

Original contributions

Radical prostatectomy in patients with preoperative prostate specific antigen 15ng/ml and higher

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Objective. To report on the outcome of patients who underwent radical prostatectomy (RP) with preoperative PSA ≥ 15 ng/ml.

Methods. Eighty-five consecutive patients with PSA ≥ 15 ng/ml (median 26 ng/ml, range 15–126 ng/ml) underwent RP between 1989 and 1997. Patients with palpable cancer 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 2 – 104 mos.). The overall relapse rate was 33%. Six patients (7%) died during follow up, three due to metastatic prostate cancer. Patients with T1c tumors had a significantly lower recurrence rate than those with palpable (cT2 and cT3) cancer ($p=0.03$). Age above 65 was found to be a significant negative prognostic factor with respect to biochemical recurrence ($p=0.01$). Adjuvant radiation was associated with significantly lower biochemical recurrence rates compared to patients who were not radiated. ($p=0.05$).

Overall, the preoperative PSA level was not found to have prognostic significance with respect to the biochemical recurrence in this group of patients. However, in patients with seminal vesicle invasion (pT3c) patients with biochemical recurrence had a significantly higher preoperative PSA ($p=0.05$).

Conclusions. In selected patients with nonpalpable prostate cancer and with preoperative PSA ≥ 15 ng/ml (median 26 ng/ml) RP is a feasible treatment option. In young patients with prostate cancer, the level of serum PSA should be used selectively as a contraindication for RP. If extra capsular tumor extension is diagnosed in these patients we encourage a multimodal treatment approach incorporating adjuvant postoperative radiation.

Radykalna prostatektomia u chorych z wysokim przedoperacyjnym poziomem PSA (>15ng/ml)

Cel. Ocena wyników leczenia radykalną prostatektomią (RP) chorych, z przedoperacyjnym wysokim poziomem PSA (15 ng/ml).

Materiał i metoda. W okresie 1989–1997, 85 chorych z poziomem PSA ≥ 15 ng/ml (mediana 26 ng/ml, przedział 15–126 ng/ml) zostało poddanych RP. Chorzy z palpacyjnie wyczuwalnym guzem stercza otrzymali 3 miesięczną neoadjuwantową hormonoterapię. U 36 chorych (42%) zastosowano wczesną (w okresie 3–4 miesięcy) adjuwantową radioterapię, ze względu na stopień zaawansowania pT3 i/lub stwierdzenie dodatnich marginesów chirurgicznych.

Wyniki. Mediana obserwacji wyniosła 58 miesięcy (2–104). Nawrót choroby wystąpił u 33% chorych. 6 chorych (7%) zmarło w okresie obserwacji, 3 wskutek raka stercza z przerzutami. U chorych z guzami T1c obserwowano znacząco niższy odsetek nawrotów ($p=0,03$), niż w grupie chorych z guzem wyczuwalnym w przedoperacyjnym badaniu per rectum (cT2 i cT3). Wiek powyżej 65 lat okazał się być znaczącym negatywnym czynnikiem prognostycznym w odniesieniu do odsetka nawrotów biochemicznych ($p=0,01$). U chorych uzupełniająco napromienianych obserwowano znacząco niższy odsetek nawrotów biochemicznych w porównaniu do chorych, u których nie stosowano radioterapii ($p=0,05$). Wykazano, że przedoperacyjny poziom PSA nie miał istotnego znaczenia prognostycznego w odniesieniu do częstości nawrotów biochemicznych w analizowanej grupie chorych. Jakkolwiek, chorzy z zajęciem pęcherzyków nasiennych (pT3c), u których znacznie częściej obserwowano nawroty biochemiczne, mieli znacząco wyższy poziom przedoperacyjnego PSA ($p=0,05$).

Wnioski. U wybranych chorych z niewyczuwalnym palpacyjnie w badaniu per rectum rakiem stercza i przedoperacyjnym poziomem PSA ≥ 15 ng/ml (mediana 26 ng/ml), radykalna prostatektomia może stanowić opcję terapeutyczną. U młodych cho-

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rych z rakiem stercza, przedoperacyjny poziom PSA w surowicy nie powinien sam w sobie stanowić przeciwwskazania do RP. W przypadku stwierdzenia raka przekraczającego torebkę stercza, autorzy polecają wielodyscyplinarne postępowanie, z wykorzystaniem radioterapii uzupełniającej.

