Biochemical failure of surgical stage T3N0 prostate carcinoma with or without adjuvant radiotherapy

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Background. *Patients with extracapsular extension or seminal vesicle involvement of prostate adenocarcinoma are known to have a worse prognosis than patients without these adverse features. Multiple studies have assessed the impact of adjuvant postoperative radiotherapy on clinical outcome, but there are fewer studies examining the effect on biochemical (prostate specific antigen or PSA) failure.*

Methods. *This is a retrospective analysis of 100 patients found to have prostate adenocarcinoma extending through the prostatic capsule or involving the seminal vesicles (stage T3) after prostatectomy. Thirty-one patients received adjuvant radiotherapy to the prostatic bed and 69 patients did not receive radiotherapy. Prognostic factors were not evenly distrubuted between the two groups. Mean follow-up was 60 months.*

Results. *Actuarial freedom from PSA failure at 5 and 10 years was 64% and 31%, respectively, in the group that received radiotherapy. For the non-irradiated group, the results for the same endpoint were 55% and 30% at 5 and 10 years (p=.76). The only endpoint analyzed which was significantly improved with adjuvant radiotherapy was clinical local control, which was 95% at 10 years for the radiotherapy group and 65% at 10 years for the non-irradiated group (p=.03). Among patients who received radiotherapy, biochemical failure was similar when comparing patients with or without seminal vesicle involvement. Potency in patients undergoing nerve sparing prostatectomy was not affected by postoperative radiotherapy.*

Conclusions. *Adjuvant radiotherapy after prostatectomy in patients with stage T3 disease significantly reduced the clinical local failure rate, but did not improve the biochemical failure rate or overall survival. The benefit of adjuvant radiotherapy should be tested in clinical trials.*

Key words: prostatectomy; prostatic neoplasms- radiotherapy oncology; prostate-specific antigen; neoplasm staging

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Introduction

Following radical prostatectomy for prostate cancer, one-third to two-thirds of men are found to have disease extending through the prostatic capsule or into the seminal vesicles (stage T3).[1] Clinical failure rates are increased

in these patients compared to those with disease confined to the gland. Radiation therapy (RT) is frequently used as adjuvant therapy in this situation, but its efficacy is controversial. Multiple retrospective studies have examined the effects of adjuvant radiotherapy on clinical failure rates, with most showing improved local control.[2-6] However, most have shown no impact on overall survival. Due to the long natural history of prostatic carcinoma and the high incidence of death from intercurrent disease, it is often difficult to assess the efficacy of treatment. With the advent of prostate specific antigen (PSA) testing, the outcome of treatment modalities in prostate cancer can be evaluated with shorter follow-up and with less influence of intercurrent disease. We present a retrospective case-control analysis of the efficacy of adjuvant radiation therapy in pathologic stage T3 prostatic carcinoma, with special emphasis on biochemical (PSA) outcome.

Materials and methods

Patients

Between January 1, 1974 and January 1 1993, a total of 659 patients underwent radical retropubic prostatectomy for clinically localized prostate cancer by the authors. Surgical techniques have been described previously.[7] Of these, 184 (28%) were pathologic stage T3. Thirty-four of these patients had involvement of pelvic lymph nodes upon pathologic review and are excluded from analysis. Also, fifty patients were excluded who had hormonal therapy before RT or who have less than one year follow-up. The remaining 100 patients with more than 12 months of follow-up and PSA testing available make up the patients included in this study. Sixty-nine patients received no adjuvant treatment. Thirty-one patients received adjuvant radiotherapy to the prostatic bed within 6 months of surgery. Patients were referred for RT according to physician preference. Mean dose was 5700 centigray (cGy) using a four field technique with a megavoltage linear accelerator (6-15 MV). Doses were given in 180-200 cGy fractions, five days a week. No patient received hormonal therapy before clinical failure. Mean follow-up was 60 months for the entire group, with a range of 12 to 168 months. See Table 1 for patient characteristics according to treatment group. Note that more patients in the radiotherapy group had positive margins or seminal vesicle involvement.

Table 1. Patients characteristics

	RT	No RT
Number of patients	#1	69
Mean age	66	65
+ seminal vesicles (%)	21(32)	10(15)
+ margin (%)	26(84)	25(36)
Gleason score >6(%)	11(35)	23(33)

Follow-up

Patients were followed every three months for the first year and then every six months for two more years, then annually. Serum PSA was obtained at every follow-up visit after it became available and was determined by the Hybritech assay. Clinical failure was defined as either local, with recurrent disease noted on rectal examination or computed tomography, and/or distal, with painful metastases confirmed by bone scan. Biochemical (PSA) failure was defined as a persistent PSA above 0.5 ng/ml at least 12 months after the completion of radiotherapy. Prostatic biopsies and bone scans were not routinely performed unless clinical signs of failure were present. Therefore, clinical failure rates could be underestimated. Patients provided subjective information regarding urinary continence and sexual potency, but no objective testing of these functions was performed.

