NOWOTWORY Journal of Oncology • 2003 • volume 53
Number 2• 142–149

Original papers

Radical prostatectomy with and without adjuvant radiotherapy for pT3N0 prostate cancer

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Purpose: From 30 to over 50% of patients with cancer of the prostate (CaP) are found at surgery (RP) to have more advanced disease. Postoperative irradiation (RT) has been systematically investigated for patients with pT3N0 tumors and its value is presented in this report.
Patients and methods: A total of 622 pT3N0 CaP patients were treated with RP. Of these, 199 (32%) with lower risk factors received RP alone while 423 (68%) with higher risk factors received a planned postoperative RT (median 48 Gy). These higher prognostic factors included clinical stage, p=0.001, pathological stage, p=0.001, preoperative PSA level, p<0.0001, and Gleason score, p=0.18. Median follow up for all patients was 7 years.
Results: The 5- and 10-year actuarial survival was 92 and 73%, respectively for RP+RT patients and nearly identical for those in RP alone group, p=0.73. The 5-and 10-year disease-free survival (DFS) (PSA<0.05 ng/ml) was 69 and 51%, respectively for the former and 71 and 60%, respectively for the latter group. There was no significant difference in DFS between the two treatment groups by pathologic stage and Gleason score, p=0.77. Preoperative PSA <10 vs. 10-25 vs. >25 ng/ml did not influence overall survival but PSA >25 ng/ml was predictive of DFS, p=0.02. In multivariate analysis Gleason score was the most important predictor for overall and DFS survival, p=0.00002 while pathologic stage was predictive of clinical recurrence and DFS, p<0.00001. Patients who had RP alone experienced a similar incidence of local failure as RP-RT patients who had significantly worse prognostic factors. Postoperative RT was well tolerated and did not add to the incidence of surgical complications.
Conclusions: We hypothesize that planned postoperative RT helped to reduce the expected incidence of local recurrence and improved DFS to equal that of a lower risk patients treated with RP alone.

Radykalna prostatektomia z – lub bez – adiuwantową radiotreapią u chorych na raka prostaty w stopniu zaawansowania pT3N0

Cel pracy. Podczas wykonywania radykalnej prostatektomii u 30-50% chorych stwierdza się wyższy, niż zakładano wstępnie, stopień zaawansowania choroby nowotworowej. Celem niniejszej pracy jest przedstawienie wyników leczenia chirurgicznego, uzupełnionego o pooperacyjną radioterapię u chorych z rakiem prostaty w stopniu pT3N0.
Materiał i metody. 622 chorych z rakiem prostaty w stopniu pT3N0 poddano radykalnej prostatektomii (RP). U 199 (32%) spośród nich stwierdzono mniej istotne czynniki ryzyka i ograniczono leczenie tylko do postępowania chirurgicznego, u pozostałych 423 (68%) stwierdzono obecność czynników podwyższonego ryzyka i przeprowadzono pooperacyjną radioterapię (PR) (mediana 48 Gy). Za czynniki podwyższonego ryzyka uznano: stopień zaawansowania klinicznego (p=0,001), stopień zaawansowania patologicznego (p=0,001), poziom PSA przed operacją (p<0,0001) oraz stopień wg skali Gleasona (p=0,18). Średni okres obserwacji chorych wyniósł 7 lat.
Wyniki. 5- i 10-letnie przeżycie osiągnęło, odpowiednio, 92 i 71% chorych leczonych RP + PR. Wyniki w grupie leczonej tylko RP były niemal identyczne (p=0,73). 5- i 10-letni okres przeżycia bez objawów choroby (DFS) (PSA<0,05 ng/ml) osiągnęło, odpowiednio, 69% i 51% chorych z grupy RP + PR oraz, odpowiednio, 71% i 60% chorych z grupy RP. DFS nie różniło się w obu grupach w zależności od stopnia zaawansowania patologicznego i od stopnia wg skali Gleasona (p=0,77). Nie obserwowano związku pomiędzy poziomem PSA przed operacją (w granicach <10 vs. 10-25 vs. >25 ng/ml), a okresem przeżycia całkowitego, ale poziom PSA przed operacją >25 ng/ml był istotnym czynnikiem rokowniczym dla DFS. Analiza wieloczynnikowa wykazała, że stopień wg skali Gleasona był najważniejszym czynnikiem prognostycznym dla przeżycia całkowitego i DFS (p=0,00002), podczas gdy stopień zaawansowania patologicznego był czynnikiem prognostycznym dla wznowy klinicznej i DFS (p<0,00001). W grupie chorych, u których leczenie było ograniczone do RP wznowa miejscowa była równie

