Post Radical Prostatectomy Radiation in Intermediate and High Risk Group Prostate Cancer Patients - A Historical Series

E. Z. Neulander[1], Z. Wajsman[2]
[1] *Department of Urology, Soroka UMC, Ben Gurion University, Beer Sheva, Israel*
[2] *The Department of Urology, University of Florida, Gainesville, FL*

Abstract

Introduction and Objectives. According to the NCCN, patients with carcinoma of prostate can be categorized based on their initial PSA, clinical stage and Gleason score in three groups according to their risk of definitive treatment failure. The aim of this paper is to report on the outcome of patients with intermediate and high risk of recurrence who underwent radical prostatectomy (RP).

Materials and Methods. Eighty-five consecutive patients categorized as intermediate (17.5%) and high risk (82.5%) of failure after definitive therapy for carcinoma of prostate according to the National Comprehensive Cancer Network (NCCN) underwent RP between 1989 and 1997. Median preoperative PSA was 26 ng/ml (range 15 ng/ml - 91 ng/ml). Fifty-nine patients (70%) received 3 months neoadjuvant hormone therapy. Thirty-six patients (42%) underwent early (3-4 months after RP) adjuvant radiation for pT3 disease and/or positive surgical margins.

Results. The median follow-up was 58 months (range 12 - 104 mos.). There was no difference in the biochemical recurrence rate between the intermediate and high risk group of patients. The overall relapse rate was 33%. Cancer specific mortality was 3.5%. Patients with T1c tumors had a significantly lower biochemical recurrence rate (bRR) (7%) compared to palpable tumors (p=0.03). Age above 65 was a significant negative prognostic factor with respect to biochemical recurrence (p=0.01). Adjuvant radiation was associated with biochemical recurrence rates of 25% vs. 40% in patients who were not radiated. (p=0.05).

Conclusions. In the intermediate and high risk group of patients with nonpalpable prostate cancer, RP and adjuvant RT may provide a biochemical recurrence free rate (bRFR) comparable to that reported in other series with RP alone on patients in the low risk groups. We encourage the multimodality treatment approach incorporating adjuvant postoperative radiation in these patients.

Key-words: prostate cancer, radical prostatectomy, recurrence, radiation therapy

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

According to the NCCN, patients with carcinoma of prostate can be categorized based on their initial PSA, clinical stage and Gleason score in three groups according to their risk of definitive treatment failure. Patients with initial PSA between 10 – 20 ng/ml or Gleason score 7 or clinical stage T2b are considered having intermediate risk of treatment failure. Patients with PSA > 20 ng/ml, or cT3 or Gleason score ≥ 8 are considered as having high chance for failing definitive therapy. (1) (Ref Scardino)

Patients with PSA > 20 ng/ml have a 60-80% biochemical recurrence rate 5 years after either RP or RT. (2 Klein) Stamey showed that patients with peripheral zone cancers with PSA > 15 ng/ml have a low chance of biochemical recurrence-free status. (3, 4)

Materials and Methods

Eighty-five consecutive patients 15 (17.5%) in the intermediate risk group and 70 (82.5%) in the high risk group underwent RP between 1989 and 1997. Median serum PSA at diagnosis was 26 ng/ml (range 15 – 91 ng/ml). The median age of these patients was 63 years (range 47-75 years).

Preoperative diagnosis was made by digital rectal examination (DRE); serum PSA and transrectal ultrasound (TRUS) guided prostate biopsies.

Fifty nine patients (70% of the whole patient population) had palpable tumors and received three months of neoadjuvant hormone therapy with LH-RH analogs. Thirty six patients (42%) with positive surgical margins and /or extracapsular extension underwent adjuvant radiation therapy (RT) three – four months after RP with 64 cGy administered in 36 sessions using either a four - field box or three dimensional conformal technique.

After surgery, patients were followed with serum PSA every 4 months for the first two years and every six moths after that. Criteria for treatment failure were detectable serum PSA (PSA < 0.4 ng/ml), palpable local recurrence or bone metastases on nuclear scan. (5)

Statistical analysis

The chi square and the log-rank test were used to assess the significance of the difference between several subgroups of patients and to assess the effect on progression of the prognostic variables.

