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ORIGINAL ARTICLE

Recurrent prostate cancer: the role of salvage postoperative external radiotherapy in low risk patients

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Summary

Purpose: *The aim of this study was to present the Ioannina Radiation Therapy Department experience in the treatment of postoperative recurrent prostate cancer with postoperative external beam radiotherapy (EBRT) in initially low-risk patients for recurrence.*

Patients and methods: *The medical records of all patients who underwent salvage postoperative EBRT for either biochemical or clinical local recurrence were reviewed. Primary endpoints were the incidence of clinical and biochemical recurrences, metastases and death.*

Results: *A total of 11 patients with biochemical recurrence were included. Four of them had clinical local recurrence as well. Postoperatively, all patients had pT1-T2N0M0 stage and therefore had low risk for recurrence. However, they were admitted for EBRT with recurrent disease with a mean pre-RT prostatic specific antigen (PSA) of 10 ng/ml. The daily dose of radiotherapy (RT) was 1.8 to 2.0 Gy and the median total dose was 64.8 Gy. All of the patients but one achieved PSA nadir value (<0.5 ng/ml) after RT. With a median follow up of 21 months (range 9-42 months), 5 (45.5%) patients had biochemical failure, 2 (18.18%) developed clinical local recurrence, one (9.1%) developed bone metastases and 2 (18.18%) died. No serious long-term toxicity was observed.*

Conclusion: *Despite the small sample size of our study that precluded any further analyses on prognostic factors affecting outcomes after salvage EBRT, we achieved satisfactory results regarding local control of disease, metastases and survival.*

Key words: prostate cancer, radical prostatectomy, recurrence, salvage radiotherapy

Indroduction

Prostate cancer is one of the most common malignancies in men. Despite the advances in definite local treatment (radical prostatectomy, RT) during the last years, recurrences occur frequently. The introduction of PSA in the patients' follow up evaluation has led to earlier and more accurate diagnosis of recurrent disease. Biochemical recurrent disease has been suggested as a predictor of an oncoming clinical disease [1-4]. Treatment options for recurrent prostate cancer can be generally divided in two categories according to the type of recurrence. Distant recurrences are mainly managed with androgen deprivation therapy whereas local recurrences are mainly treated with RT. Salvage RT after radical prostatectomy has been widely used therapeutically for a persistently elevated PSA level, a rising postoperative PSA or a clinical local recurrence [5-7].

In this study we present our experience with salvage postoperative EBRT for recurrent prostate carcinoma in postoperatively low-risk patients.

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Patients and methods

The charts of patients with recurrent prostate cancer treated with salvage postoperative EBRT in the

Radiation Therapy Department of the Ioannina University Hospital were reviewed. All of the patients had initially undergone radical prostatectomy for clinically localized prostate cancer (pT1-T2N0M0 stage). Patients were staged according to the International Union Against Cancer TNM staging system [8]. Histologic grading was based on the Gleason scoring system [9].

Patients with postoperative high risk for recurrence, with characteristics such as rupture of the capsule and/or positive margins, extracapsular invasion, invasion of the seminal vesicles and persistently detectable postoperative PSA were excluded from the study. Excluded also were those patients whose clinical data could not be found or was remotely informative. All patients had received hormonal therapy as part of their initial management (before radical prostatectomy). Hormonal therapy consisted of androgen deprivation (anti-androgens and/or LHRH analogues).

Before RT, all of the patients had a detailed clinical examination and blood measurements and all of them underwent a bone scan and computed tomography (CT) of the abdomen and pelvis. All of the patients had a PSA measurement prior to RT. EBRT was given with a linear accelerator (6 MV). A box technique with 4 parallel opposed fields (anteroposterior, posteroanterior and two laterals) was used. All 4 fields were treated on each treatment session. RT was initially administered to the pelvis with an additional boost to the prostatic area after 45 Gy. During RT patients were examined weekly for radiation-induced side effects.