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częsta, co w grupie chorych leczonych RP + PR, pomimo, że ci ostatni mieli zdecydowanie gorsze czynniki prognostyczne. PR była dobrze tolerowana przez chorych i nie przyczyniła się do zwiększenia częstości występowania powikłań chirurgicznych. Wnioski. Sądzimy, że zastosowanie planowej pooperacyjnej radioterapii przyczyniło się do zredukowania przewidywanej częstości wystąpienia wznów miejscowych i pozwoliło poprawić DFS, zrównując je z wartościami obserwowanymi u chorych, u których nie stwierdzano obecności czynników podwyższonego ryzyka, a którzy byli leczeni tylko RP. W celu obiektywnej oceny roli radioterapii adiuwantowej u chorych z rakiem prostaty pT3N0 konieczne jest przeprowadzenie badań randomizowanych.

Key words: prostate cancer, radiotherapy surgery
Słowa kluczowe: rak prostaty, radioterapia pooperacyjna

Adenocarcinoma of the prostate (CaP) is the most common malignancy in the US (Table I) and its incidence is the highest in the world [1]. The incidence of CaP is increasing with the age of population, being very uncommon (1 in 10,000) among those under the age of 40 years and very common (12.5%) in males between 60 and 79 years of age. The American males have one in six lifetime chance of developing CaP. CaP is also an important cancer in the European Community being responsible for 9% of all cancer deaths in males [2]. On the other hand, this tumor while common in Poland is clearly of a lesser importance in that country than the primary lesions of the lung or cervix [1]. Mortality due to CaP was in 2000, 11.2 per 100,000 population in Poland, which ranked 32nd in the world while that of the US was 17.9 per 100,000, which ranked 18th in the world (Table II) [1]. In the 1990's the incidence of CaP in the US has stabilized and in 2002 it is expected to be diagnosed in 189,000 patients with 30,200 of these are estimated to die of this disease in the same year.

The management of CaP in the US is one of the success stories in the American oncology. Most (84%) patients are being diagnosed with local disease with only 6% presenting with distant metastasis at diagnosis [1]. Major improvements in surgery and radiotherapy as well as the availability of an effective hormonal management over the past 25 years resulted in a steep improvement in survival. The 5-year relative survival for all stages in the US for the period of 1974-1976 was 73% and for the period of 1992-1997 it was 96% [1]. As the proportion of patients diagnosed with tumor confined to the prostate increased, there has been a greater interest in treating patients with RP rather than with definitive radiotherapy. This increased emphasis on RP is particularly evident among younger patients. In patients < 55 years of age who were diagnosed in the US with localized disease the incidence of RP in 1985 was 35% and it increased to 69% in 1990 [3]. Increased incidence of RP affected all age groups except for those > 80 years of age (Table III). There is no prospective randomized trial comparing treatment outcomes in CaP patients managed with definitive radiotherapy or surgery. The prospect for such a trial remains poor. It is of interest to review outcomes in 146,979 patients treated for CaP in the US between 1973 and 1990 [4]. Of the 107,103 patients with locoregional disease, 60% had RP, 12% had radiotherapy alone, 16% had RT+RP combination and the remaining 12% received no definitive therapy. The median survival was