Key words: PSA, radical prostatectomy, radiotherapy

Słowa kluczowe: PSA, radykalna prostatektomia, radioterapia

Introduction

In spite of PSA screening, 15 % of the prostate cancer patients are diagnosed with a PSA >20 ng/ml [1-4]. Patients with PSA >10 ng/ml, with non-palpable or localized prostate cancer are good candidates for either RP or RT [1]. Patients with higher (>20 ng/ml) PSA have a 60-80% biochemical recurrence rate 5 years after either RP or RT [5]. Stamey showed that patients with peripheral zone cancers with PSA above 15 ng/ml have a low chance of biochemical recurrence -free status [6, 7]. There is no consensus in terms of what level of PSA should be considered a contraindication for RP.

Material and methods

From a database of 500 consecutive patients who underwent RP between 1989 and 1997 at the University of Florida, eighty-five patients with serum prostate specific antigen (PSA) \geq 15 ng/ml at diagnosis, (median 26 ng/ml, range 15-126 ng/ml) were reviewed. The median age of these patients was 63 years (range 47-75 years). Median PSA of patients with PSA \geq 15 ng/ml who underwent RP between 1989-1992 was 31ng/ml (range 15-126) compared to 20 ng/ml (range 15-90) in patients operated between 1993-1997. Patients with extreme values of PSA were operated according to the patient's decision after appropriate informed consent based on literature data available at that time.

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

Patients with palpable tumors received three months of neoadjuvant hormone therapy with LH-RH analogs. After RP, patients with positive surgical margins and extracapsular extension received adjuvant radiation therapy with 64 Gy administered in 36 sessions using a four – field technique, three – four months after RP.

Patients with positive lymph nodes (8 patients = 9.5 %) received long term HT.

The same pathologist reviewed the postoperative specimen slides. (WM) After surgery, the 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: detectable serum PSA, biopsy proven and /or palpable local recurrence or bone metastases on nuclear scan. At the time of biochemical failure, patients were started on hormone therapy (continuous or intermittent), while patients who did not receive adjuvant RT and suspected of having local failure received salvage radiation therapy.

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 Cox proportional hazard estimate and the Logistic regression analysis were used for the multivariate statistical analysis of the prognostic variables found to be significant by the univariate analysis. [8]

Results

85 consecutive patients were reviewed. The median follow up was 58 months (range 2-104 mos.). Three patients (3.5%) died of metastatic prostate cancer. The overall progression rate was 33 % (28 patients). The median time to 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. Table I summarizes the distribution of the patients according to the prognostic variables and relapse rates.

The recurrence rates according to different clinical stages are illustrated in Table I and in Figure 1. Patients with T1c cancers had significantly lower biochemical recurrence rates compared to patients with palpable cancer ($p = 0.03$) (7% vs. 33%). The biochemical recurrence rates corresponding to the pathological stages are illustrated in Table I and Figure 2. Strikingly, the patients in the pT2 group had higher relapse rate (51%) than the patients with extra capsular extension (pT3a-b = 6%), ($p=0.02$, Table I and Figure 2).

Table I. The distribution of patients according to PSA, clinical stage (cT), pathological stage (pT), specimen Gleason score (pGI) and median age. The values marked with asterisk have statistical significance

		Patient number (%)	Relapse (%)	P value
PSA	15-20	36 (42%)	14 (39%)	
	21-40	25 (30%)	6 (24%)	
	>40	24 (28%)	8 (33%)	
cT	T1c	14 (16.4%)	1 (7%)*	P=0.03
	T2	48 (56.4%)	16 (33%)	
	T3	23 (27.2%)	11 (48%)	
pT	PT2	37 (43.5%)	19 (51%)*	P=0.02
	PT3a, b	16 (23.5%)	1 (6%)*	
	PT3c	20 (23.5%)	8 (40%)	
	PT4	4 (5%)	0%	
	N+	8 (9.5%)	0%	
pGI	\leq 6	27 (32%)	12 (45%)*	P=0.01
	7	21 (25%)	5 (23%)	
	\geq 8	37 (43%)	11 (30%)	
Age	\leq 65	46 (54%)	11 (24%)*	P=0.01
	>65	39 (46%)	17 (43.5%)	

The pT3c group (seminal vesicle invasion) had a relapse rate of 40%. Within the pT3c-group, 16 patients (75 %) received adjuvant radiation. Eight (50%) of these

