Radiotherapy in the Management of Prostate Cancer After Radical Prostatectomy
Detlef Bartkowiak, Dirk Bottke, Thomas Wiegel

Abstract and Introduction

Abstract

The choice of treatment options for prostate cancer patients who have undergone radical prostatectomy depends on their risk profile, which is determined by the tumor node metastasis (TNM) status, histopathologic findings, and the pre- and post-radical prostatectomy PSA characteristics. The results of large clinical studies with a 10-year follow-up or more are the backbone of predictive models for risk estimates that incorporate these criteria and also for guideline recommendations. For low-to-intermediate-risk prostate cancer patients and older patients, observation with – in case of biochemical recurrence – early salvage radiotherapy can be advised after R0 resection, thus, avoiding overtreatment. After R1 resection, adjuvant radiotherapy should be considered. Patients with two or more positive lymph nodes and/or with distant metastasis may benefit from adjuvant hormone deprivation therapy. Beyond this rough outline, detailed analysis of subgroups is still required (and ongoing) to enable individually optimized treatment.

Introduction

Recently, model calculations on prostate cancer (PC)-specific mortality have been published that apply three independent models on Surveillance, Epidemiology and End Results data to understand the progress that has been achieved in tackling this disease since the 1990s. It was concluded that changes in the primary treatment alone can not explain the positive development. Nor does PSA screening for early diagnosis deserve all the credit as "changes in secondary disease management may have been primarily responsible for the early decline in mortality".[1]

A comprehensive review on postprostatectomy radiotherapy (RT) appeared in this journal in 2011.[2] Therefore, in the present paper, we will focus on the most recent publications on this topic. Nonetheless, some basic studies and well-established facts have to be recalled in brief. We will adopt the recently updated recommendations from the German interdisciplinary S3-guideline for the management of PC,[201] which may, in a few aspects, deviate from the various regional or national routines.

Owing to an increased awareness and screening of PSA, PC is now the most frequent male malignancy in developed countries; it ranks third in mortality.[3] Regarding the side effects and quality of life, active surveillance or watchful waiting are options for patients with a low-risk profile/localized disease and/or higher age.[4–9] Alternatively, and for more advanced stages, radical prostatectomy (RP) or RT are primary treatment options.[201,202] Men with organ-confined disease have the best prognosis. Infiltration of the seminal vesicles or positive surgical margins, however, correlate with increased relapse rates and, generally, advanced tumor stage, a high Gleason score and a high pre-RP PSA level are risk factors.[10–16] As might be assumed intuitively, the experience of the operating surgeon is another decisive factor.[17] However, even a favorable pattern of risk parameters does not exclude recurrences; their overall absolute rates in terms of biochemical relapse are 15–30%,[18–21] while with adverse features, figures above 60% (also including cases of clinically manifest local failure and metastasis) have been reported.[22,23]

Post-RP Treatment Options

Within a few weeks after RP (but not after primary RT), PSA should fall below detection limits (biochemically no evidence of disease; bNED), since its serum half-life is only 2–3 days.[24] While minimum detectable concentrations are approximately 1 pg/ml or lower,[25,26] a PSA of 0.2 ng/ml is now a widely accepted threshold to state biochemical relapse if confirmed in a second measurement.[19,27,28,201] As rising PSA values precede metastatic progression and tumor-specific death by several years,[29] they serve as a surrogate marker of recurrence after primary therapy. However, a positive detection after intended radical extirpation may result from cancer regrowth (including regional lymph nodes), but also from distant metastases or from residual normal prostate tissue. In these latter cases, local salvage treatment is futile. Moreover, patients with (slowly) rising PSA values do not always develop distant metastases. Although there is no fixed relation between PSA and the risk of (bone) metastasis, bone scintigrams at a PSA <7 ng/ml are rarely positive, while at >20 ng/ml they are quite likely to be positive.[30,31]
Adjuvant RT

ART implies that the patient achieved an undetectable post-RP PSA level (depending on the detection system that has to be documented) and, despite this apparent success, is irradiated. Evidently, a dilemma results from the unavoidable overtreatment by ART, which must be justified by clinical advantage. Overtreatment is estimated to involve 40–50% of the patients, which is the percentage of stable remissions 5 years after RP alone.\[34,46\] Furthermore, in patients whose tumors already spread beyond the pelvis, ART is useless and 30% of ART patients are expected to develop progression or die despite treatment.\[34,47\] Such concern probably causes low ART application rates.\[48–50\] However, ART might be superior to (delayed) SRT for those patients who ultimately develop post-RP recurrence and who could profit from early initiation of RT.

