Adjuvant Radiotherapy Results following Radical Prostatectomy—A Critical Review

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Abstract

Objectives: The author attempts to better define the treatment of patients with locally advanced prostate cancer following radical prostatectomy.

Methods: The data of the most recent series in the international literature have been analysed.

Results: The risk of biochemical or clinical relapse in the literature is not clear. Recently, two randomised phase 3 trials have been published showing a statistical significant benefit of adjuvant irradiation with respect to biochemical and clinical progression-free survival. Toxicity of adjuvant radiotherapy was moderate in these studies. However, the range of patients with pT3 disease is large (extracapsular extension with/without positive margins, positive margins only, and seminal vesicle invasion), and the challenging question now is whether we can find a subgroup of patients with pT3 disease who will benefit most from adjuvant irradiation to prevent overtreatment for a considerable number of patients, and to reduce toxicity and costs.

Conclusions: Instead of offering all patients immediate adjuvant treatment, patients with minor risk of relapse could be monitored carefully and offered salvage radiotherapy once biochemical relapse is observed.

Keywords: Adjuvant Radiotherapy Radical prostatectomy Prostate cancer

Since the introduction of prostate-specific antigen (PSA) and the increased awareness, prostate cancer has been diagnosed at an earlier stage. However, biochemical relapses following treatment with curative intent are observed in approximately 30–50% of the patients at 10 yr [1,2]. This observation can be explained by the fact that, although there is a shift to earlier stages and lower tumour volumes, 38–52% of the patients undergoing a radical prostatectomy have extraprostatic disease at pathologic examination [3,4]. The challenging question has always been whether patients who underwent a radical prostatectomy and whose pathologic examination showed capsular penetration or even positive margins could benefit from adjuvant therapy. The concept of immediate postoperative irradiation was already described in 1965 by George et al [5]. The first question to be answered is whether either of the two findings does matter with respect to relapse of the disease. Swindle et al [6] analyzed 1389 patients...
with cT1–3 prostate cancer who underwent radical prostatectomy. A pT2 stage was found in 847 patients and 6.8% had positive margins, while pT3 was found in 522 patients, 23% of whom had positive margins. A positive surgical margin was found to be an independent predictor of 10-yr progression-free probability, which is in accordance with other reported series [7–10]. However, recently Vis et al [11] reported on a cohort of 281 patients with a median follow-up of 7 yr, in whom they found that the margin status was only of limited predictive value for PSA relapse and local recurrent disease: Only 33.3% showed a biochemical relapse and 6.1% had a local recurrence.

Several nonrandomised studies [12,13] have been published to assess the value of adjuvant radiation therapy in case locally advanced disease was demonstrated in the surgical specimen. These studies have shown that adjuvant radiation therapy was able to eradicate microscopic disease that was left and could reduce the local relapse rate. Lennernäs et al [14] reviewed 417 articles (1990–2002) dealing with postoperative radiotherapy after radical prostatectomy. No randomised studies were found, but postoperative radiotherapy appeared to have a beneficial effect on local control, especially if pT3–4 disease, invasion of the seminal vesicles, positive surgical margins, high Gleason score, and high postoperative PSA were demonstrated. No survival advantage was described from adjuvant irradiation. The European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary group and Radiotherapy group launched, in 1992, a prospective randomised phase 3 trial [15] to assess the value of immediate postoperative radiotherapy on progression-free survival in patients with pT3 disease; the results were recently published. In this study 502 patients were randomized to immediate (within 16 wk following radical prostatectomy) postoperative radiation (target total: 60 Gy), and 503 patients were randomized to be treated preferably with radiotherapy once local relapse, clinical or biochemical, was demonstrated (recommended dose: 70 Gy). After a median follow-up of 5 yr, biochemical progression-free survival was significantly improved in the irradiated group (74% vs. 52.6%). Clinical progression-free survival was also significantly improved (85.1% vs. 77.5%). In this first analysis a difference in overall survival and cumulative incidence of distant metastases was not evident between the two arms: 92.3% versus 93.1% and 6.1% versus 6.3% for the immediate or delayed groups respectively. Longer follow-up and more events in this study are needed to demonstrate a possible difference in these two end points. In this randomised trial the toxicity of immediate radiotherapy was higher, but this finding was only grade 2 or 3 late effects and, until now, no major toxicity was reported.