Statistics

Data were analyzed by actuarial analysis using the product-limit method,[8] and subgroups were compared using the Cox-Mantel method.[9] All follow-up times were calculated from the date of surgery. Patients dying with no evidence of disease were censored from analysis of local control, PSA failure, and clinical failure, but not overall survival.

Results

Patients in the radiotherapy group had a significantly improved local control rate, 95% at 5 and 10 years, compared to the non-irradiated group, which had 76% and 65% local control at 5 and 10 years as seen in Figure 1 (p=.03). When analyzing local and distant clinical failure rates, the radiotherapy group had a better outcome (84% and 62% vs. 62% and 42% at 5 and 10 years), but the results were not statistically significant (p=.15). Overall survival was also not significantly different between the two groups, with the 10 year survival rates being 64% in the radiotherapy group and 47% in the non-irradiated group (p=.83). Freedom from biochemical (PSA) failure is shown in Figure 2. Again, no difference is noted between the radiotherapy patients, with PSA control of 64% and 31% at 5 and 10 years, and the non-irradiated patients, with 55% and 30% PSA control at 5 and 10 years (p=.76). See Table 2 for a summary of actuarial results.

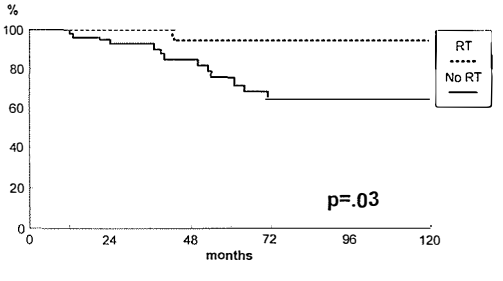

Figure 1. Local control in pathologic stage T3 prostate cancer with or without adjuvant radiation therapy (RT).

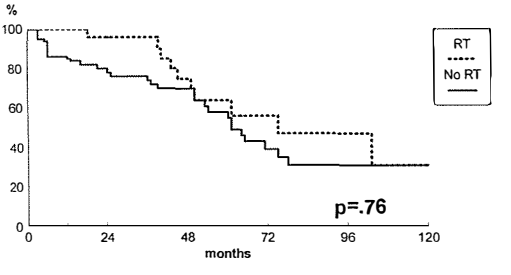

Figure 2. Freedom from biochemical (PSA) failure in patients with pathologic stage T3 prostate cancer with or without adjuvant radiation therapy (RT).

Seminal vesicle involvment did not predict for increased PSA failure in the radiotherapy group (Figure 3). In the non-irradiated group, there were only 10 patients with seminal vesicle involvement, but they did not have a significantly worse outcome, compared to those patients without seminal vesicle involvement. Margin status also was not a significant factor

Table 2. Actuarial results

	Local contol (%)*	Local +/- distal control (%)	Overall survival (%)	PSA control (%)
RT				
5 yrs	95	84	92	64
10 yrs	95	62	64	31
No RT				
5 yrs	76	62	97	55
10 yrs	65	42	47	30

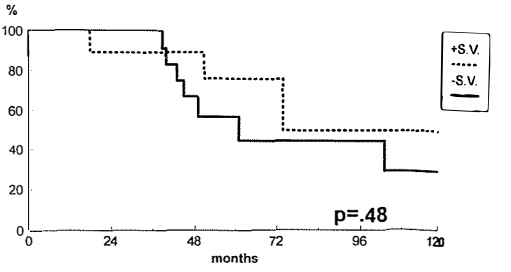

Figure 3. Freedom from biochemical (PSA) failure in patients with pathologic stage T3 prostate cancer receiving radiation therapy according to seminal vesicle (SV) involvement.

in the radiotherapy group, but the number of negative margin patients was small.

Complications were acceptable, with both groups having three patients with urethral stricture requiring dilatation. Significant long-term incontinence occurred in less than five percent of patients in both groups. Five of nine patients (55%) who had unilateral or bilateral nerve sparing prostatectomy in the radiotherapy group are able to obtain erections significant for intercourse. This is similar to the non-irradiated patietns, with 11 of 21 (52%) maintaining potency. There were no treatment related deaths. More detailed surgical complications have previously been reported.[7]

Discussion

Due to the inaccuracy of clinical staging techniques for prostate cancer, we are frequently faced with the dilemma of how to manage patients found to have extracapsular extension or seminal vesicle involvement after prostatectomy. Multiple retrospective studies have assessed the impact of adjuvant radiotherapy on the clinical outcome of these patients.[2-6] Most show improvement in local control rates with adjuvant radiotherapy to close to 100% compared to 75-85% without radiotherapy. However, these studies have shown no significant improval in survival. Due to the long natural history of prostate cancer and the high rate of death from intercurrent disease, it is difficult to assess the efficacy of treatment modalities with respect to survival. With the introduction of PSA testing, outcome of treatment can be determined with shorter follow-up and with less effect of intercurrent disease. This is one of the few reports analyzing the PSA failure rates after postprostatectomy radiotherapy for stage T3 disease. We found a statistically signifcant difference in local control in the two groups, but not in biochemical failure. Overall survival and clinical disease free survival had 17% and 20% differences, respectively, between the two groups, but these differences were not statistically significant due to small patient numbers and short follow-up. The increased percentage of patients with poor prognostic factors in the radiotherapy group, such as positive margins and positive seminal vesicles, could have also biased the results in favor of the no RT arm.