All patients were followed up on an outpatient basis after RT every 3 months for the first 2 years, every 6 months for the 3rd and 4th year, and annually thereafter. Their evaluation included assessment of treatment-related toxicity, a physical examination including rectal examination, full blood count and biochemical analyses including PSA. A chest radiograph and CT of the pelvis and abdomen were performed once a year. Bone scans or skeletal X-rays were obtained on indication. Patients were evaluated for new local recurrence, biochemical failure (biochemical evidence of disease), and distant metastases. A patient was considered to have a new biochemical failure in case of two consecutive measurements of increased serum PSA regardless of the magnitude of the increase. The time between the two PSA measurements required was at least 30 days. The PSA nadir value was defined as the lowest PSA level with a cut-off at 0.5 ng/ml achieved at any time after RT. The follow-up time was calculated from the last day of RT. The time to biochemical relapse was calculated from the last day of RT to the time of the first abnormal PSA value. All of the patients or their families were contacted by phone to provide additional data about their current condition if they did not show up to their last programmed visit.

Endpoints of this study were the incidence of disease progression (local recurrence or metastases), biochemical failure (PSA relapse) and mean survival time of all patients. Kaplan-Meier analysis was used for overall and disease-free survival plots. A p-value <0.05 was considered statistically significant; all p-values were two-tailed. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 10.0 Inc, Chicago IL).

Results

Eleven patients (mean age 73.5 years, range 61-86 years) with recurrence after radical prostatectomy for localized prostate cancer were included in our study. Postoperatively, these patients were classified as pT1-T2N0M0 with low risk for recurrence according to the histological examination and all PSA values were normal. Salvage EBRT was given because of a rising postoperative PSA (biochemical recurrence). Four patients had both biochemical and clinical evidence of local recurrence. No patient presented with metastatic disease on starting EBRT.

Radiotherapy was given within a median time of 36 months (range 8-108 months) after radical prostatectomy. The daily dose was 1.8-2.0 Gy and the median total dose was 64.8 Gy (range 45-68.4 Gy). The mean PSA value before starting RT was 10ng/ml (range 3.2-75 ng/ml). All patients but one achieved PSA nadir value (PSA <0.5ng/ml) after RT. According to Gleason score one patient was of low risk (2-4), 7 patients were of intermediate risk (5-7) and 3 patients were of high risk (8-10). No patient received supplementary brachytherapy or chemotherapy. The main patient characteristics are presented in Table 1.

The median follow up time was 21 months (range 9-42 months). All of the patients tolerated irradiation without interruption of their treatment. Most of them developed acute side effects (diarrhea, cystitis) during RT and were treated conservatively. No serious gastrointestinal or genitourinary late side effects requiring surgical intervention or hospitalization were seen.

Five patients developed biochemical recurrence (45.5%; 95% confidence interval [CI] 16.8-76.6). The mean biochemical relapse-free survival was 19 months (95% CI 13-25). The biochemical disease-free survival is presented in Figure 1. Two of these patients also developed clinical local recurrence (18.18%; 95% CI

Table 1. Patient characteristics

Patient no	*Age (years)*	*Pre-RT PSA (ng/ml)*	*Gleason score*	*Time of RT from surgery (months)*	*DD/ TD (Gy)*	*Follow up (months)*	*Time to PSA nadir (months)*
1	61	8.8	8	12	1.8/64.8	24	1.5
2	80	5.1	5	36	2.0/66.0	9	9
3	74	3.2	6	72	2.0/60.0	20	8
4	76	5.1	8	12	1.8/64.8	11	1
5	69	54.4	5	96	1.8/64.8	42	12
6	86	10	6	24	2.0/64.0	30	2
7	76	75	2	84	2.0/68.0	12	3
8	66	4	8	24	2.0/66.0	21	6
9	72	32.1	7	36	2.0/45.0	39	NA
10	80	12	7	108	2.0/66.0	27	1.5
11	68	10.7	7	48	2.0/64.0	12	2

RT: radiotherapy; pre-RT PSA: PSA value before radiotherapy; DD: RT daily dose; TD: RT total dose; PSA nadir: the lowest PSA level with a cut-off value at 0.5 ng/ml achieved any time after RT; NA: not achieved

2.3-51.8) and 1 patient developed bone metastases (9.1%; 95% CI 0.2-41.3). The mean clinical relapse-free survival was 31 months (95% CI 20-41). The clinical disease-free survival is presented in Figure 2.

