Platinum Priority – Prostate Cancer

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Long-term Impact of Adjuvant Versus Early Salvage Radiation Therapy in pT3N0 Prostate Cancer Patients Treated with Radical Prostatectomy: Results from a Multi-institutional Series

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Abstract

Background: Three prospective randomised trials reported discordant findings regarding the impact of adjuvant radiation therapy (aRT) versus observation for metastasis-free survival (MFS) and overall survival (OS) among patients with pT3N0 prostate cancer treated with radical prostatectomy (RP). None of these trials systematically included patients who underwent early salvage radiation therapy (esRT).

Objective: To test the hypothesis that aRT was associated with better cancer control and survival compared with observation followed by esRT.

Design, setting, and participants: Using a multi-institutional cohort from seven tertiary referral centres, we retrospectively identified 510 pT3pN0 patients with undetectable prostate-specific antigen (PSA) after RP between 1996 and 2009. Patients were stratified into two groups: aRT (group 1) versus observation followed by esRT in case of PSA relapse (group 2). Specifically, esRT was administered at a PSA level <0.5 ng/ml.

Intervention: We compared aRT versus observation followed by esRT.

Outcome measurements and statistical analysis: The evaluated outcomes were MFS and OS. Multivariable Cox regression analyses tested the association between groups (aRT vs observation followed by esRT) and oncologic outcomes. Covariates consisted of pathologic stage (pT3a vs pT3b or higher), pathologic Gleason score (<6, 7, or ≥8), surgical margin status (negative vs positive), and year of surgery. An interaction with groups and baseline patient risk was tested for the hypothesis that the impact of aRT versus observation followed by esRT was different by pathologic characteristics. The

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nonparametric curve fitting method was used to explore graphically the relationship between MFS and OS at 8 yr and baseline patient risk (derived from the multivariable analysis).

**Results and limitations:** Overall, 243 patients (48%) underwent aRT, and 267 (52%) underwent initial observation. Within the latter group, 141 patients experienced PSA relapse and received esRT. Median follow-up after RP was 94 mo (interquartile range [IQR] 53–126) and 92 mo (IQR 70–136), respectively (p = 0.2). MFS (92% vs 91%; p = 0.9) and OS (89% vs 92%; p = 0.9) at 8 yr after surgery were not significantly different between the two groups. These results were confirmed in multivariable analysis, in which observation followed by esRT was not associated with a significantly higher risk of distant metastasis (hazard ratio [HR]: 1.35; p = 0.4) and overall mortality (HR: 1.39; p = 0.4) compared with aRT. Using the nonparametric curve fitting method, a comparable proportion of MFS and OS at 8 yr among groups was observed regardless of pathologic cancer features (p = 0.9 and p = 0.7, respectively). Limitations consisted of the retrospective nature of the study and the relatively small size of the patient population.

**Conclusions:** At long-term follow-up, no significant differences between aRT and esRT were observed for MFS and OS. Our study, although based on retrospective data, suggests that esRT does not compromise cancer control and potentially reduces overtreatment associated with aRT.

**Patient summary:** At long-term follow-up, no significant differences in terms of distant metastasis and mortality were observed between immediate postoperative adjuvant radiation therapy (aRT) and initial observation followed by early salvage radiation therapy (esRT) in case of prostate-specific antigen relapse. Our study suggests that esRT does not compromise cancer control and potentially reduces overtreatment associated with aRT.

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1. **Introduction**

Despite the widespread use of prostate-specific antigen (PSA) screening over the last two decades, approximately 25% of contemporary patients treated with radical prostatectomy (RP) for localised prostate cancer (PCa) show locally advanced disease at final pathology in both European and American series [1,2]. These patients often present concomitant adverse pathologic features such as poorly differentiated disease and positive surgical margins, and they are at higher risk of recurrence and cancer-related death [3,4].

Two options essentially can be offered currently to pT3 node-negative PCa patients with undetectable postoperative PSA: immediate adjuvant radiation therapy (aRT) to the prostatic fossa or initial biochemical monitoring followed by early salvage radiation therapy (esRT) before PSA level exceeds 0.5 ng/ml [5,6].

The postsurgical management of these patients still represents a continuous matter of debate. Two main issues may be identified from the current literature. The first one relates to the lack of level-1 evidence in this field. Three randomised clinical trials compared aRT with initial observation in patients affected by locally advanced PCa [7–9]. However, the study design of these historical trials did not systematically include in the observational arm the patients who underwent esRT at a PSA level <0.5 ng/ml. Conflicting results emerged from these trials for the outcomes of metastasis-free survival (MFS) and overall survival (OS). The specific reasons for such a discrepancy might be related to the heterogeneity of patient populations and the lack of defined treatment protocols.

Second, the currently available evidence supporting the oncologic safety of salvage radiation therapy (sRT) is still based on retrospective studies [10–13]. A substantial proportion of patients who received salvage treatment in these retrospective studies had PSA values >0.5 ng/ml, whereas the PSA level at sRT was shown to be an important predictor of oncologic outcomes [14]. In these retrospective studies, the outcome was biochemical recurrence (BCR) following sRT, and the evaluation of hard clinical endpoints, such as clinical recurrence and survival, is still lacking [10–13].

To address these shortcomings, we evaluated MFS and OS at long-term follow-up using a multi-institutional series of pT3pN0 patients who underwent aRT versus initial observation followed by esRT in case of PSA relapse. We hypothesised that aRT was associated with better cancer control and survival compared with initial observation.

2. **Materials and methods**

2.1. **Patient population**

After institutional review board approval, we identified 764 patients treated with RP and pelvic lymph node dissection at seven tertiary referral centres between 1996 and 2009. Retrospective chart reviews were used at four institutions. All patients had histologically confirmed pT3pN0 R0–R1 adenocarcinoma of the prostate. No patient received any neoadjuvant or adjuvant hormonal therapy. All patients had an undetectable postoperative PSA (defined as <0.1 ng/ml).

Patients who were initially observed and then treated with sRT at a serum PSA >0.5 ng/ml were excluded from our analyses (n = 127). Patients with missing information on pathologic stage (n = 24), pathologic Gleason score (n = 47), or surgical margin status (n = 56) were likewise excluded. These selection criteria yielded 510 evaluable individuals with complete clinical, pathologic, and follow-up data.

Patients were stratified into two groups according to the postoperative management: aRT (group 1: n = 243; 48%) versus initial observation followed by esRT in case of PSA relapse (group 2: n = 267; 52%). Specifically, aRT was administered within 6 mo after RP to patients.
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