Stein *et al.*[10] at UCLA reported on twenty-four patients who received adjuvant radiotherapy for pathologic stage T3 disease found at prostatectomy and 91 patients who had no further treatment. This study found a statistically significant difference in freedom from PSA failure, with 75% in the radiotherapy group free of PSA failure at 5 years versus 43% without PSA failure in the non-irradiated patients ($p<.043$). Median follow-up was 43 months. In this study, the radiotherapy group had more patients with positive seminal vesicles, but fewer patients with capsular invasion or positive margins. In our study, all poor prognostic factors were higher in the radiotherapy group and this could have contributed to the fact that no improvement in freedom from PSA failure was seen.

Freeman *et al.*[11] found a freedom from PSA failure of 66% at 5 years in 95 patients with pathologic stage T3 disease after postoperative radiotherapy. Zietman *et al.*[12] had similar

results of 64% PSA control at 5 years in sixty-eight patients with similar surgical findings. Both of these studies found that failure rates were higher in patients with seminal vesicle involvement. Our study showed no difference in PSA failure based on seminal vesicle involvement, but a larger number of patients may be necessary to demonstrate this difference. Jacobson *et al.*[3] found that clinical local control improved from 70% to 100% if postoperative radiotherapy was added to patients with seminal vesicle involvement.

A few studies have examined the freedom from PSA failure in patients undergoing prostatectomy without adjuvant therapy. Robinow *et al.*[13] reported a freedom from PSA failure of only 37% at 3 years in forty-one patients with pathologic stage T3 disease. They noted an increased failure rate in patients with positive margins, whose PSA control was only 34%, compared to patients with only capsular invasion or seminal vesicle involvement. Frazier *et al.*[14] noted a 51% freedom from PSA failure in 124 patients with pathologic stage T3 disease, but the data were not analyzed actuarially, so the true PSA failure rate may be higher. Comparing these data with those of studies using adjuvant radiotherapy show a trend toward improved biochemical control with postoperative radiotherapy, at least at 5 years. However, follow-up is short in most of these studies and longer follow-up is needed to determine if this represents a true improvement in survival or just a delay in progression of disease. As seen in our study, the difference in biochemical failure seen at 5 years was no longer seen at 10 years. Nevertheless, deferring the morbidity of relapse seems worthwhile, especially since it has been shown that adjuvant radiotherapy is much more effective when there is only microscopic disease present, as opposed to after clinical recurrence.[15] A prospective intergroup study is currently open and randomizes patients with stage T3 disease to adjuvant radiotherapy or no further therapy.[16] This study should provide important information on this controversial topic.

Since some patients with pathologic stage T3 prostate cancer do not fail without adjuvant therapy, there has been interest in treating patients with radiotherapy only if the PSA is detectable postoperatively or increases after being undetectable postoperatively.[17,18] McCarthy *et al.*[18] reported that patients who were treated with adjuvant radiotherapy for delayed PSA elevation had a PSA control rate (68%) as high as those treated immediately postoperatively (67%). Patients with persistently detectable PSA levels after prostatectomy had a significantly lower biochemical control rate, with only 33% having a persistent undetectable PSA (p=.0008). These results suggest that adjuvant radiotherapy may be delayed until PSA levels rise in patients with undetectable PSA after prostatectomy, but longer follow-up is needed.

Early analysis of complications in our study shows no significant difference in the radiotherapy and non-irradiated groups. This has been shown in other studies.[2-6] Freeman *et al.*[11] analyzed morbidity extensively in their adjuvant radiotherapy study and compared the findings to the morbidity of patients they treated with prostatectomy alone. Eighty-eight percent of patients in both groups had urinary control or only mild stress incontinence. Urinary stricture rates were also similar in the two groups. However, in the postoperative radiotherapy group, only 18 percent of patients retained potency sufficient for intercourse after unilateral or bilateral nerve sparing prostatectomy, compared to a 46% potency rate for patients not receiving radiotherapy. In our study, postoperative radiotherapy did not decrease potency.

In conclusion, adjuvant radiation therapy for pathologic stage T3 prostate cancer significantly improves clinical local control rates in this and other studies. Early PSA follow-up demonstrates a trend toward improved biochemical control rates with adjuvant radio-

therapy, but this may not persist with longer follow-up. A prospective, randomized trial is currently investigating this clinical dilemma, and should provide valuable information. The optimal timing of radiation therapy has yet to be determined, as it may be possible to treat patients with equal success only when PSA rises after it has been undetectable postoperatively. Complications of adjuvant radiotherapy are acceptable.

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