Thompson et al [16] also recently reported a randomised clinical trial testing the concept of postoperative radiotherapy in locally advanced prostate cancer. In this trial 425 men were randomised between 1988 and 1997; the median follow-up was 10.6 yr. The data of the EORTC study were confirmed. A significant reduction in PSA relapse and disease recurrence was demonstrated when patients received immediate irradiation, median PSA relapse-free survival was 10.3 yr versus 3.1 yr, and median recurrence-free survival was 13.8 yr versus 9.9 yr. However, improvements in metastasis-free survival and overall survival were not statistically significant: 14.7 yr versus 13.2 yr and 14.7 yr and 13.8 yr, respectively. In the EORTC trial [17] the patients with pT3 disease were further subclassified as having positive margins without extracapsular extension, positive margins with extracapsular extension, extracapsular extension without positive margins, and invasion into the seminal vesicles. In the analysis of these subgroups, all four categories of pT3 disease benefited from immediate adjuvant radiotherapy with respect to biochemical and clinical progression-free survival, although the benefit for the patients with negative surgical margins was less clear. It was not clear from the evaluation what the extent of the positive surgical margin was and at which location the margin was positive; these parameters should be further investigated to determine whether they influence the risk of relapse. The improvement of surgical techniques to reduce the number of positive surgical margins thus seems of utmost importance to reduce the local recurrence rates [6,18,19]. Although, theoretically, positive surgical margins are a plausible explanation for being a prognosticator for biochemical recurrence, it is still remarkable that several groups reported only a moderate impact of the margin status and the chance of recurrence [11,20]. A possible explanation for these different findings could be the pathologic examination of the surgical specimen. The impact of pathologic staging and determination of the margin status of radical prostatectomy specimens were considered important prognosticators for recurrence in the EORTC study [15]; therefore, review pathology of all the radical prostatectomy specimens was included. Van der Kwast et al [21] reported on a series of 552 specimens, and found a high concordance between review pathology and local pathologists for seminal vesicle invasion.
will not be effective. Toxicity data were very groups, because in these cases local radiotherapy to evaluate as has been demonstrated by several prostatectomy and PSA doubling time is important the biochemical failure in relation to the radical recurrence post-radical prostatectomy; thus, the time of usually present with an early biochemical recur-

sion in the original radical prostatectomy speci-
men are also predictors for a worse outcome for salvage radiotherapy. In the EORTC study [15], the timing of salvage therapy could be delayed until local relapse was demonstrated, which could be too late for a good outcome of salvage radiotherapy, because patients can have distant metastases already at that moment. Patients with locally advanced prostate cancer, and certainly if the combination of extraprostatic extension and posi-
tive margins was found with high Gleason scores, have a high chance of microscopic metastatic disease already, although it cannot be identified with current imaging studies. These patients will usually present with an early biochemical recur-
rence post-radical prostatectomy; thus, the time of the biochemical failure in relation to the radical prostatectomy and PSA doubling time is important to evaluate as has been demonstrated by several groups, because in these cases local radiotherapy will not be effective [31]. Toxicity data were very moderate in the EORTC study [15]; the cumulative incidence of events of grade 3 toxicity was 4.2% in the radiation group compared with 2.6% in the wait-

and-see group. In this trial, however, radiation was not given if the patient still had voiding problems post-radical prostatectomy. Further follow-up is also needed to see if this low toxicity rate will be maintained. In the SWOG study rectal complications were seen in 3.3% of patients receiving adjuvant radiotherapy versus 0% in the observation arm, urethral strictures 17.8% versus 9.5% and total urinary incontinence 6.5% versus 2.8%, respectively. Choo et al [32] prospectively evaluated the quality of life in patients with locally advanced prostate cancer receiving radiotherapy and 2 yr of androgen suppression in a phase 2 setting. Only 78 patients were included, but validated questionnaires were used and no negative impact on different quality-of-life dimensions was found. These data cannot be used to support the use of adjuvant irradiation, because the numbers are too small and there was no comparison with a “no treatment” group, and because 2 yr of androgen suppression was included in the treatment group, but no adverse effects were found in this study.

On the basis of these data, how should the patient with pT3 disease nowadays be counseled? Two randomized trials provide level 1 evidence that adjuvant irradiation provides a significant benefit with respect to biochemical and clinical progression-free survival. One trial, however, showed that this benefit did not translate into an improved overall survival and metastasis-free survival. Offering adjuvant irradiation to all patients with pT3 disease will be overtreatment for a considerable number of patients: In the observation arms of the EORTC [15] and SWOG [16] studies 52.6% and 38% did not show a biochemical relapse. Definition of high-risk groups, thus, is necessary to reduce the overtreatment rate, and to reduce the side effects and costs of this adjuvant treatment. In the EORTC study it has been shown that patients with positive margins especially benefit from adjuvant irradiation, so this group of patients are candidates for this treatment approach. Of course the primary aim should be that surgical techniques are improved to prevent positive margins. For the other groups of patients, a careful monitoring can be offered with PSA determinations; once the PSA starts to rise, salvage radiotherapy can be initiated, although one should keep in mind the observation, reported by Pound et al [31], that it takes a median time of 96 mo from biochemical relapse to develop metastatic disease. These considerations should be discussed with the patient, and on an individual basis the further treatment or follow-up should be discussed awaiting further evaluations of the EORTC [15] and German studies [33].
References