Three randomized clinical trials have dealt with the significance of ART in patients with locally advanced PC, namely:

- The SWOG 8794 trial:\[51,52,204\] the primary end point in this study was metastasis-free survival. bNED was a secondary end point (PSA cut-off 0.4 ng/ml). A total of 425 men with pT3 N0 M0 PC were randomized after RP. At least one of the following criteria for extraprostatic disease had to be fulfilled: extracapsular tumor; positive surgical margins; or seminal vesicle invasion. An undetectable post-RP PSA was not required (a third of the tests were >0.2 ng/ml). A total of 211 men were assigned to observation and 214 to ART with 60–64 Gy. With the recruiting period from 1988 to 1997, therapy was based on 2D plans;

- The EORTC trial 22911:\[33,53\] PSA progression was the 'revised primary end point' (initially it was metastasis-free survival), defined as PSA 0.2 ng/ml above the post-RP minimum. After RP, 503 patients were randomly assigned to the wait-and-see arm and 502 to ART. Patients with T2–3 N0 M0 PC and at least one of these criteria were eligible: capsule perforation; positive surgical margins; or invasion of seminal vesicles. ART (no 3D planning) patients received 50 Gy to the prostate bed plus a 10 Gy boost (five fractions) to a reduced volume, starting irradiation within 16 weeks after surgery;

- The ARO trial 96-02:\[54\] the primary end point was bNED (PSA threshold <0.1 ng/ml). This study focused on patients with pT3 N0 tumors with positive or negative surgical margins and an undetectable PSA. A total of 192 men were eligible for active surveillance and 193 for ART with 60 Gy, planned in 3D and beginning 6–12 weeks post-RP. Ultimately, 114 patients underwent RT (starting within 12 week post-RP) and 154 patients had a wait-and-see policy.

For these three studies, with their different inclusion criteria and treatment conditions, systematic reviews are already available.\[2,55–59\] It is agreed in unison that up to the reporting date, ART improved bNED; the overall hazard ratio ranges from 0.4 to 0.6 in favor of ART. In the early trial reports, reliable information was not available for all long-term effects. Meanwhile, the SWOG trial was updated with a median follow-up of over 12 years, now stating a significantly improved metastasis-free and overall survival with a hazard ratio of 0.7 for both end points;\[34,47\] the authors calculated that, on average, 12.2 patients had to be treated with ART to prevent one case of metastatic disease and 9.1 patients to prevent one death at 12.6 years of median follow-up. However, it has been argued that the survival benefit after ART was largely due to a lower rate of competing-cause deaths without evidence of distant metastasis, and that the impact of ART on metastatic disease and cancer-specific death was still uncertain.\[21\] In contrast to SWOG, no significant difference for
these end points was achieved in the EORTC trial after 10.6 years median follow-up. The ARO-96 trial reported on 53 months of overall median follow-up and, therefore, there were too few events to report on survival with any statistical significance. In all three trials, ART increased the risk of (mostly mild) normal tissue complications, involving bowel and bladder function. Erectile dysfunction, which was assessed only in the SWOG trial, occurred independent of the treatment arms. Technical advancements should help reduce side effects even after higher doses, as shown for first-line RT.

