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CLINICAL INVESTIGATION **Genitourinary Cancer**

OUTCOME AFTER CONFORMAL SALVAGE RADIOTHERAPY IN PATIENTS WITH RISING PROSTATE-SPECIFIC ANTIGEN LEVELS AFTER RADICAL PROSTATECTOMY

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Purpose: **This study attempts to improve our understanding of the role of salvage radiotherapy (SRT) in patients with prostate-specific antigen (PSA) relapse after radical prostatectomy with regard to biochemical control, rate of distant metastasis, and survival.**

Methods and Materials: **We performed a retrospective analysis of 96 men treated with conformal prostate bed SRT (median, 64.8 Gy) at a single institution (median follow-up, 70 months). The majority had intermediate- or high-risk prostate cancer. Fifty-four percent underwent a resection with positive margins (R1 resection). The median time interval between surgery and SRT was 22 months.**

Results: **After SRT, 66% of patients reached a PSA nadir of less than 0.2 ng/mL. However, the 5-year biochemical no evidence of disease rate was 35%. Seminal vesicle involvement was predictive for a significantly lower biochemical no evidence of disease rate. All patients with a preoperative PSA level greater than 50 ng/mL relapsed biochemically within 2 years. The 5-year distant metastasis rate was 18%, the 5-year prostate cancer–specific survival rate was 90%, and the 5-year overall survival rate was 88%. Significantly more distant metastases developed in patients with a PSA nadir greater than 0.05 ng/mL after SRT, and they had significantly inferior prostate cancer–specific and overall survival rates. Resection status (R1 vs. R0) was not predictive for any of the endpoints.**

Conclusions: **Men with postoperative PSA relapse can undergo salvage treatment by prostate bed radiotherapy, but durable PSA control is maintained only in about one-third of the patients. Despite a high biochemical failure rate after SRT, prostate cancer–specific survival does not decrease rapidly.** **© 2012 Elsevier Inc.**

Conformal radiotherapy, Prostate cancer, Biochemical relapse, Salvage treatment, Prognostic factors.

INTRODUCTION

Radical prostatectomy leads to cure in a high proportion of patients with organ-confined prostate cancer treated with this invasive approach (1). In a large fraction of the remaining patients, rising prostate-specific antigen (PSA) levels might indicate that not all cancer cells were removed successfully, often with considerable lead time, *i.e.*, several years before the location of recurrence becomes clinically apparent. If an isolated PSA increase (biochemical relapse) results from recurrence in the prostate bed, salvage radiotherapy (SRT) to this area might result in long-term local control and prevent the development of metastases from locally recurrent tumors. Despite challenges related to patient selection or detection of the true extent of microscopic disease after surgery, several clinical studies suggest that SRT should be considered in selected patients with biochemical recurrence after radical prostatectomy. Initiation of treatment when the cancer burden is low appears prudent because the local control rate depends on the number of cancer cells that must be sterilized by SRT.

Randomized trials in patients with histopathologic adverse risk factors have shown that immediate postoperative radiotherapy (RT) reduces the risk of biochemical recurrence and improves local disease control (2–4). As the data from the randomized trials mature, the impact of postoperative RT on survival continues to be debated (5, 6). When postoperative surveillance is chosen, some patients will become candidates for delayed RT or SRT. In

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Table 1. Patient characteristics (n = 96)

Parameter	Data
Median follow-up (mo) (range)	70 (12–130)
Median SRT dose (Gy) (range)	64.8 (59.4–66.6)
% with SRT dose >64.8 Gy	20
Median interval from prostatectomy to SRT (mo) (range)	22 (3–151)
Median age (y) (range)	65 (37–77)
Median initial PSA value (ng/mL) (range)	11.6 (2.4–220)
Median PSA value before SRT (ng/mL) (range)	0.65 (0.2–4.0)
T stage (%)	
T1	1
T2	39
T3	54
T4	6
Gleason score (%)*	
≤6	28
7	33
8–10	39
Median	7
WHO histologic grade (%)	
1	3
2	63
3	34
% with incomplete resection (positive surgical margin, R1)	54
% with seminal vesicle invasion	25
% with capsule involved	78
% with capsule penetrated	54
% with neoadjuvant endocrine therapy before prostatectomy	10
% with neoadjuvant endocrine therapy before SRT	13 (median duration, 4 mo)

Abbreviations: SRT = salvage radiotherapy; PSA = prostate-specific antigen; WHO = world health organization.

