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Adjuvant Radiotherapy after Radical Prostatectomy: Indications, Results and Side Effects

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) level as a sign of local and/or systemic tumor progression. Apart from a large number of retrospective investigations, available results are present only from three randomized studies which have either been completely published or are only in abstract form. **Results:** For pT3 prostate carcinomas the data from the three randomized studies agree, showing an around 20% reduced biochemical progression rate after 4–5 years. With these data the results of numerous retrospective studies have been confirmed. The majority of the authors use total doses of 60 Gy with single doses of 2 Gy. From one randomized study an increased local control rate is proposed as the basis for the extended freedom from biochemical progression. The rate of acute and late side effects after three-dimensional radiotherapy with 60 Gy is very small and the rate of severe side effects is below 2%. The data for pT2 prostate carcinomas with positive margins are worse. Here controversy exists, and further investigations are required. In principle, however, adjuvant radiotherapy seems reasonable also for pT2 carcinomas with positive margins (determined by bNED – no biochemical evidence of disease). **Conclusions:** The effectiveness of adjuvant radiotherapy for patients with pT3 tumors and positive margins with and without detectable PSA levels is discussed. A survival

advantage has not been demonstrated to date. For patients with positive margins in organ-limited prostate carcinomas (pT2 R1) randomized studies are recommended. It is unclear whether adjuvant radiotherapy is superior to radiotherapy for PSA levels increasing from the undetectable range after radical prostatectomy. To answer this question randomized studies are needed.

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Introduction

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

While for tumor stage pT2 the meaning of the positive margins is controversial, it is indisputable that in tumor stage pT3 positive margins represent an independent risk for biochemical progression [5–7]. According to this positive margin, it seems reasonable to suppose that the remaining microscopic tumor is usually obvious at the height of the anastomosis region, but also in the resection bed of the prostate. The remaining microscopic tumor is the target of adjuvant percutaneous 3D radiotherapy, which is usually performed at 60 Gy over 6 weeks. For the majority of authors a condition for the definition of ‘adjuvant radiotherapy’ is reaching an undetectable prostate-specific antigen (PSA) range, although this definition varies greatly (between <0.1 and <0.03 ng/ml). Up to 60% of the patients thus defined have an increase in PSA from the undetectable range within 5 years, usually without a clinically provable correlate [3]. On the other hand it is well known that in 35–54% of the patients with rising PSA levels after radical prostatectomy without a clinical correlate, vital tumor tissue was only found by punch biopsies from the urethrovesical anastomosis [8]. These results support the use of adjuvant radiotherapy after radical prostatectomy. How urologists proceed in patients with positive margins, in particular in stage pT2 R1 and also in stage pT3 R1, is controversial. Different authors recommend ‘watchful waiting’, delayed or immediate hormone therapy, adjuvant radiotherapy, or only radiotherapy in cases of increasing PSA [9–13]. Adjuvant radiotherapy became more attractive after implication of 3D treatment as well as intensity-modulated radiotherapy, thus reducing acute and late side effects [14]. This overview examines the results and possible therapeutic sequences for patients after radical prostatectomy with or without positive margins.

Adjuvant Radiotherapy for Patients with pT2 Tumors and Positive Margins

The meaning of positive margins after radical prostatectomy for pT2 carcinomas is controversial. Although some authors saw no independent prognostic factor for bNED (no biochemical evidence of disease), in other studies the positive apical margin with pT2 carcinomas was identified as being an independent prognostic factor [5, 11]. There are no randomized studies comparing ‘wait and see’ and adjuvant radiotherapy. In only one retrospective study on ‘matched pair conditions’ two cohorts of 76 patients each were compared. The 5-year

bNED rate amounted to 88% for patients with adjuvant radiotherapy compared to 59% with ‘wait and see’ ($p < 0.05$). Here no difference between positive basal or apical margins was found [15]. A randomized comparison is presently being prepared by the Interdisziplinäre Studiengruppe Prostatakarzinom in Germany. In the subgroup analysis of the EORTC trial 22911 [16], patients with pT2 R1 tumors were at a similar risk of failure as men presenting with extracapsular extension with or without positive surgical margins and without invasion of the seminal vesicles. The indications for adjuvant radiotherapy in patients with pT2 prostate cancer and positive margins are individual risk factors.

Adjuvant Radiotherapy for pT3 pN0 Tumors with or without Positive Margins

A large number of retrospective, non-randomized studies are available. Here, in particular, different prognostic factors were examined such as positive margins, infiltration of the periprostatic tissue or seminal vesicles and Gleason score of >7 . From these retrospective studies with adjuvant radiotherapy, a significant improvement in the local tumor control rate of up to 95–100% was achieved [9, 12, 17–19] (table 1). A number of retrospective researchers also come to the conclusion that in the adjuvant situation radiotherapy with 60 Gy results in a significant increase in freedom from biochemical progression (table 2). The order of magnitude of this increase at 4–5 years varies between 20 and 50% depending on the researcher [12]. In a study by Valicenti et al. [20] a matched-pairs analysis of 72 patients was performed. In this analysis, patients were grouped according to the Gleason score (<7 vs. ≥ 7), preoperative PSA value (≤ 10 vs. >10 ng/ml), seminal vesicle infiltration (positive vs. negative), and margin status (positive vs. negative). The 5-year freedom from PSA relapse was 89 vs. 55% ($p < 0.05$) in favor of the treated patients [20]. Various authors were able to identify different risk factors. Clear indications resulted from the fact that sole seminal vesicle infiltration, in particular with negative margins, is not sufficiently treated with adjuvant radiotherapy alone [21]. In the majority of cases, positive margins, expanded organ-exceeding tumor growth, as well as preoperative PSA values of >10 ng/ml could be identified [12, 13]. Inconsistent data are present with regard to the importance of adjuvant radiotherapy for patients with a Gleason score of 8–10.

