# Adjuvant radiotherapy after radical prostatectomy

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## Abstract

**Background:** Within 5 years following radical prostatectomy, between 15 and 60% of patients with pT3 prostate carcinomas show an increasing prostate-specific antigen (PSA) as a sign of local and/or systemic tumour progression. Adjuvant radiotherapy (RT) for positive margins (R1) aims to reduce residual tumour cells in the prostatic bed, thus possibly reducing the biochemical progression rate. Apart from a large number of retrospective investigations, available results are presented from three randomised studies which have either been published completely (or in abstract form).

**Results:** For pT3 prostate carcinomas, agreeing data are presented from three randomised studies, which show around a 20% reduced biochemical progression rate (bNED) after 4 to 5 years. With these data the results of numerous retrospective studies were confirmed. The majority of the authors used total doses of 60 Gy. From one randomised study an increased local control rate was demonstrated as basis for the extended freedom of biochemical progression. The rate of acute and late side effects after three-dimensional (3-D) planned radiotherapy with 60 Gy is very small and the rate of severe side effects is below 2%. The data situation for pT2 prostate carcinomas with positive margins is worse. Here, controversial data are presented, which require further investigation. Only retrospective data demonstrated a 25% advantage for adjuvant RT. Therefore, adjuvant radiotherapy also seems reasonable for pT-2 carcinomas with positive margins.

**Conclusions:** The effectiveness of adjuvant radiotherapy for patients with pT-3 tumours with positive margins with and without undetectable PSA levels with 60 Gy total dose has been demonstrated. A survival advantage has not been shown until now. 3-D treatment planning remains the standard technique for these patients. For patients with positive margins in organ-limited prostate carcinomas (pT2 R 1) randomised studies are recommended. It remains unclear whether the adjuvant RT is superior to the radiotherapy for rising PSA levels out of the undetectable range after radical prostatectomy.

## Introduction

Postprostatectomy examination of clinically staged T1/2 adenocarcinomas of the prostate reveal a pathologic stage T3/4 in up to 25% of cases; this probability increases to over 40% in clinical T2b tumours [1–3]. Radical prostatectomy is also frequently performed in patients with clinical stage T3 carcinomas. In these patients the probability of postoperative tumour growth beyond the organ is 80%. In approximately 20% of the cases it concerns a clinical overstaging [4]. The positive margin after radical prostatectomy is of substantial prognostic importance [3,5]. While this is rare in the stage pT2, for pT3-tumours it is also common in hospitals with high volume surgery. The absolute number for the amount in the tumour stage pT2 is 5 to 10% R1-resections, in the stage pT3 10 to 40%, whereby also in large centres, up to 25% R1-resections for pT3 carcinomas are not unusual [1].

While in the tumour stage pT2 the meaning of the positive margins is controversially discussed, it is indisputable that in the tumour stage pT3, positive margins represent an independent risk for biochemical progression [5–7]. By this positive margin it seems reasonable to suppose that the remaining microscopic tumour, usually obvious at the height of the anastomosis region, is also in the resection bed of the prostate. This remaining microscopic tumour represents the target volume of the adjuvant percutaneous 3-D planned radiotherapy, which is usually performed with 60 Gy over 6 weeks. A condition for the definition ‘adjuvant radiotherapy’ is, with the majority of the authors, reaching the PSA undetectable range, whereby the definition of the same is very different (between <0.1 and <0.03 ng/ml). In such a way, up to 60% of defined patients (pT3R1), achieve an increase of PSA from the undetectable range within 5 years, usually without clinically provable correlation [3]. On the other hand,

it is well-known that in 35–54% of the patients with rising PSA after radical prostatectomy without clinical correlation, only by punch biopsies from the urethrovesical anastomosis was vital tumour tissue found [8]. These results support the use of adjuvant RT after radical prostatectomy. The proceeding of urologists with patients with positive margins, in particular in the stage pT2 R1, but also in the stage pT3 R1, is controversial. Different authors represent both the beginning of 'watchful waiting', the delayed or the immediate hormone therapy, the adjuvant radiotherapy or the RT only in case of rising PSA [9–13]. Adjuvant radiotherapy became more attractive after implication of 3-D treatment planning as well as intensity modulated radiotherapy (IMRT), thus reducing acute and late side effects [14–16]. This overview examines the results and possible therapy sequences for patients after radical prostatectomy with or without positive margins and with or without achieving an undetectable PSA after RP.