Table I. Estimated incidence and deaths from GU cancer in the US in 2002 [1]

Site	Incidence			Mortality		
	M+F	Male	Female	M+F	Male	Female
Prostate	189,000	189,000	-	30,200	30,200	-
Bladder	56,500	41,500	15,000	12,600	8,600	4,000
Kidney+	34,200	20,700	13,500	12,300	7,600	4,700
Testis	7,500	7,500	-	400	400	-
Other	1,200	1,200	-	200	200	-
All GU site	288,400	259,900	28,500	55,700	47,000	8,700
All cancer	1284,900	637,500	647,400	555,500	288,200	267,300

Table II. Death rate per 100,000 population in four selected countries in 2000 [1]

Country	All sites		Prostate	Lung		Breast
	M	F	M	M	F	F
Poland	205 (6)*	111 (16)	11 (32)	71(2)	11 (15)	17 (30)
USA	162 (22)	116 (10)	18 (18)	53 (13)	27 (1)	21 (12)
Hungary	272 (1)	142 (1)	18 (18)	86 (1)	20 (5)	25 (7)
Germany	177 (16)	117 (8)	18 (15)	46 (20)	10 (18)	24 (8)

* Rank in the world

Table III. Radical prostatectomy for CaP patients 1985-1990 [3]

Age (years)	1985		1990	
	N	%	N	%
< 55	32	35	340	69
55- 64	193	27	1,999	55
65- 69	197	21	2,213	46
> 70	130	9	2,045	24
Total	552	21	6,597	43

103 months for RT treated patients, 93 months for RT+RP, 73 months for RP alone and 50 months for those receiving no specific therapy.

Reported modern studies with treatment results following RP in patients with localized CaP demonstrated an excellent overall and disease-free survival (DFS) as well as a low incidence of toxicity and good quality of life [5]. Surgical results in patients with high (7-10) Gleason score, however, are disappointing with the 5-year DFS of only 33% [6]. Treatment results obtained with contemporary radiotherapy have also been excellent and the treatment was compatible with virtually unchanged quality of life in an overwhelming majority of patients [7-10]. It is to be noted that radiotherapy treated patient population typically represents patients with greater risk factors for tumor recurrence than those selected for surgical therapy.

In spite of major efforts to define accurately the true tumor extent prior to surgery or radiotherapy, this accurate definition remains an elusive goal. The primary reason for it is our inability to diagnose preoperatively microscopic extraprostatic tumor extension in addition to not being able to accurately predict positive surgical margins [11, 12]. The incidence of pathological stage pT3N0 varies widely in the published reports. It ranges from a low of <20% to a high of >50% [11-20].

Patients who are diagnosed with pT3N0 disease present a therapeutic dilemma since the optimal treatment for it is far from being settled. Some advocate no adjuvant therapy because of an unpredictable incidence of tumor recurrence; others recommend adjuvant treatment consisting of radiotherapy while hormonal therapy alone is also being supported [21-23]. It has been clearly established that the incidence of tumor recurrence in pT3N0 patients depends on a number of important prognostic factors such as: 1. Pathological stage; 2. Gleason score; 3. The number of positive surgical margins; 4. Preoperative PSA level; 5. Preoperative tumor volume; 6. Seminal vesicle invasion; 7. Perineural invasion; 8. Perivascular invasion; and 9. Lymphatic invasion [11-20]. A considerable experience is required to evaluate the above risk factors and recommend the most optimal treatment in a given patient.

The purpose of this report is to present this medical center experience with the planned management of patients diagnosed with pT3N0M0 disease.