Results

Median follow up was 58 months (range 12 –104 mos.). Three patients (3.5%) died of metastatic prostate cancer. The overall progression rate was 33 % (28 patients). Median time to biochemical progression was 27 months (range 4 – 75 mos.). Six patients (7%) had DRE detectable local and biochemical recurrence, while 22 patients (26%) experienced only biochemical recurrence. Tables 1 and 2 summarize the distribution of the patients according to the risk groups, prognostic variables, relapse rates and statistical significance.

	Patient number	Relapse/%	P value
PSA 15-20 ng/ml	15 (17.5%)	6 (40%)	
Gleason score 6	9 (60%)	4 (44%)	
Gleason score 7	6 (40%)	2 (33%)	
cT1c	4 (26.5%)	0	P= 0.03
cT2	11 (73%)	6 (54.5%)	

Table 1: Fifteen patient with intermediate risk of recurrence: PSA 15-20 ng/ml, or/and Gleason score ≤ 7 and/or localized prostate cancer on digital rectal examination. The distribution of patients according to the preoperative prognostic factors and the corresponding PSA failure rates are presented.

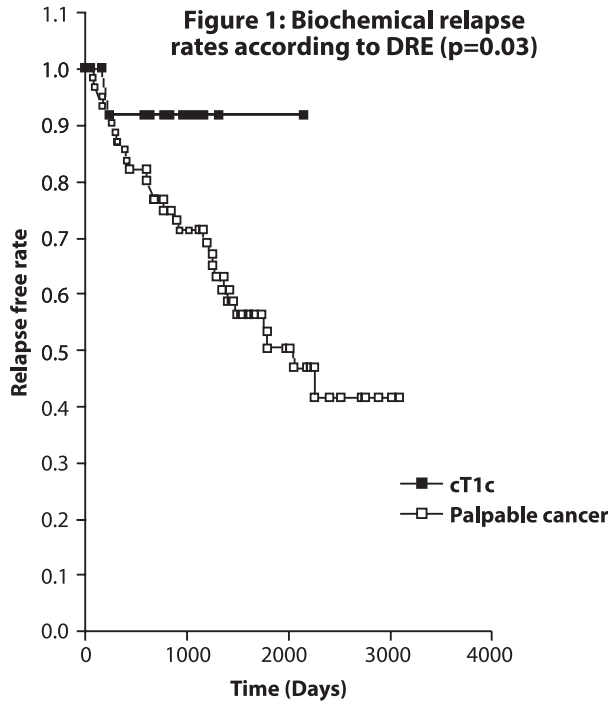
		Patient number	Relapse	P value
PSA	<20ng/ml	19 (27%)	7 (37%)	
	≥20ng/ml	51 (73%)	16 (31%)	
Gleason score	6	17 (24%)	9 (53%)	
	7	14 (20%)	2 (14%)	
	≥8	39 (55.7%)	12 (31%)	
Clinical stage	cT1c	10 (14%)	1 (10%)	P= 0.03
	cT2	37 (52.8%)	11 (30%)	
	cT3	23 (32.8%)	11 (48%)	

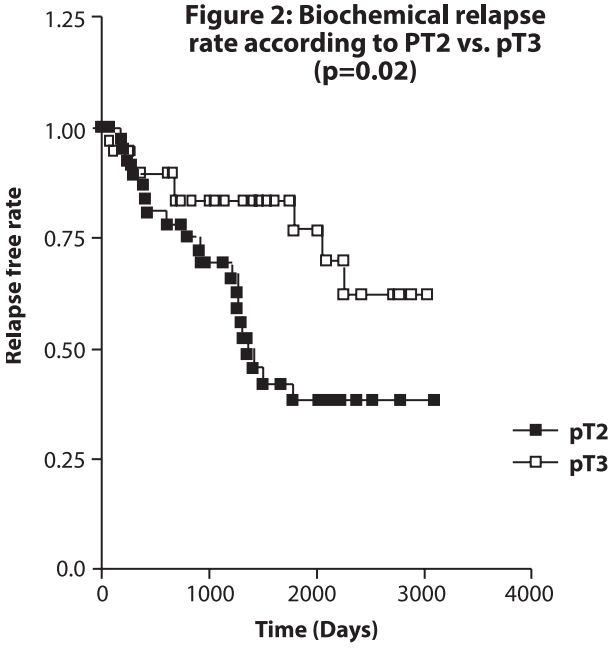
Table 2: Seventy patients with high risk for relapse: PSA > 20 ng/ml, and/or Gleason score ≥ 8 and/ or clinical stage cT3. The distribution of patients according to the preoperative prognostic factors and the corresponding PSA failure rates are presented.