In a retrospective analysis, ART within a half-year post-RP has been reported. Such a delay may occur due to healing complications. A strict definition of ART would rather refer to an undetectable PSA than to the onset of radiation. However, for patients with intermediate- or high-risk profile, ART with 60–64 Gy 3–4 months post-PR has been recommended, while one retrospective analysis of 334 ART patients (including 37% non-3D) found an advantage for bNED and disease-free survival after 70.2 versus 66.6 Gy (median dose given in 1.8 Gy fractions). A total of 64 Gy is the intended dose in the ongoing RAVES study by the Trans-Tasman Radiation Oncology Group. Patients with adverse prognostic factors are randomized either to ART, initiating within 4 months post-RP or to early SRT triggered by PSA rising to ≥0.2 ng/ml. The primary end point in this study is biochemical failure, defined as PSA >0.4 ng/ml and rising. In the international RADICALS trial, 66 Gy in 33 fractions or alternatively 55 Gy in 20 fractions are planned. With its large patient number, RADICALS should help to answer the question under which conditions ART is superior to SRT.

Salvage RT

After RP, patients should be followed up with PSA measurements. If the post-RP PSA value re-rises from subthreshold to >0.2 ng/ml and this is confirmed after at least 2 weeks, then this is commonly regarded as biochemical relapse. A threshold as low as 0.02 ng/ml has been discussed, while on the other hand, there may be concerns about persisting normal prostate tissue. Once relapse is established, SRT should commence as early as possible, ideally at a PSA <0.5 ng/ml. More than 60% of patients who were treated like that could achieve an undetectable PSA level again, thus enabling up to 80% progression-free survival 5 years later. In the SRT setting, PSA kinetics, expressed as PSA doubling time or velocity, allows clues as to whether the recurrence is local or systemic, with a rapidly raising PSA more likely to be associated with metastatic disease and poorer clinical outcome. However, a systematic analysis of the predictive value of pre-RP PSA kinetics has emphasized the importance of the definition of the dynamic parameter. While there are still no randomized prospective studies available to prove the advantage from SRT for bNED, local or systemic failure, or survival, observational studies suggest a benefit especially for patients with a low pre-RT PSA.

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RT for post-RP PSA persisting above detection limit can be subsumed under SRT. Stephenson et al. have developed an 11-parameter nomogram to predict post-SRT recurrence where the contribution of status ‘persistently elevated post-RP PSA’ is minimal.[19] In a similar tool for 15-year PC-specific survival, that status does not occur.[71] Indeed, in a retrospective analysis of 159 patients comparing persisting PSA versus PSA rising from subthreshold values, no significant difference (p > 0.2) was found in the Kaplan–Meier risk of bNED after a median follow-up of 42 months.[72]

### Target Volume

If the post-PR management of PC involves RT, then the clinical target volume (CTV) is a critical aspect. The sites of local recurrence can guide its optimization. There have been various attempts to define common outlines for CTVs of PC,[73–75] and also for organs at risk of normal tissue complications.[76] However, depending on the applied techniques and accepted constraints, a satisfactory consensus has not yet been achieved.[77] The RTOG consensus was achieved considering two PC cases, one T2c with positive margins at both sides of the apex and one T3b with extracapsular extension at the right base and right seminal vesicle, but with negative margins.[73] In summary, the CTV below the level of the superior edge of the symphysis pubis should extend from the posterior edge of pubic bone to anterior rectal wall, inferiorly 8–12 mm below the vesicourethral anastomosis and laterally to the levator ani muscles/obturator internus. Above the upper edge of the symphysis the volume lies between the posterior 1–2 cm of the bladder wall to the mesorectal fascia, superiorly up to the level of the cut end of the vas deferens or 3–4 cm above the top of the symphysis (whichever is higher) and laterally to the sacrorectogenitopubic fascia. In the post-RP situation, the CTV must include normal tissue (where microscopic dissemination might occur), while the planning target volume is significantly larger to account for tissue motions.
Extending the field to the whole pelvis has been beneficial in the adjuvant setting combined with HT for lymph node-positive patients who have a significantly decreased cancer-specific survival with two[78] or more than two involved[79,80] nodes. In a retrospective SRT cohort analysis (247 patients), whole pelvis exposure could not significantly improve bNED in patients with pre-RP high-risk markers compared with low-risk patients, but it did so in the subgroup of patients with pre-SRT PSA levels ≥0.4 ng/ml.[81] Data on a slightly smaller cohort (160 patients) indicated that men with a high risk (≥20% according to the Partin criteria[82]) of nodal involvement significantly profit from whole pelvic treatment, both in the ART and SRT setting.[81] Therefore, while whole pelvic treatment is still under discussion, it has already been recommended for consideration in patients with ≥20% risk of positive pelvic nodes.[83]

