Post Radical Prostatectomy Adjuvant Radiation in Patients with Seminal Vesicle Invasion - A Historical Series

E. Z. Neulander[1], K. Rubinov[2], W. Mermershtain[2], Z. Wajsman[3]

[1] *Department of Urology, Soroka UMC, Ben Gurion University, Beer Sheva, Israel*

[2] *Department of Oncology, Soroka UMC, Ben Gurion University, Beer Sheva, Israel*

[3] *Department of Urology, University of Florida, Gainesville, Florida, US*

Abstract

Introduction and Objectives. The reported rate of seminal vesicles invasion in RP series varies between 6-26%. Invasion of seminal vesicles by adenocarcinoma of the prostate is considered an adverse prognostic factor and consequently patients are at high risk of cancer recurrence after radical prostatectomy. The reported biochemical recurrence free rates at 5 years after RP are between 5-60% (median 30%). The aim of this paper is to assess the role of postoperative radiation in patients with seminal vesicle (SV) invasion after radical prostatectomy (RP).

Materials and Methods. From a database of 500 consecutive patients who underwent RP at the University of Florida, sixty two (12%) were diagnosed with seminal vesicle invasion. All patients underwent adjuvant radiation (RT). Median age was 65 (range 48-77), median pre RP PSA was 15 ng/ml (range 4.3-91). Median pre RT PSA was 0.2 ng/ml (range 0.1 – 19 ng/ml). The PSA cut off value signifying serological failure after RP was ≥ 0.4 ng/ml. Median follow up was 56 months (range 12-104).

Results. Thirty three patients (53%) relapsed serologically. Median time to PSA failure was 34 months (range 1-75). One patient (1.6%) died of metastatic prostate cancer. Pre RT PSA was the most significant prognostic factor with respect to serological failure (p=0.003). Perineural invasion (PNI) was also found as statistically significant prognostic factor (p=0.05). Pre operative PSA, pathological Gleason score, extra capsular cancer extension in addition to SV invasion (ECE) and positive surgical margins were not found to be significant prognostic factors with respect to PSA failure.

Conclusions. When analyzed in the light of other reports in the literature, the present study suggests that adjuvant radiation given in pT3c patients that have undetectable PSA after RP, the PSA recurrence rate at 5 years is lower than that of patients treated with RP alone.

Key-words: radical prostatectomy, radiation, seminal vesicle invasion

Correspondence to: Dr. Endre Z. Neulander M.D.
Department of Urology, Soroka UMC, Ben Gurion University
Be'er Sheva, code 8499000, Israel
Tel: +972 8 646 1600
E-mail: endre@bgu.ac.il

Introduction and Objectives

The reported rate of seminal vesicles invasion in RP series varies between 6-26% [1, 2]. Invasion of seminal vesicles by adenocarcinoma of the prostate is considered an adverse prognostic factor and consequently patients are at high risk of cancer recurrence after radical prostatectomy. The reported biochemical recurrence free rates at 5 years after RP are between 5-60% (median 30%) [2].

Seminal vesicle invasion was shown to be a significant predictor of local relapse and also of distant metastases (3, 4). Biopsy proven local recurrence may range as high as 30% with advanced pathological stages [5].

It is obvious that the majority of these patients cannot be cured by a single modality of therapy and consequently a multimodality treatment approach seems warranted. Post RP RT was shown to decrease local recurrence in parallel with biochemical failure in patients with high risk of recurrence based on their adverse post RP pathology [6].

We analyzed the role of adjuvant RT in sixty twoconsecutive patients who underwent RP at the University of Floridaand on the final pathology were diagnosed as having SV invasion.

Materials and Methods

From a database of 500 consecutive patients who underwent RP between 1989 and 1997at the University of Florida, 62 (12%) were diagnosed with SV invasion. Median age was 65 (range 48-77). Median preoperative PSA was 15 ng/ml (range 4.3–91 ng/ml). Nine patients (14.5%) had non palpable cancer on DRE, clinical stage T1c, at the time of diagnosis.

The same pathologist reviewed the postoperative specimen slides (WMM).

Seminal vesicle invasion was defined as tumor invading the muscular layer of the seminal vesicle outside the prostate [2].