Serum PSA at diagnosis was not found to be a significant predictor of biochemical recurrence after therapy.

We found no difference in the progression rates between patients in the intermediate and the high risk group.

Patients with cT1c (non palpable) cancers had significantly lower biochemical recurrence rates compared to patients with palpable cancer (7% vs. 33%, Figure 1, p = 0.03).





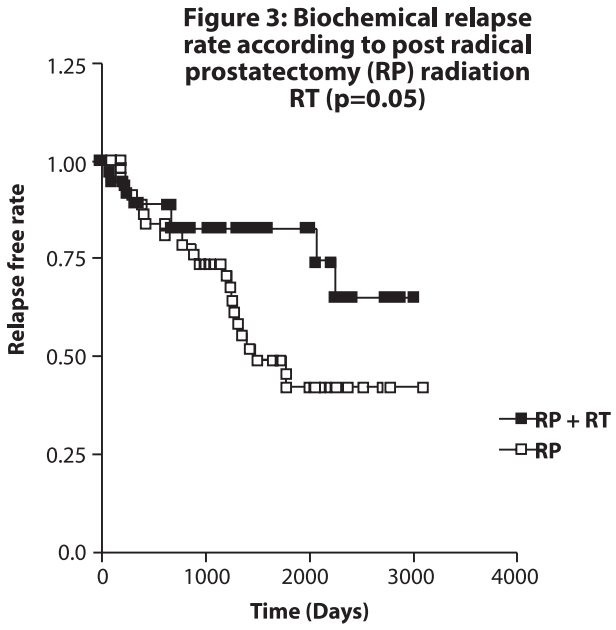
Patients in the pT2 group had higher relapse rate (51%) than the patients with extra capsular extension (pT3a-b = 6%), (p=0.02, Figure 2).

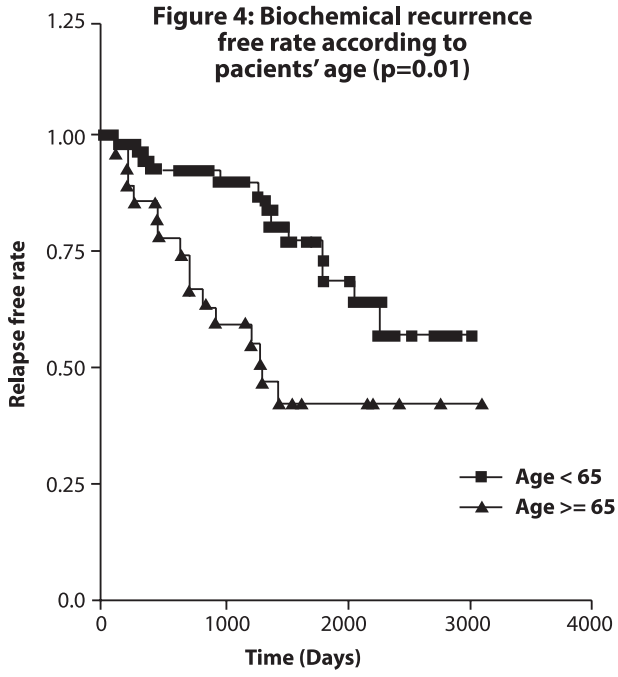
Patients with Gleason score 6 had significantly higher relapse rates compared to patients with Gleason score ^{3} 7. (p=0.005). Gleason score 6 also correlated significantly with pT2 pathological stage. (r = 0.25, p = 0.01)

Patients with seminal vesicle invasion had a PSA recurrence rate of 40 % without having prognostic impact on biochemical recurrence in this group of patients.

