potentially also overall survival in high-risk patients. Lacking direct comparative studies, the equivalence of SRT to ART remains to be proven. After PSA relapse, SRT with at least 66 Gy should start as early as possible (with PSA <0.5 ng/ml). Whole pelvic radiation therapy can be offered as an attractive option for high-risk patients. Modern techniques such as intensity-modulated RT (IMRT) and image-guided RT (IGRT) should be used. Serious side effects are low, confirming the suitability of this approach. According to the RTOG-96–01 trial, peripheral androgen deprivation therapy can improve bNED and reduce the rate of metastatic disease.

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Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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