Preoperative diagnosis was made by digital rectal examination (DRE); serum PSA and transrectal ultrasound (TRUS) guided prostate biopsies. All 52 patients with palpable tumors (85.5%) received three months of neoadjuvant hormone therapy with LH-RH analogs. Three – four months after RP Adjuvant RT was administered 3-4 months after RP using 64 cGy administered in either a four field box or a three dimensional conformal radiation technique. No pelvic boosts were administered. Patients did not receive androgen ablation after RP.

After surgery, patients were followed with serum PSA every 4 months for the first two years and every six months after that. Criteria for treatment failure were serum PSA ≥ 0.4 ng/ml, or clinical failure defined as palpable local recurrence or bone metastases on nuclear scan [7].

Statistical analysis

The chi square test was used to assess the significance of the difference between several subgroups of patients. The Univariate log-rank test was utilized to assess the effect on progression of the prognostic variables. The Logistic regression analysis was used for the multivariate statistical analysis of the prognostic variablesfound to be significant by univariate analysis.

Results

Median follow up was 56 months (range 12 –104 months). Six patients (9.8%) developed bone metastases during follow up. Four patients (6.5%) died during follow up, one of them (1.6%) due to metastatic prostate cancer. The overall recurrence rate was 53.2% (33 patients). Median time to progression was 34 months (range 1 – 75 months).

Of the 33 (53.2%) patients that had PSA recurrence, 6 patients (9.2%) had also DRE detectable local recurrence.

Table 1 summarizes the distribution of patients according to prognostic variables, PSA recurrence rates and the corresponding statistical significance.

Median pre RP PSA for the entire group was 15 ng/ml (range 4.3-91). Preoperative PSA was not found as a prognostic factor in our patient population.

Thirty six patients (58%), had pre RT PSA < 0.4 ng/ml. PSA recurrence in these patients was 33% vs. 81% in patents with pre RT PSA ≥ 0.4 ng/ml (p=0.003, Table 1 and Fig. 1).

Figure 1: Biochemical recurrence rate in pT3c pts. according to the pre RT PSA (p=0.003)

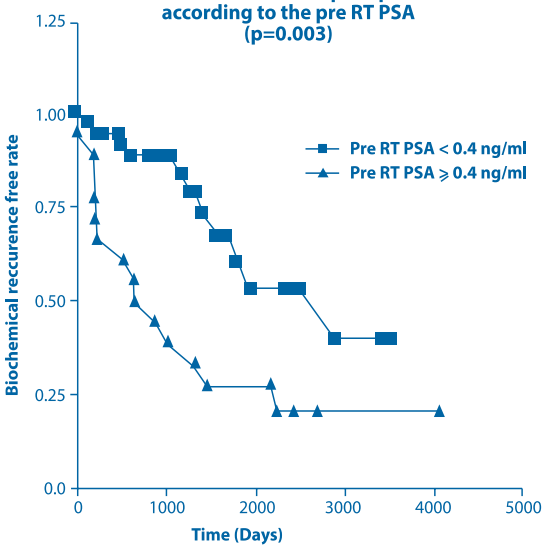


Table 1. Distribution of patients according to prognostic variables and PSA failure rates; perineural invasion (PNI); extra capsular extension (ECE)

		Number of pts. (%)	Number relapsed (%)	P Value
Pre op. PSA	≤10 ng/ml	14 (22%)	7 (50%)	
	> 10-20	26 (42.5%)	14 (54%)	
	> 20 ng/ml	22 (35.5%)	12 (54.5%)	
Pre RT PSA	< 0.4	36 (58%)	12 (33%)	0.003
	≥ 0.4	26 (42%)	21 (81%)	
	< 1	48 (77.5%)	19 (41.5%)	0.0001
	≥ 1	14 (22.5%)	14 (100%)	
Gleason score	6	7 (11%)	5 (71.5%)	
	7	20 (32%)	13 (65%)	
	≥ 8	35 (57%)	15(43%)	
ECE	negative	21 (34%)	13 (62%)	
	positive	41 (66%)	20 (49%)	
Surgical margins	negative	28 (45%)	13 (46.5%)	
	positive	34 (55%)	20 (59%)	
PNI	negative	26 (42%)	10 (38%)	0.05
	positive	36 (58%)	23 (64%)	

If RT was administered at a PSA ≥ 1 ng/ml, the PSA recurrence rate was 100% (Table 1 and Fig. 2, p=0.0001).