Table 1. Comparison of radical prostatectomy with and without adjuvant radiotherapy (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. [17]	46	96	113	80
Wiegel and Bressel [19]	56	100	–	–
Schild et al. [25]	60	100	228	83
Syndikus et al. [26]	89	100	88	79
Petrovic et al. [18]	201	95	–	–

However, in no series could an increase in overall survival be proven. This is probably related to the number of patients investigated. In order to be able to prove a survival advantage of 5–10%, the number of patients must be between 500 and 1,000 and a median follow-up of 8–10 years is required. This is verified by the RTOG studies [22] in particular.

Randomized Trials

In the meantime data of three randomized phase-III studies have been presented. Of these, study 22911 of the EORTC and a study of the South Western Oncology Group have been published [16, 23, 24]. Another study is available but only in abstract form at present [13]. In principle all 3 studies are positive. For the total collective they uniformly show an advantage in bNED after 4–5 years of about 20%.

In the EORTC study, 1,002 patients were randomized to radiotherapy with 60 Gy or ‘wait and see’, and the results have been published by Bolla et al. [23]. However, the median PSA value before beginning radiotherapy was 0.2 ng/ml, indicating unfavorable patient selection. After 5 years, the bNED for irradiated patients was 74% compared with 52.6% in the control arm ($p < 0.05$) [16, 23]. The absolute advantage of radiotherapy was 21%. Parallel to this, the rate of locoregional recurrences, diagnosed by clinical palpation, was significantly reduced by adjuvant radiotherapy. The meaning of this finding is limited due to the false-positive rate of mere clinical palpation of up to 30% [23].

The study of the Arbeitsgemeinschaften Radiologische Onkologie und Urologische Onkologie der Deutschen

Table 2. Comparison of radical prostatectomy with and without adjuvant radiotherapy (RT) for pT3 prostate carcinoma – 5-year biochemical disease-free survival in retrospective studies

Reference	With RT		Without RT	
	n	5-year undetectable, %	n	5-year undetectable, %
Zietman et al. [29]	84	73	62	27
Schild et al. [25]	60	57	228	40
Syndikus et al. [26]	89	93	88	74
Valicenti et al. [20]	36	89	36	55
Choo et al. [27]	73	88	52	65
Vargas et al. [28]	23	52	72	30

Krebsgesellschaft (ARO 96-02/AUO AP 09/95) differs in that the condition for entrance and randomization into the ‘wait and see’ arm or adjuvant radiotherapy with 60 Gy was an undetectable PSA after radical prostatectomy. 385 patients were randomized, 78 of these did not reach the undetectable PSA range and were excluded according to the study protocol. The remaining 307 patients were randomized to ‘wait and see’ ($n = 153$) or adjuvant radiotherapy with 60 Gy ($n = 154$). The median follow-up was 40 months. After 4 years a significant advantage of 21% for biochemical freedom from progression was observed [13].

With the randomized phase-III study of the South Western Oncology Group, which started in the pre-PSA era, the primary endpoint was an expected advantage for metastasis-free survival after 10 years. This primary endpoint was not reached, the study thus regarded the primary endpoint negatively. However, after 10 years bNED resulted in a significant advantage for adjuvant radiotherapy (38 versus 23%, absolute 15%) [16].

While a significant advantage for bNED was proven in all 3 studies, at present there is still no advantage in overall survival results. A randomized study in patients only irradiated for an increasing PSA after radical prostatectomy does not exist. For these reasons it is justifiable to treat patients with positive margins after radical prostatectomy with 60-Gy adjuvant radiotherapy.

Acute and Late Sequences of Adjuvant Radiotherapy

The rate of severe acute and late sequences after adjuvant radiotherapy with 60 Gy is low. In the German multicenter study the rate of severe grade-III acute or late se-

quences was below 1%, because all irradiated patients had 3D treatment [13]. Low grade-I/II side effects involving the rectum and bladder occur in up to 5–15% of patients, but doses of about 60 Gy given in the frame of 3D radiotherapy are rarely associated with serious long-term side effects (<3–4% grade III/IV according to the RTOG-EORTC grading system) [12, 16, 17, 23]. It is important that adjuvant radiotherapy does not have a negative influence on continence after radical prostatectomy. To date, no data exist with regard to the loss of sexual potency after nerve-sparing radical prostatectomy and adjuvant radiotherapy. In the future this problem will arise more frequently in patients with pT2 R1 resections who today are often operated with nerve-sparing radical prostatectomy.

In summary, there is a well-documented indication for adjuvant radiotherapy for pT3 carcinomas with positive margins, both after reaching an undetectable PSA and when PSA persists after radical prostatectomy; however, the total dose should then be at least 66 Gy. The indication for adjuvant radiotherapy in patients with pT2 prostate cancer and positive margins depends on individual criteria, because at present no randomized data exist. On the other hand, there is no survival advantage for irradiated patients. It still needs to be examined whether adjuvant radiotherapy is superior to radiotherapy for rising PSA. The rate of severe late sequences is low.

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