## Adjuvant radiotherapy for patients with pT2 tumours and positive margins

The meaning of positive margins after radical prostatectomy for pT2 carcinomas is controversially discussed. In other studies, some authors saw no independent prognostic factor for bNED, e.g. the positive apical margin with pT2 carcinomas was identified as an independent prognostic factor [5,11]. Randomised studies comparing 'wait and see' and adjuvant radiotherapy are not present. In one retrospective study on 'matched pair conditions' two cohorts were compared, 76 patients within each case. The 5-year bNED rate amounted to 88% for the patients with adjuvant RT compared with 59% with 'wait and see' ($P < 0.05$). Here, no difference between positive basal or apical margins resulted [17]. In the subgroup analysis of EORTC trial 22911, patients with pT2 R1 tumours were at similar risk of failure as men presenting with extra capsular extension with or without positive surgical margins but without invasion of seminal vesicles. In this randomised trial, patients with pT2 R1 tumours profited from adjuvant RT with 60 Gy compared to patients with pT3 tumours. The advantage was about 10% bNED for 5 years [18]. However, this phase III trial was not primarily focused on pT2 tumours. For these reasons the indication for adjuvant radiotherapy for patients with pT2 prostate cancer and positive margins can be seen due to individual risk factors. A randomised comparison (60 Gy versus 'wait and see') is being prepared at present by the 'Interdisziplinäre Studiengruppe Prostatakarzinom' in Germany.

## Adjuvant RT for pT3 pN0 tumours with or without positive margins

A large number of retrospective, non-randomised studies are available to answer this question. Here in particular, different prognostic factors were examined like positive margins, infiltration of the periprostatic tissue or seminal vesicles and Gleason Score >7. From these retrospective studies with adjuvant radiotherapy, a significant improvement of the local tumour control rate up to 95–100% was achieved [9,12,19–21]. A number of retrospective examiners also came to the conclusion that in the adjuvant situation, radiotherapy with 60 Gy results in a significant extension of the bNED. The order of magnitude of this extension, counted in 4 to 5 years, varies depending on examiners between 20 and 50% [12]. In a study by Valicenti and colleagues, a 'matched pair'-analysis of 72 patients was performed. In this analysis, patients were grouped according to Gleason score (<7 versus ⩾7), preoperative PSA value (⩽10 versus >10 ng/ml), seminal vesicle infiltration (positive versus negative), and margin status (positive versus negative). 5-year freedom from PSA relapse was 89 versus 55% ($P < 0.05$) in favour of the treated patients [22]. Different authors could identify different factors of risk. The authors concluded that the sole seminal vesicle infiltration, in particular with negative margins, was not sufficiently treated with an adjuvant RT alone [23]. In the majority of cases the positive margins expanded organ-exceeding tumour growth, and a preoperative PSA value >10 ng/ml, could also be identified as a risk factor [12,13]. Over the importance of the adjuvant radiotherapy for patients with a Gleason score of 8–10, inconsistent data are present due to the high rate of biochemical progression.

In no series, however, could an extension of the overall survival be proven. This is probably connected

Table 1
Comparison of RP with and without adjuvant RT for pT3 prostate carcinoma – clinical local control

| Reference | With RT | | Without RT | |
|---|---|---|---|---|
| | *n* | 5-year local control rate, % | *n* | 5-year local control rate, % |
| Anscher, *et al.* [19] | 46 | 96 | 113 | 80 |
| Wiegel & Bressel [21] | 56 | 100 | – | – |
| Schild, *et al.* [24] | 60 | 100 | 228 | 83 |
| Syndikus, *et al.* [25] | 89 | 100 | 88 | 79 |
| Petrovic, *et al.* [20] | 201 | 95 | – | – |

Table 2
Comparison of RP with and without adjuvant RT for pT3 prostate carcinoma – 5-year biochemical disease-free survival – retrospective studies

| Reference | With RT | | Without RT | |
|---|---|---|---|---|
| | *n* | 5-year 'undetectable', % | *n* | 5-year 'undetectable', % |
| Zietman et al. [26] | 84 | 73 | 62 | 27 |
| Schild et al. [24] | 60 | 57 | 228 | 40 |
| Syndikus et al. [25] | 89 | 93 | 88 | 74 |
| Valicenti et al. [22] | 36 | 89 | 36 | 55 |
| Choo et al. [27] | 73 | 88 | 52 | 65 |
| Vargas et al. [28] | 23 | 52 | 72 | 30 |

with the number of the investigated patients. In order to be able to prove a survival advantage of 5 to 10%, between 500 and 1000 patients and a median follow-up of 8 to 10 years are required. This fact is verified from the RTOG studies [29,30].

## Randomised trials

Data from three randomised phase III studies are presented. Of these, the study 22911 of the EORTC and the study 8794 of the SWOG are published [18, 30,31]. One further study is available only in abstract form at present [13]. In principle all three studies are positive. They show uniformly, for the total collective, an advantage of bNED after 4 to 5 years of about 20%.