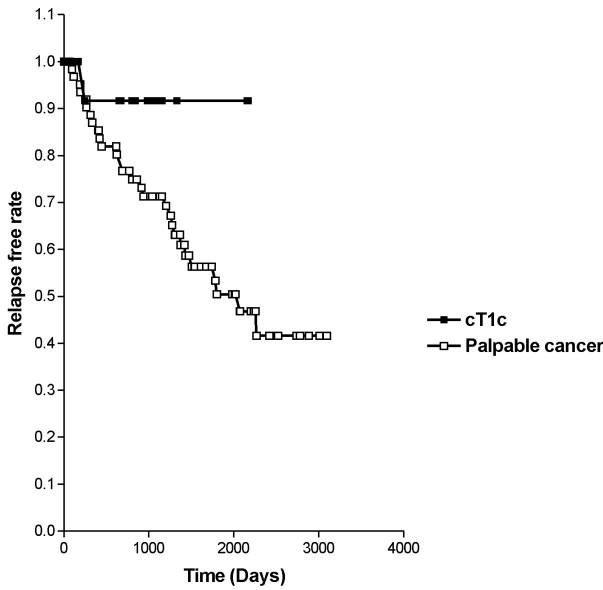


Figure 1. Biochemical relapse rates according to DRE ($p=0.03$)

patients relapsed. The mean preoperative PSA of the pT3c patients who recurred was significantly higher than that of the patients who did not (44 ng/ml vs. 27 ng/ml, $p=0.05$).

None of the patients with pT4 disease relapsed. However, the group is very small (four patients) and consequently has no statistical power.

Overall, 23 (27%) patients had positive surgical margins (+SM). Positive surgical margins were not associated with a higher biochemical relapse rate.

36 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 compared to those who did not ($p=0.05$, Figure 3). The preoperative PSA was not statistically different in these two groups (29 ng/ml versus 21 ng/ml).

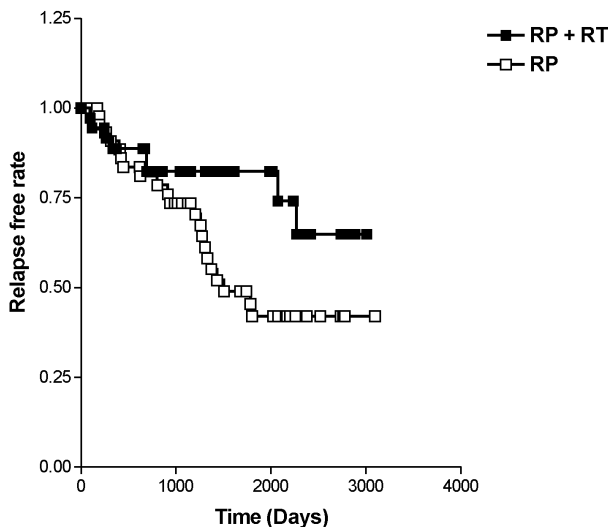


Figure 3. Biochemical relapse rate according to post radical prostatectomy (RP) radiation (RT) ($p=0.05$)

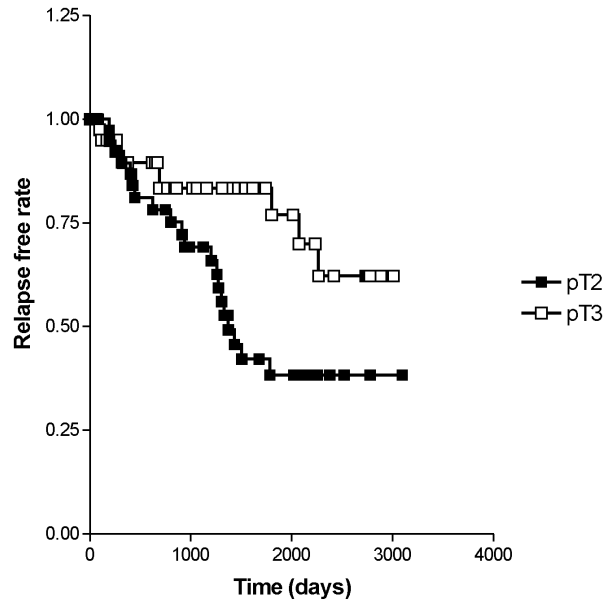


Figure 2. Biochemical relapse rate according to pT2 vs. pT3 ($p=0.02$)

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).

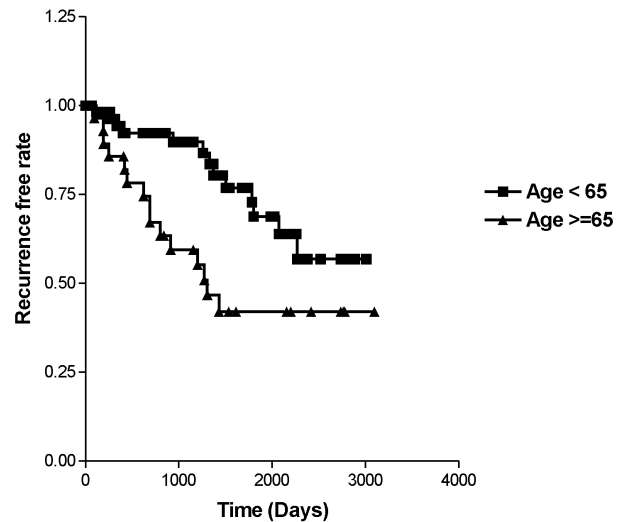


Figure 4. Biochemical recurrence free rate according to patients' age ($p=0.01$)

There was a significantly higher relapse rate in patients with Gleason score 6 in comparison to the patients with Gleason score ≥ 7 . ($p=0.01$, Figure 5). Also, Gleason score 6 was found more frequently in pT2 patients (correlation coefficient, $r = 0.25$, $p = 0.01$). As stated before, the pT2 stage group also had higher biochemical relapse rate than the rest of the patients.