Two patients died of disease (18.18%; 95% CI 2.3-51.8). The mean survival time was 37 months (95% CI 31-43 months). The overall survival is presented in Figure 3.

Discussion

Radical prostatectomy has been widely used as an effective treatment of localized prostate cancer. However, the incidence of recurrence remains high varying from 27% to 53% in reported series [6,10-12] despite the improvement in diagnostic methods and surgical techniques. Patients with high risk for recur-

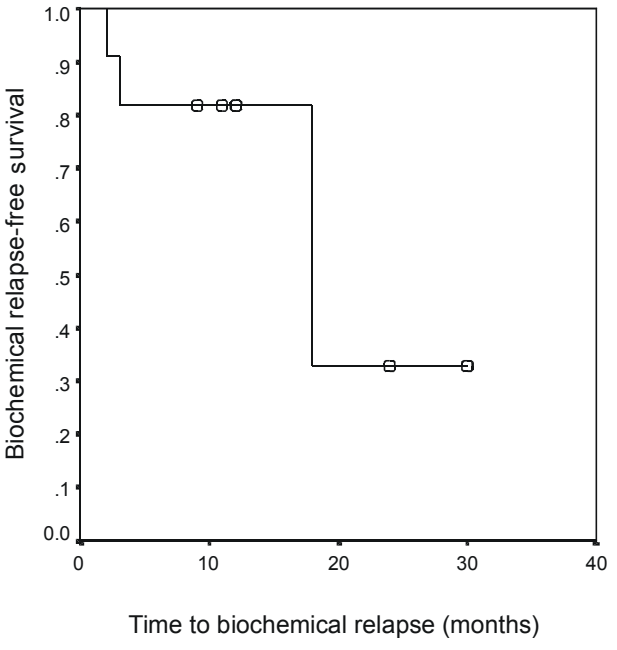

Figure 1. Biochemical relapse-free survival. Squares represent censorings.

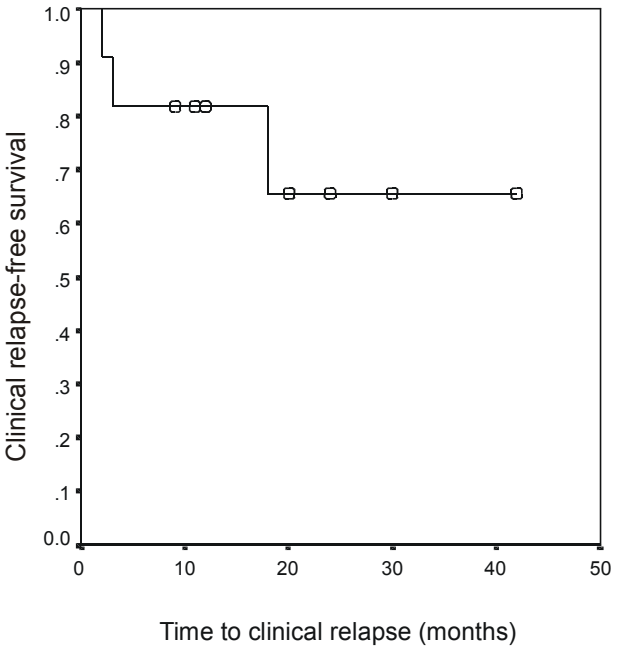

Figure 2. Clinical relapse-free (local recurrence or metastasis) survival. Squares represent censorings.