Twenty three patients (27%) had positive surgical margins (+SM). Positive surgical margins were not associated with a higher biochemical relapse rate.

Thirty six patients (42 %) were treated with adjuvant postoperative radiation. Overall, there was a statistically significant difference in the biochemical recurrence rate in the favor of patients who received adjuvant radiation (9/36 patients = 25% recurrence rate) compared to those who did not (19 /49 patients = 40% recurrence rate, p=0.05, Figure 3).





Patients with age above 65 at the time of RP were found to have a statistically significant higher biochemical relapse rate compared to younger patients. (p=0.01, Figure 4).

Discussions

Categorizing patients in risk groups according to the chances of failing therapy, based on clinical staging, Gleason score and initial PSA, helps in terms of unifying prognostic factors and possibly reaching more valid conclusions when comparing different series and treatment forms.[1]

The chances for biochemical relapse free status with PSA > 15 – 20 ng/ml are remote according to some authors.[2, 3, 4] Hanks et al concluded that RT alone is not an optimal therapy for the patients with high risk prostate cancer. Only 28 % of his patients with PSA > 20 ng/ml were biochemical relapse free at four years of followup. A multimodality approach was therefore suggested as appropriate in these cases and the importance of local control was emphasized.[5] Moul et al reporting on prostate cancer patients with initial PSA > 40 ng/ml, who underwent RP with or without adjuvant therapy, concluded that RP alone is unlikely to cure these patients and that a multimodality therapeutic approach is warranted incorporating HT and postoperative radiation.[6]

D'Amico et al showed that patients with high risk carcinoma of prostate treated with definitive radiation have 60% chance of PSA relapse if pre RT PSA is 10 ng/ml. Patients in the high risk group, who fail RT have a 50% chance of dieing from carcinoma of prostate in the next 5 years.[7]

Scardino et al reported an actuarial 5 year biochemical recurrence free rate of 50% after RP in patients with preoperative PSA = 20 - 100 ng/ml and clinically localized disease.[8]

In our study, we found no difference in terms of PSA recurrence between the intermediate and the high risk group of patients. The intermediate risk group represented only 17.5% of the patient population and this may be a possible criticism of the paper.

The overall PSA recurrence free rate was roughly 70% matching the over all biochemical recurrence rate at 5 years reported in the literature on all patients selected for RP.

PSA at diagnosis was not found as a prognostic factor with respect to biochemical recurrence.

This has been reported previously. Brandli et al showed that preoperative PSA had no prognostic significance in patients undergoing RP with preoperative PSA 20 – 100 ng/ml.[9] 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.[10]

Patients with nonpalpable prostate cancer, cT1c had a biochemical recurrence rate significantly lower (7%) compared to patients with palpable cancers (cT2 - 33% and cT3 - 48%, p=0.03), and compared to other reported series. (8) The majority (60%) of T1c patients had pathological extracapsular disease and consequently received adjuvant radiation which may account for the low PSA failure rate.[11]

The relapse rate for the pT3a-b cases in the present study was only 6%. All of these patients in our series received adjuvant radiation, fact that may explain the lower PSA relapse rate.[11]

The relapse rate of patients with seminal vesicle invasion (pT3c) was 40%, comparable to other published results with RP alone.[12]

The relapse rate in the pT2 group in our study was 51% surprisingly higher than in the pT3 group. This phenomenon has been previously reported by Zincke et al on patients with Gleason score ≥ 8 who underwent RP with and without adjuvant therapy.[13]

One possible explanation for this phenomenon, is the fact that 92% of the pT2 patients in our group were initially palpable cancers on DRE and received neoadjuvant HT. It is conceivable that the use of neoadjuvant HT resulted in a pathological "down staging" and consequently, none of the pT2 patients received RT, fact that may account for the higher relapse rate in this group of patients.[14)]

Conclusions

This is a retrospective study and consequently it suffers the criticism of such a report. In spite of these facts, we were able to point out some significant facts.