The multivariate logistic regression and Cox proportional hazard estimate analysis failed to identify any particular individual prognostic factor within the factors identified as statistically significant by the univariate analysis.

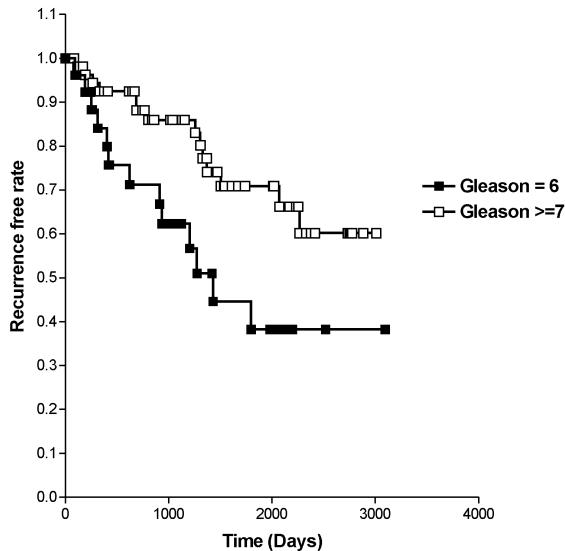


Figure 5. Biochemical recurrence rate according to Gleason score ($p=0.01$)

Discussion

Serum PSA is an important prognostic variable in patients with prostate cancer [1]. The chances for biochemical relapse free status with PSA >15-20 ng/ml are remote according to some authors, and consequently RP may not be justified [4, 5].

On the other hand, Hanks et al. also concluded that RT alone is not an optimal therapy for the patients with high PSA. Only 28 % of his patients with PSA >20 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 [2].

Scardino et al. reported an actuarial 5 year biochemical recurrence free rate of 50 % after RP in patients with preoperative PSA = 20-100 and clinically localized disease [10].

In the present study, the overall biochemical relapse rate was 33 %, significantly lower than in the Scardino et al. data [10].

Patients with nonpalpable prostate cancer had a biochemical recurrence rate significantly lower (7%) compared to patients with palpable cancers (cT2 – 33% and cT3 – 48%, $p=0.03$). The distribution of PSA was not significantly different within the different clinical stages. The majority (60%) of T1c patients had pathological extracapsular disease and consequently received adjuvant radiation. The biochemical relapse rate of the patients with nonpalpable prostate cancer was significantly lower than in other reported series [10].

The relapse rate for the pT3a, b cases in the present study was only 6 %, comparable to the data published by Valicenti et al. on patients with pT3 stage but with lower preoperative PSA [11]. Seventy percent (70%) of the pT3a, b patients, (11/16) received adjuvant radia-

tion with 64Gy, a fact that may explain this low relapse rate [12].

The relapse rate of patients with seminal vesicle invasion (pT3c) was 40%, comparable to other published results [13].

The relapse rate in the pT2 group in our study was 51% (19/37 patients), surprisingly higher than in the pT3 group. It is conceivable that the use of neoadjuvant HT in 92 % (34/37 patients) of the pT2 patient group resulted in a pathological „down staging” [14]. Consequently, none of the pT2 patients received any RT [15].

Conclusions

This is a retrospective study and consequently it suffers the drawbacks of such a report. It also contains data on patients with preoperative PSA that nowadays would refrain many urologists from any curative therapeutic attempt. In spite of these facts, we were able to point out some significant conclusions.

Overall, preoperative PSA (median 26 ng/ml) had no prognostic significance in the present study, however, in patients with seminal vesicle invasion preoperative PSA correlated significantly with the biochemical relapse rate.

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

Neoadjuvant HT may hamper the optimal pathological staging and consequently it may deprive some patients of adjuvant RT if such an approach is contemplated.

Patients under the age of 65, with cT1c prostate cancer did significantly better in terms of biochemical relapse, when compared to the rest of the patients. RP may be a feasible therapeutic option in these patients. We encourage the selective use of a multimodality treatment approach, incorporating adjuvant radiation after RP.

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

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Paper received: 10 April 2002

Accepted: 2 May 2002