Perineural invasion was detected in 58% of the post RP pathology specimens. PSA recurrence was detected in 64% of these patients vs. 38% if perineural invasion was not present (Fig. 3, p= 0.05).

Figure 2: Biochemicalrelapse rate according to pre RT PSA in pT3c pts(p=0.0001)

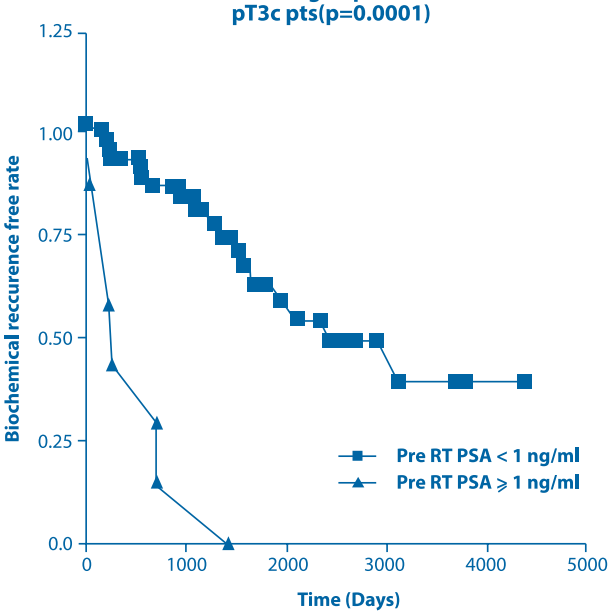
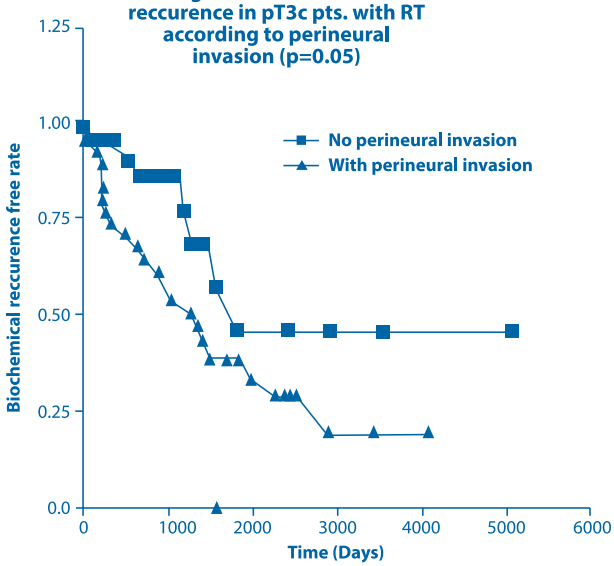


Figure 3: Biochemical reccurence in pT3c pts. with RT according to perineural invasion (p=0.05)



Seven patients (11%) had Gleason score 6 on the final pathology specimen, while 32% and 57% had Gleason scores of 7 and ≥ 8 respectively. Gleason score was not found as prognostic factor in our group of patients.

Extra capsular extension (ECE) of cancer (in addition to seminal vesicle invasion) was diagnosed in 66% of the patients, while 55% of all patients had positive surgical margins after RP. ECE and positive surgical margins were not found to represent a significant prognostic factor in our patient group.

Multivariate logistic regression analysis revealed that the most important prognostic factor with respect to PSA failure was the pre RT PSA. Patients who had persistently elevated PSA after RP, had significantly worse biochemical outcome than patients in whom after surgery PSA became undetectable (Fig. 1 and 2).

Radiation related complications: four patients (6.5%) suffer from chronic grade 2-3 proctitis, while three patients (5%) from grade 2-3 radiation cystitis. The grade and rate of stress incontinence was not significantly impacted upon by adjuvant radiation, 15% of the patients having some degree of urinary incontinence after RP.

Discussions

SV invasion represents an adverse prognostic factor in patients with radical prostatectomy. Many authors report that at 5 years follow up, roughly 1/3 of patients with SV invasion, are PSA recurrence free, if RP is the single treatment form [1, 8]. Given the high biochemical recurrence rate in these patients complementary treatment forms are warranted.