1. Patients with extra capsular tumor extension treated with adjuvant postoperative radiation had a biochemical relapse rate comparable to that of patients with organ - confined disease in other reported series.

2. Neoadjuvant HT may hamper the optimal pathological staging and consequently it may deprive some patients of adjuvant RT.

3. Patients with life expectancy of 10-15 years (age 65 or less), with non palpable prostate cancer did significantly better in terms of biochemical relapse, when compared to the rest of the patients in spite of the fact that most of them were in the high risk group. In these patients the 5 year PSA relapse free status matches the results on low risk patients reported on in other series.

RP is a feasible therapeutic option in high risk patients with carcinoma of prostate. None of the patients had their cancer volume evaluated in the final pathologic specimen and since cancer development is a continuous sometimes geometrically volume increasing process, older patient may have had larger volume of cancers and consequently did worse than younger patients with the same characteristics, except the cancer volume that was not analyzed.

4. We encourage the use of a multimodality treatment approach, incorporating adjuvant radiation after RP in these patients.

5. We also suggest that in young patients the level of pre treatment serum PSA should be used carefully and selectively as a contraindication for RP.

References

1. Scherr D, Swindle PW, Scardino PT.: *National Comprehensive Cancer Network guidelines for the management of prostate cancer.* Urology. 2003 Feb;61(2 Suppl 1):14-24.
2. Klein EA: *Radiation therapy versus radical prostatectomy in the PSA era: An urologist's view.* Sem. Rad Onc, Vol 8 (2): 87-94, 1998
3. Masanori M, Stamey TA, McNeal JE, et al: *An analysis of 148 consecutive transitional zone cancers: Clinical and histological characteristics.* J Urol, Vol. 163, 1751 – 1755, 2000.
4. Stamey TA, Yemoto CM, McNeal JE, et al: *Prostate cancer is highly predictable: Prognostic equation based on all morphological variables in radical postatectomy specimens.* J Urol, Vol. 163, 1155 – 1160. 2000
5. Andrew J. Stephenson, Michael W. Kattan, James A. Eastham, Zohar A. Dotan, Fernando J. Bianco Jr, Hans Lilja, and Peter T. Scardino: *Defining biochemical recurrence of prostate cancer after radical prostatectomy: A proposal for a standardized definition*. J Clin Oncol 24:3973-3978. © 2006
6. Vanasupa BP, Paquette EL, Wu H, Sun L, McLeod DG, Moul JW.: *The role of radical prostatectomy in patients with pretreatment prostate-specific antigen > or = 40 ng/mL.* Urol Oncol. 2002 Jul-Aug;7(4):167-72.
7. D'Amico AV, Cote K, Loffredo M, Renshaw AA, Chen MH.: *Pretreatment predictors of time to cancer specific death after prostate specific antigen failure.* J Urol. 2003 Apr;169(4):1320-4.
8. Gillioglugil O, Leibman BD, Kattan MW, et al: *Hazard rates for progression after radical prostatectomy for clinically localized prostate cancer.* Urology, Vol. 50: 03-99, 1997.
9. 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.
10. 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.
11. Valicenti RK, Gomela LG, Ismail M, et al: *The efficacy of early adjuvant radiation therapy for pT3N0 prostate cancer: A matched pair analysis.* Int. J. Radiation Oncology Biol. Phys., Vol. 45 (1); 53 – 58, 1999.
12. Valicenti RK, Gomela LG, Ismail M, et al: *Pathologic seminal vesicle invasion after radical prostatectomy for patients with prostate carcinoma.* Cancer, Vol 82; 1909 – 1914, 1998.
13. Lau WK, Bergstralh EJ, Blute ML, Slezak JM, Zincke H.: *Radical prostatectomy for pathological Gleason 8 or greater prostate cancer: influence of concomitant pathological variables.* J Urol. 2002 Jan;167(1):117-22.
14. Soloway MS, Sharifi R, Wajsman Z, et al: *Randomized prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded by androgen blockade in clinical stage B2 (T2bNxM0) prostate cancer.* J Urol, Vol. 154, 424 – 428, 1995.