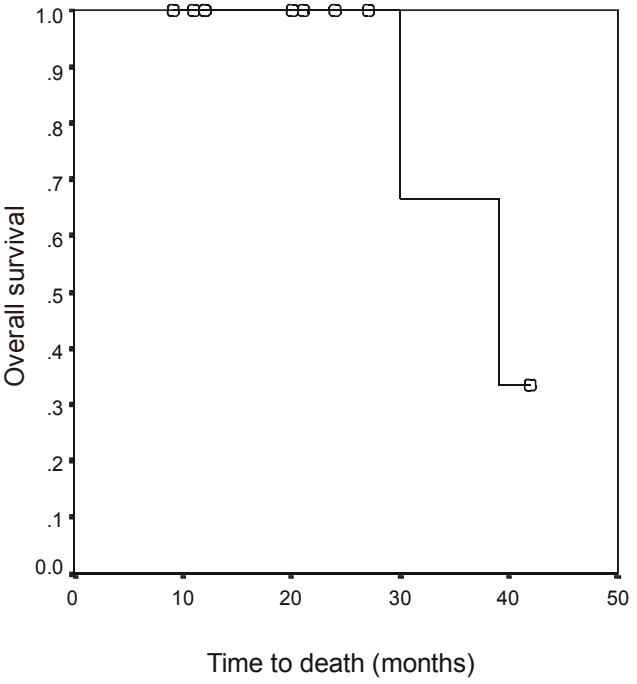

Figure 3. Overall survival. Squares represent censorings.

rence are those with tumor characteristics such as positive surgical margins, seminal vesicle invasion, rupture of the capsule, extracapsular invasion, high Gleason score and persistently detectable postoperative PSA [13-15]. Recurrences of prostate cancer can be divided in 3 categories: biochemical, local and distant. Postoperative EBRT is extensively used as an adjuvant therapy in high-risk patients. Salvage RT is used in patients with evidence of biochemical or clinical local recurrence.

Several retrospective studies from single institutions have tried to compare the efficacy of adjuvant RT with salvage RT [16-18]. These studies suggested that adjuvant RT offers an improvement in the biochemical control of the disease. However, salvage RT has been used as an option for patients with recurrent disease. Salvage RT can be performed in patients with persistently detectable postoperative PSA, delayed PSA failure after initially undetectable postoperative PSA, and in those patients with clinical local recurrence. The efficacy of this modality in each group varies, due to probable different biologic behavior and extension of recurrent disease. Choo et al. [7] evaluated this efficacy and reported that patients with delayed PSA failure had the most favorable outcome. A persistently elevated PSA after radical prostatectomy is considered as an indicator of systemic involvement, and therefore RT offers no benefit in this group of patients [7]. These patients are candidates for androgen deprivation therapy.

However, although salvage RT provides satisfactory local disease control, it remains unclear whether this control corresponds to improved overall and disease-free survival. A number of prognostic factors regarding the efficacy of salvage RT have been reported [5,6,14,19-22]. Among these factors the most commonly suggested are seminal vesicle invasion, Gleason score, preoperative PSA value, pre-RT PSA value, RT dose, interval between surgery and biochemical failure and conjunctive use of androgen suppression.

This study presents our experience with salvage RT for recurrent prostate cancer after radical prostatectomy. All patients had stage T1-T2 N0M0 disease initially, with no characteristics of locally advanced tumors after histological examination (low-risk patients). Despite that our patients had advanced local disease with a mean pre-RT PSA value of 10 ng/ml, we achieved satisfactory outcomes for both local disease control and survival. A pre-RT PSA value of 1-1.5 ng/ml is considered to be the cut-off level for the efficacy of RT. The American Society of Therapeutic Radiology and Oncology recommends salvage RT before a PSA level of 1.5 ng/ml [23]. It has been reported that patients with pre-RT PSA value of 1.2 ng/ml or less were almost twice as likely to be disease-free at 5 years compared with those of higher PSA levels [14]. Our patients could have improved outcomes if they were treated earlier with lower pre-RT PSA levels. The small number of patients included in our study is a limitation that made our results to be considered with caution and precluded any subgroup analyses for predictive factors. Additionally, the role played by hormonal therapy is of unknown significance, given that it was administered as part of the initial management of primary tumors and not for recurrent disease. Other factors such as advanced age, limited follow up and heterogeneity in total radiotherapy dose might have biased our results.

Larger, homogenous and prospective studies should be designed in order to assess the effectiveness of salvage RT for recurrent prostate cancer. Better patient selection and better treatment techniques might achieve improved outcomes in the future. The supplementary use of androgen deprivation therapy might be a weapon upon which prospective therapies should be based for either local control of recurrence and prevention of systemic disease. Finally, the role of biopsy from the prostate bed prior to salvage RT remains unclear and should be a matter for further investigation.

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