In the study of the EORTC, 1002 patients were randomised to radiotherapy with 60 Gy or 'wait and see' and the results were published by Bolla and colleagues [30]. The median PSA value before the beginning of RT, however, was 0.2 ng/ml, as indication of an unfavourable patient selection. After 5 years bNED for irradiated patients, 74% compared with 52.6 % in the control arm ($P < 0.05$) [18,31]. The absolute advantage by radiotherapy was 21%. Parallel to this, the rate of locoregional recurrences, however, only diagnosed by clinical palpation, was significantly reduced by adjuvant radiotherapy. The meaning is limited because of the mere clinical palpation in up to 30% which remains false positive [31].

The results of a randomised phase III study of the South Western Oncology Group (SWOG 8794) were published recently [32]. Four hundred and seventy-three men with pT3 disease were randomised to either observation or adjuvant RT to the prostate bed, of whom 410 (87%) were evaluable. The median follow-up was 9.7 years. Once again, adjuvant RT was associated with a statistically significant improvement in biochemical disease-free survival (47% versus 23% event-free at 10 years, HR 0.51, 95% CI 0.39, 0.67, $P < 0.001$). Interestingly, adjuvant RT was also associated with a trend towards better metastasis-free survival (71% versus 61% at 10 years, HR 0.80, 95% CI 0.57–1.11, $P = 0.17$), and overall survival (74% versus 63% at 10 years, HR 0.76, 95% CI 0.54–1.07, $P = 0.11$). The authors also detected an advantage for patients with adjuvant RT compared with those who were irradiated for PSA-increase. Although the results for overall survival from this trial did not reach statistical significance, they certainly suggest that, in comparison with observation (with or without late salvage radiotherapy), adjuvant RT may lead to a clinically meaningful improvement in overall survival.

The study of the 'Arbeitsgemeinschaft Radiologische Onkologie und Urologische Onkologie der Deutschen Krebsgesellschaft' (ARO 96–02/AUO AP 09/95) differs in the point that the condition for entrance and randomisation in 'wait and see' or adjuvant radiotherapy with 60 Gy was an undetecable PSA after radical prostatectomy. 385 patients were randomised; 78 of these did not reach the undetectable PSA range and were excluded according to study protocol. The remaining 307 patients were randomised for 'wait and see' ($n = 153$) and for adjuvant radiotherapy with 60 Gy ($n = 154$). The median follow-up was 40 months. After 4 years, a significant advantage of 21% for the biochemical freedom of progression was observed [13].

While a significant advantage for bNED was proven in all three studies, no advantage in overall survival resulted. A randomised study with patients only irradiated for rising PSA after radical prostatectomy does not exist. It is well justifiable for these reasons to treat patients with positive margins after RP with adjuvant radiotherapy with 60 Gy.

Several randomised trials have demonstrated that the addition of hormone therapy improves overall survival in men receiving primary radiotherapy for prostate cancer with high progression risk e.g. EORTC 22863 [33], RTOG 86–10 [30] and RTOG 85–31 [29] and the study of D'Amico and colleagues [34]. However, there are no reported randomised controlled trials addressing the role of hormone therapy in men receiving post-operative radiotherapy to the prostate bed.

The Early Prostate Cancer (EPC) Program accrued 4,400 men who had curative treatment and were

randomised between observation versus 2 years adjuvant bicalutamide 150 mg. At a median follow-up of 7.4 years, there is a statistical significant benefit for additional hormonal treatment, but no difference in overall survival. This very large trial serves to underline that at present there is no proven role for adjuvant hormone therapy alone after curative treatment [35,36].

One randomised controlled trial, RTOG 96–01 [RTOG Website 2006], recruited 840 patients with PSA failure after radical prostatectomy and randomised them between early salvage RT alone versus early salvage RT plus 2 years of hormone therapy with bicalutamide 150 mg daily, with overall survival as the main outcome measure. The first outcome data are not expected until 2008 [37].

Three retrospective studies have compared the outcome of salvage RT for increasing PSA after RP alone versus salvage RT plus short-term (4–6 months) hormone therapy, and have observed improved biochemical control rates with the addition of hormone therapy [38–40].

The current pattern of practice, with no consensus regarding the need for, or duration of, hormone therapy in men receiving post-operative RT, combined with the increasing popularity of radical prostatectomy, provides a strong rationale for a phase III study. RADICALS will investigate the question of RT alone versus RT plus short-term hormone therapy versus RT plus long-term hormone therapy in this setting. The duration of short-term hormone therapy will be 6 months, based on Trans-Tasman study [41], and long-term hormone therapy will be 24 months, based on RTOG 92–02 [42] and RTOG 96–01.