### Radiation Dose & Toxicity

With reference to the three randomized studies (see sections ‘Adjuvant RT’ and ‘SRT versus ART’),[33,51,54] a dose of 60–64 Gy for external-beam ART is the consensus in the German S3-guidlines.[201] The situation is less clear for SRT ( ). To avoid radiation toxicity, most SRT studies do not exceed 70 Gy. It has been suggested that at least 66 Gy should be administered.[35,84,201] In a meta-analysis, the dose to achieve 50% tumor control in terms of 5-year bNED was calculated to be 66.8 Gy with a further gain of 3.8% per Gy.[85] Notably, that study predicts a 6 Gy lower 50% isoeffective dose for ART than for SRT, which, according to recently published model calculations, should enable a tangible reduction of toxicity to the gastrointestinal (GI) and genitourinary (GU) tract.[86] For R1 patients who are candidates for ART,[206] such a dose reduction may have a positive impact on the quality of life. However, in a comparison of ART with median 70.2 Gy and SRT with median 72 Gy, grade ≥2 and grade 3 late urinary toxicity were nearly identical (23.9 vs 23.7% and 12 vs 10%) after 8 years.[87] Even 76 Gy have been deemed safe with intensity-modulated SRT, yielding a 5-year risk of grade 2–3 toxicity of 22 and 8% for GU and GI symptoms, respectively.[88] Monitoring the PSA over the course of radiation can distinguish RT responders and nonresponders, and it has been suggested to increase the dose for responders, assuming that they are likely to profit from the more aggressive treatment (while reducing the dose might put cure rates at risk).[84]

#### Table 1. Selected studies on postprostatectomy salvage radiotherapy in ascending order of presalvage radiotherapy PSA level.

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</table>

HT can influence the outcome of bNED or PFS. Therefore, data sets without HT are highlighted. To facilitate comparisons, 5-year bNED/PFS readouts from Kaplan-Meier plots are included. bNED: Biologically no evidence of disease; HT: Hormone therapy; PFS: Progression-free survival; SRT: Salvage radiotherapy.

Based on published data from 13 studies on nearly 1800 patients, a nonlinear model for normal tissue complication probability suggests >5% grade ≥3 GI reactions above 68 and 69 Gy in the GU and GI tract, respectively. However, the text sources include only one study with a treatment dose >69 Gy and figures on grade ≥3 toxicity, and no contributions from IMRT. IMRT, which is meant to allow dose escalation, showed a reduction in grade ≥2 GI toxicity compared with 3D conformal RT in a study on 285 SRT patients. After a median follow-up of 60 months, the advantage of dose escalation regarding bNED and local control was not significant in the same patient cohort. Hypofractionated salvage IMRT (108 patients; median follow-up: 32.4 months) has been reported to induce 7% acute and 3% late GU toxicity grade ≥2. Acute GI tract reactions grade ≥2 occurred in 15 patients and late reactions in four patients. No grade ≥3 events were reported. The promising bNED results (67% at 4 years) await confirmation through longer follow-up. A retrospective analysis of 196 patients could show that bladder filling checks and image guidance can limit acute grade 3 GU toxicity after high-dose (76 Gy) IMRT to as low as 1–3%, while grade 3 GI tract events were not observed in this study. Where reported, sexual function was frequently and severely impaired (range: 25–88%), while the contribution of RT to this problem is low compared with the impact of surgery alone. In SWOG trial patients, the offset was less than 10% above the approximately 85% post-RP level with a slight recovery over 5 years in both therapy arms (the updated European Association of Urology guideline lists post-RP impotence as the most frequent side effect at 25–100%). During the same period, global health-related quality of life estimates deteriorated in RP-alone patients, but improved from 45 to 70% in ART patients. However, quality-of-life estimates should be regarded against the background of age-related health conditions (including comorbidity), of the status of being a cancer patient and in the post-RP setting of the side effects of surgery.