In our study, the PSA recurrence free rate, for patients with undetectable PSA after RP, was roughly 70% at 5 years follow up, significantly better than in patients in whom PSA did not become undetectable after surgery (19%) and significantly better than the recurrence rates reported in the literature with RP alone.

Early post RP radiation in patients with seminal vesicle invasion was addressed previously by Valicenti et al. At 3 years follow up the PSA recurrence rate was 52% in patients with persistently elevated PSA after RP and treated with adjuvant radiation. Patients with undetectable PSA after RP had only 16% PSA failure rate at 3 years after adjuvant RT. Patients not radiated had a 52% PSA failure rate. The authors' conclusion was that adjuvant RT in patients with seminal vesicle invasion and undetectable PSA after RP may be justified [9].

Our data concurs at 5 years follow up with the same trend reported by Valicenti et al at 3 years. Longer follow up however, is necessary in order to draw conclusions regarding the overall and cancer specific survival.

Other, additional prognostic factors such as Gleason score, preoperative PSA, and tumor volume may further subcategorize pT3c patients in different recurrence risk groups.

The presence of perineural invasion in prostate needle biopsy was recognized previously as an adverse prognostic factor for patients undergoing radiation, while PNI in the pathology specimen is a negative prognostic factor in patients undergoing RP [10, 11, 12]. In our study, on univariate analysis, the presence of perineural invasion was found as an adverse prognostic factor for biochemical failure (Fig. 3).

The presence of extra capsular extension (ECE) of tumor in addition to seminal vesicle invasion was not associated with higher rates of PSA relapse in our group. Wheeler et al demonstrated that ECE correlates with higher tumor volume [13]. Soloway et al reported worse biochemical failure rates in patients having high tumor volume together with SV invasion in the RP specimen. Their data was on patients that did not receive RT after RP [1].

According to several authors postoperative RT reduces PSA failure rates in patients with ECE and positive SM [14]. Since our patients received adjuvant RT, this may explain the lack of prognostic significance of ECE and surgical margin status in our patient population.

We did not find Gleason score as a significant prognostic factor in our group of patients. Soloway et al explain the same finding in their patient population, with the fact that the majority ofpatients were harboring Gleason grade 4. Their experience correlates with ours; 90% of our patients had Gleason score ≥ 7 and consequently the majority of our patients had Gleason grade ≥ 4 in their pathology [1].

We did not find preoperative PSA as being a prognostic factor in our patient population. This has been reported previously. Fair et al found no difference in the outcome of patients receiving neoadjuvant HT with preoperative PSA < 10 ng/ml and patients presenting with PSA ≥10 ng/ml (15). Brandli et al showed that preoperative PSA had no prognostic significance in patients undergoing RP with preoperative PSA 20 – 100 ng/ml (16). Naguchi et al demonstrated that in patients with large volume of carcinoma of prostate, pre RP PSA does not reflect PSA failure rates after RP [17].

Fifty two of our patients (85%) received neoadju-

vant HT before RP. This may represent a potential criticism of our results. However, Soloway et al demonstrated recently that there was no difference in their study between patients with SV invasion who did or did not receive HT before RP (1).

Adjuvant radiation has been shown previously of being safe and with minimal impact on the original post prostatectomy continence rate.

Chronic grade 2-3 proctitis and cystitis developed in roughly 6% of our patients. It is probable that with the advent of the three dimensional conformal radiation and intensity modulation techniques, these complication rates could be reduced.

Conclusions

Based on the present studyand other reports in the literature we may conclude that patients with seminal vesicle invasion after RP may benefit form adjuvant radiation if their PSA becomes undetectable after surgery.

We advocate adjuvant radiation in patients with seminal vesicle invasion and undetectable PSA after RP.

Longer follow up is needed in order to assess the impact of post RP RT on cancer specific survival rate in these patients.