The EORTC are developing a new clinical trial of adjuvant treatment after radical prostatectomy. The current proposal randomises patients between adjuvant radiotherapy alone versus adjuvant radiotherapy plus 12 months of hormone therapy. If this trial goes ahead, it will complement data from the hormone duration randomisation of the RADICALS trial.

In addition to the trials listed above, it is also pertinent to consider RTOG P-0011, which was originally designed as a 3-arm trial in men at high risk of recurrence following radical prostatectomy, with the randomisation between adjuvant RT, long-term adjuvant hormone therapy (24 months) or RT plus long-term hormone therapy. The trial failed to accrue in the USA. This was initially attributed to the lack of RT in one of the trial arms. Modification to a 2-arm trial comparing adjuvant RT ± hormone therapy improved recruitment, but was insufficient to prevent trial closure. The reasons for the ultimate failure of this trial are not known completely [37].

## Radiation techniques, dose and target volume definition

3-D conformal radiotherapy techniques (3DRT) are generally used. Patients are treated in supine position with a leg fixation device. For pT2 tumours with positive margins the radiation treatment volume should include the prostate bed with a safety margin of 10 mm. For pT3a/b tumours, the radiation treatment volume should include the prostate bed including the site of the seminal vesicles basis/the seminal vesicles (Fig. 1). The total dose should be 60 Gy or slightly higher (not more than 64 Gy).

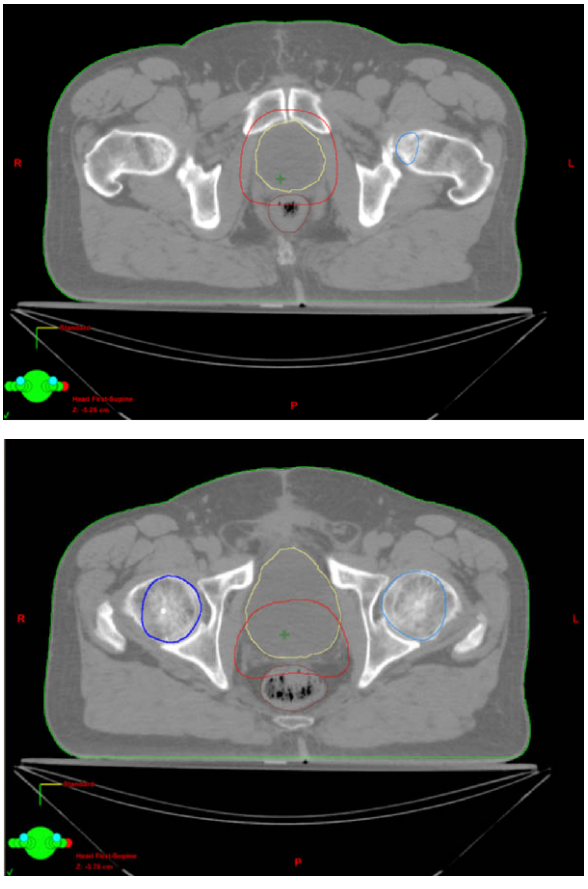

Fig. 1. Planning target volume: (top) prostate bed including a safety margin; (bottom) prostate bed including seminal vesicles basis.

## Acute and late side effects of adjuvant radiotherapy

The rate of severe acute and late sequences after adjuvant radiotherapy with 60 Gy is low. In the

German multicentre study, the rate of severe grade III acute or late sequences was below 1%, because all irradiated patients had 3-D treatment planning [13]. Low grade I/II side effects involving the rectum and bladder occur in up to 5–15% of patients, but doses about 60 Gy given in the frame of 3-D RT treatment planning are rarely associated with serious long-term side effects (<3–4% grade III/IV according to the RTOG-EORTC grading system) [12,18,19,30,24,25, 27,28,26]. It is important that adjuvant radiotherapy does not have a negative influence on continence after radical prostatectomy. To date, no data exists for the question of a loss of sexual potency after nerve-sparing RP and adjuvant RT. This problem will more frequently arise in the future with patients with pT2 R1 resections, who are today often operated with nerve-sparing RP.

In summary, there is a well documented indication for adjuvant radiotherapy for pT3 carcinomas with positive margins, both after reaching an undetectable PSA and at persisting PSA after RP, whereby the total dose should be then at least 66 Gy. The indication for the adjuvant radiotherapy for patients with pT2 prostate cancer and positive margins can be seen due to individual criteria, even if no randomised data exist at the present time. On the other hand, there is no survival advantage for irradiated patients. It must still be examined whether the adjuvant radiotherapy is superior to the radiotherapy for rising PSA. The rate of severe late side effects is low.

## Conflict of interest statement

There are no conflicts of interest.

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