* Twenty-four patients (twenty-five percent) without information. Only the WHO grade is known in these cases.

this setting, data from randomized trials are lacking, and nonrandomized trials question the equivalence of immediate RT and SRT (7, 8). The majority of SRT studies also have limited follow-up and therefore not fully mature survival and toxicity data. These limitations led us to evaluate a single-institution cohort with a median follow-up of 70 months after conformal SRT.

METHODS AND MATERIALS

This retrospective analysis includes 96 men with prostate cancer treated with radical prostatectomy in whom a biochemical relapse had developed and 3-dimensional conformal SRT was performed at the University Hospital of Technische Universität, Munich, Germany. All patients had received a radical prostatectomy as the initial treatment with removal of the prostate and the seminal vesicles. In addition, 86 patients (90%) had had a lymphadenectomy. A biochemical recurrence after radical prostatectomy was defined as an increase in the serum PSA above the postoperative nadir and an absolute PSA value before SRT initiation of 0.2 ng/mL or more. Patients were treated with SRT between December 1993 and December 2002. Inclusion criteria were selected according to Stephenson *et al.* (9): a pre-SRT PSA of 0.2 ng/mL or more and 4.0 ng/mL or less and no adjuvant hormonal therapy after SRT. None of the patients had clinical or radiologic evidence of macroscopic disease at the time of initiating SRT (isotope bone scan, computed tomography [CT] of pelvis and abdomen). We also performed transrectal ultrasound examination in 30% and magnetic resonance imaging of the pelvis in 40%. Patient characteristics are shown in Table 1. Dose was prescribed according to International Commission on Radiation Units & Measurements 50 guidelines. The 95% isodose encompassed the planning target volume, and the maximum dose did not exceed 107% of the prescribed dose. Dose per fraction was 1.8 Gy (77%) or 2.0 Gy (23%). CT scans were used to define the clinical target volume (CTV) based on histology and surgery reports. Target definition was carried out in concordance with the guidelines of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group (10). In case of seminal vesicle involvement, the CTV was expanded to include this area. None of the patients received treatment to the pelvic lymph nodes. The margins added to the CTV to create the planning target volume were 1.0 cm. All patients were treated with 6- to 15-MV photons from a linear accelerator via 4 to 5 individually shaped treatment fields. Treatment planning was carried out with the HELAX TMS planning system (Nucletron, Veenendaal, The Netherlands). Efforts were made to limit the risk of late bladder and rectum toxicity. The CTV could be modified after 50 Gy in patients with a defined area of high risk for residual disease. These boost volumes were based on pathology reports and were applied in situations where the positive margins were confined to the prostatic apex or other regions that could be identified on the planning CT scan while the tumor did not involve the basis of the prostate or seminal vesicles. However, individual decisions about the safety of CTV reduction were made by the treating radiation oncologists.

Biochemical recurrence

A biochemical recurrence after SRT was defined as a PSA value above 0.2 ng/mL. Additional treatment after biochemical failure was at the discretion of the patient's urologist. No uniform criteria for further intervention were applied. The incidence of local and pelvic recurrences after SRT was not consistently assessed.

Statistics

For comparison of dichotomous variables, we used the chi-square test and Fisher exact test, where applicable, and for

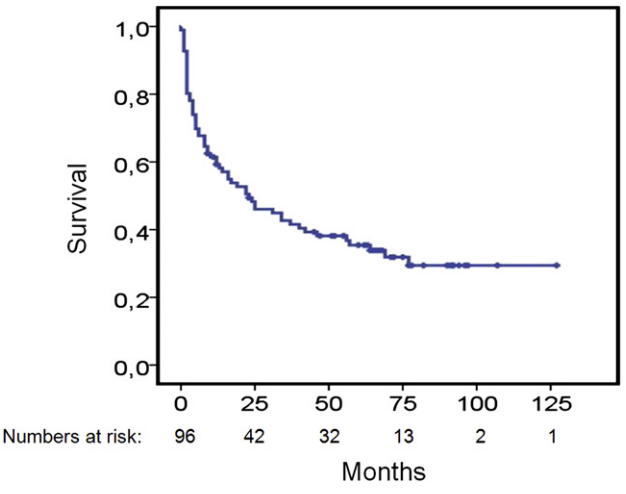

Fig. 1. Actuarial biochemical relapse–free rates (bNED).