SRT versus ART

While urgently awaited prospective randomized trials are underway to compare SRT and ART, several retrospective/indirect analyses into that question have been conducted. In a first report, 75 patients receiving ART at a median dose of 60 Gy were compared with 71 patients who had SRT at 70 Gy. Although 49% of the SRT patients and only 3% of the ART patients received adjuvant HT, the 5-year post-RT bNED rate was 66 versus 88% in favor of ART (p < 0.0008). Both Kaplan–Meier curves plateaued at the respective levels for over 4 years.

In a case–control analysis, 361 ART patients were compared with 722 non-ART patients, who were selected to match the cases by treatment period, age, pre-RP PSA, tumor stage, Gleason score and surgical margin status. While 10-year bNED after ART was significantly improved over non-ART (63 vs 45%), there was no difference in overall survival. In the same study, an SRT cohort of 856 patients who were treated after biochemical relapse (median PSA: 0.8 ng/ml) was followed up over a median of 5.9 years. A total of 63% of the SRT patients achieved an undetectable PSA after SRT and the hazard ratio for local recurrence after SRT was 0.13. However, similar to ART, no improved overall survival could be shown after SRT.
A straight retrospective comparison with salvage (76 Gy) and adjuvant (74 Gy) IMRT patients (n = 89 in both arms) who were matched for personal and tumor characteristics, resulted in a significant bNED advantage from ART calculated either from the time of RP or from the end of RT (90 vs 65% 3 years post-RT and 91 vs 84% post-RP). However, the pre-RT PSA was a key parameter for that difference: a subcohort (n = 38) receiving early SRT (at PSA <0.5 ng/ml) had a 3-year post-RT bNED rate of 86%, quite different from the delayed SRT group, who had 46% bNED, but very similar to ART patients. Therefore, while overall Kaplan–Meier rates of bNED calculated in either mode suggested a benefit from ART, it was concluded that ART and early SRT did not yield significantly different results. This study included tumor stages from pT2 to pT4 and approximately 30% of the patients had received HT.[100]

A similar case-matched study was restricted to pT3–4 N0 patients. A total of 96 men were included in either treatment arm, with none receiving HT. Even excluding patients with a pre-SRT PSA above 2 ng/ml from the analysis (thus, leaving the median at 0.7 ng/ml), a statistically significant bNED advantage from ART was seen, both calculated from the date of RP and from the end of RT.[101]

The largest retrospective case-matching study to evaluate ART versus early SRT only included pT3 N0 R0/R1 patients. HT was excluded. A total of 390 out of 500 observation-plus-early-SRT patients (median pre-SRT PSA was 0.2 ng/ml) were propensity matched with 390 ART patients. At 2 and 5 years after surgery, bNED rates were 91 and 78%, respectively, for ART versus 93 and 82%, respectively, after SRT. Subgroup analyses also did not yield significant differences for the two approaches. It was concluded that early SRT does not impair PC control but clearly helps to reduce overtreatment, which is a major issue in ART.[46]

This last aspect has also been emphasized in an approach to model the outcome of STR and ART under consideration of quality of life.[102] results from the three randomized ART trials[33,51,54] and one large SRT study[19] were used to estimate and validate transition probabilities during the course of disease. Psychological distress and the major normal tissue complications, namely erectile dysfunction, bowel dysfunction, urinary obstruction and urinary incontinence, were accounted for in utility calculations. In summary, ART was predicted to show a slightly better outcome than observation plus SRT in terms of bNED, metastasis-free and overall survival. However, within the limits of accuracy of modeling, when side effects were included into decision-making, a preference for (early) SRT resulted for patients who would comply with the tight surveillance routine; but if 50% of the patients in the observation arm fail to receive SRT, ART is the favorable treatment. According to one report, only a third of 303 patients with post-RP recurrence received salvage treatment within a mean of 12 months.[103] In a study covering two decades, 340 (49%) out of 697 patients continued sole observation after biochemical relapse: “before 1995, approximately 70% of recurrent patients remained untreated 3 years after biochemical recurrence while after 2000 more then half were treated within 3 years”.[104]