References

1. Sofer M, Savoie M, Kim SS, Civantos F, Soloway MS.: *Biochemical and pathological predictors of the recurrence of prostatic adenocarcinoma with seminal vesicle invasion.* J Urol. 2003 Jan;169(1):153-6.
2. Epstein JI, Partin AW, Potter SR, Walsh PC: *Adenocarcinoma of the prostate invading the seminal vesicle: prognostic stratification based on pathologic parameters.* Urology. 2000 Aug 1;56(2):283-8.
3. Byar DP, Mostofi FK.: *Carcinoma of the prostate: prognostic evaluation of certain pathologic features in 208 radical prostatectomies. Examined by the step-section technique.* Cancer. 1972 Jul;30(1):5-13.
4. Anscher MS, Prosnitz LR.: *Radiotherapy vs. hormonal therapy for the management of locally recurrent prostate cancer following radical prostatectomy.* Int J RadiatOncolBiol Phys. 1989 Nov;17(5):953-8.
5. Zietman AL, Shipley WU, Willett CG.: *Residual disease after radical surgery or radiation therapy for prostate cancer. Clinical significance and therapeutic implications.* Cancer. 1993 Feb 1;71(3 Suppl):959-69. Review.
6. Do LV, Do TM, Smith R, Parker RG.: *Postoperative radiotherapy for carcinoma of the prostate: impact on both local control and distant disease-free survival.* Am J ClinOncol. 2002 Feb;25(1):1-8.
7. Andrew J. Stephenson, Michael W. Kattan, James A. Eastham, Zohar A. Dotan, Fernando J. BiancoJr,HansLilja, and Peter T. Scardino: *Defining Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy: A Proposal for aStandardized Definition.* J ClinOncol 24:3973-3978. © 2006
8. Tefilli MV, Gheiler EL, Tiguert R, Banerjee M, Sakr W, Grignon DJ, Pontes JE, Wood DP Jr.: *Prognostic indicators in patients with seminal vesicle involvement following radical prostatectomy for clinically localized prostate cancer.* J Urol. 1998 Sep;160(3 Pt 1):802-6.
9. Valicenti RK, Gomella LG, Ismail M, Mullholland SG, Petersen RO, Corn BW.: *Pathologic seminal vesicle invasion after radical prostatectomy for patients with prostate carcinoma: effect of early adjuvant radiation therapy on biochemical control.* Cancer. 1998 May 15;82(10):1909-14.
10. D'Amico AV, Wu Y, Chen MH, Nash M, Renshaw AA, Richie JP. *Perineural invasion as a predictor of biochemical outcome following radical prostatectomy for select men with clinically localized prostate cancer.* J Urol. 2001 Jan;165(1):126-9.
11. Anderson PR, Hanlon AL, Patchefsky A, Al-Saleem T, Hanks GE.: *Perineural invasion and Gleason 7-10 tumors predict increased failure in prostate cancer patients with pretreatment PSA <10 ng/ml treated with conformal external beam radiation therapy.* Int J RadiatOncolBiol Phys. 1998 Jul 15;41(5):1087-92.
12. Endrizzi J, Seay T.: *The relationship between early biochemical failure and perineural invasion in pathological T2 prostate cancer.* BJU Int. 2000 Apr;85(6):696-8.
13. Wheeler TM, Dillioglugil O, Kattan MW, Arakawa A, Soh S, Suyama K, Ohori M, Scardino PT. *Clinical and pathological significance of the level and extent of capsular invasion in clinical stage T1-2 prostate cancer.* Hum Pathol. 1998 Aug;29(8):856-62.
14. Valicenti RK, Gomella LG, Perez CA.: *Radiation therapy after radical prostatectomy: A review of the issues and options.* SeminRadiatOncol. 2003 Apr;13(2):130-40.
15. Fair WR, Betancourt JE: *Update on Memorial Sloan-Kettering Cancer Center studies of neoadjuvant hormonal therapy for prostate cancer.* Mol Urol. 2000 Fall;4(3):241-8; discussion 249-50.
16. Brandli DW, Koch MO, Foster RS, Bihrle R, Gardner TA.: *Biochemical disease-free survival in patients with a high prostate-specific antigen level (20-100 ng/mL) and clinically localized prostate cancer after radical prostatectomy.* BJU Int. 2003 Jul;92(1):19-23.
17. Noguchi M, Stamey TA, McNeal JE, Yemoto CM.: *Preoperative serum prostate specific antigen does not reflect biochemical failure rates after radical prostatectomy in men with large volume cancers.* J Urol. 2000 Nov;164(5):1596-600.