When comparing ART with SRT, it must be kept in mind that a considerable number of ART patients would be relapse-free even without RT. The proportion is likely to be the same as in the observation arms of the three randomized studies (see the 'Adjuvant RT' section),[33,51,54] which was approximately 50% after 5 years. Further follow-up of the survival end points may help to identify patients who would have had a benefit from ART.

**Second Malignancies**

One point that was not included in the above model is the risk of second malignancies. This is an issue of growing concern specifically with modern multiportal radiation techniques.[105] Presumably, the risk is most prominent after first cancer therapy at a younger age. After PC treatment with definitive IMRT (n = 897) or brachytherapy (n = 413), no significantly increased rates of second cancer were observed within or out of the treatment field.[106] While the cohorts were small and follow-up was comparably short regarding the potentially long latency of radiation-induced tumors, there was a positive trend toward early diagnosis, resulting from routine surveillance and increased awareness of patients after the first malignancy.

**Conclusion & Recommendations**

Treatment decisions after prostatectomy require risk assessment. This is now facilitated by the Markov projection[102] and validated nomograms.[19,71,82,107–109] For low-to-intermediate-risk PC, observation and SRT can be recommended after R0 resection. Upon reincreasing PSA, SRT with at least 66 Gy should be applied as soon as possible (PSA <0.5 ng/ml). Until the ongoing trials[45,47,205] hopefully settle the question about when ART (with 60–64 Gy) is the better choice, ART should be regarded as an option at least in the case of R1.[54] Even now there is evidence that modern techniques (IMRT and image-guided RT) should offer an improved tumor control and help to minimize side effects.[89,110]
Future Perspective

Active surveillance for low-to-intermediate-risk patients will certainly remain in the focus in the next years. Extended follow-up will be necessary to judge on disease-specific survival because absolute event numbers are comparably low. The long-term results of the completed studies will identify subgroups of patients who profit from ART, but for others, such as N+ with ≤2 involved nodes, new randomized trials are planned in order to achieve statistically significant results. For SRT, the correct timing is a challenge as PSA measurements become more and more sensitive. Side effects and quality of life are leading issues for the comparison of SRT and ART, so that altered doses and fractionation schemes (including hypofractionation) may be discussed in the future. Technically, arc therapy or IMRT and image-guided RT are likely to become standards within the next decade. The resulting reduction of toxicity may influence the decision about how and when to apply RT in post-RP PC patients.

Sidebar

Executive Summary

Post-radical Prostatectomy Treatment options

- Compliant patients with low-to-intermediate risk are candidates for active surveillance and salvage radiotherapy (SRT).
- For intermediate- or higher-risk patients, specifically with R1 resections, adjuvant radiotherapy (ART) is an alternative.
- Node-positive patients with >2 nodes involved benefit from hormone therapy.
- The characterization of subgroups that profit from the different treatment options is still incomplete.

Radiation Toxicity

- Normal tissue complications are rare after both ART and SRT.
- Active surveillance clearly avoids overtreatment during the first 5 years after radical prostatectomy, but SRT doses are usually higher than ART doses.
- For some patients, important quality-of-life parameters, general age-related conditions, the cancer diagnosis and surgery have a stronger impact than radiotherapy (RT).

Future Directions

- In clinical trials subgroup analysis will identify patients who profit most from the various treatment strategies.
- Optimal implementation of all recent techniques, namely arc, intensity-modulated and image-guided RT will decisively influence the decision-making for post-radical prostatectomy RT.

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Papers of special note have been highlighted as:
* of interest
** of considerable interest