Materials and methods

Patient characteristics

From 1976 to 1998, a total of 1,976 patients were treated with RP in this medical center. Of these 622 (31%) had pT3N0 disease and are the subject of this report. In our earlier reports, we have identified pT3N0 patients who had a lower risk of tumor recurrence and were recommended not to receive adjuvant radiotherapy while those with a higher probability of failure received a planned course of adjuvant RT [24-26]. Due to an encouraging treatment results noted in our interim reports a progressively greater proportion of pT3N0 patients were considered for planned RT [24-26]. Patient age ranged from 40 to 84 years with the median age of 66 years for RP+RT and 67 years for RP alone patients. Since patients were selected for adjuvant RT by the study two urologists it is not surprising that they had a higher probability of factors adversely influencing prognosis than those treated with RP alone. These important prognostic factors included: clinical stage, $p=0.001$, pathological stage, $p=0.001$, preoperative PSA level, $p<0.0001$ and Gleason score, $p=0.24$ (Table IV). RP+RT patients had a greater probability to be diagnosed with clinical stage T3, had a higher incidence of seminal vesicle involvement and a higher median preoperative serum PSA level (Table IV). All patients had histological confirmation of diagnosis of CaP. Gleason score was available in 420 (99.3%) of RP+RT and in 196 (98.5%) of RP patients (Table IV).

Patients considered for surgery had detailed general and urological history and physical examination performed. This included digital rectal examination (DRE). Transrectal ultrasound examination was performed in all study patients with other imaging studies performed on as needed basis. PSA was routinely available since 1987 and 532 (85.5%) study patients had preoperative serum level measured. PSA undetectable level was defined as <0.05 ng/ml. PSA failure was defined as two determinations of >0.05 ng/ml. Important details of PSA techniques used in this study have been reported (24-26). Local failure was biopsy confirmed while distant metastases were diagnosed based on imaging studies. Patients were staged according to the American Joint Committee Staging System of 1997 [27]. Follow-up schedule was as follows: every three months in the first post-treatment year, every four months in the second year, every six months in the third year and annually thereafter. Prior to each follow-up visit PSA level was obtained. Interim history was obtained and physical examination performed including DRE. Median follow-up for all patients was 73 months with a range from 2 to 20 years. RP+RT patients had a median follow-up of 84 months and RP alone patients had a median follow-up of 59 months.

Treatment

Surgery

Patients selected for RP had to meet the following criteria: 1. Good general condition, 2. Expected survival >10 years, and 3. Capsule confined disease. Modified radical retropubic prostatectomy with limited pelvic lymphadenectomy was performed in 55% of RP+RT and in 33% of RP alone patients while bilateral nerve sparing procedure was performed in 38% of the former and in 59% of the latter patients. The remaining patients of each group were treated with a unilateral nerve sparing procedures. Details on surgical techniques used in this study have been reported elsewhere [21, 28-31].

Radiotherapy

Radiotherapy was scheduled to begin from 42 to 90 days of RP. This period of time was felt to be necessary to allow for healing,

Table IV. Distribution of patients by clinical stage, pathological stage, Gleason score, preoperative PSA and treatment

Parameter	RP[1]+RT[2]	%	RP	%	Total	p-value
Clinical stage						
T1	17	4.0	13	6.5	30	
T2	339	80.1	177	89.4	516	
T3	67	15.8	9	4.5	76	0.001
Pathological stage						
pT3a	296	70	180	90	423	
pT3b	127	30	19	10	199	<0.0001
Gleason score[3]						
2-4	12	3	6	3	18	
5-6	157	37.4	87	44.4	244	
7-10	251	59.8	103	52.6	354	0.24
Pre-op PSA[4] (ng/ml)						
Mean	15.9	-	8.9	-	13.5	
Median	10.0	-	7.4	-	9.1	
Minimum	0.05	-	0.05	-	0.05	
Maximum	200	-	41	-	200	<0.0001

[1] Radical prostatectomy
[2] Adjuvant radiotherapy
[3] Gleason score was not available in 6 patients
[4] PSA was not available in 90 patients treated prior 1987

particularly at the site of anastomosis. Patients were to receive 45 Gy at 1.8 Gy daily fractions for pT3aN0 and 54 Gy for pT3bN0 tumors. The median radiation dose given was 48 Gy. Radiation dose was defined to the 95% isodose line. A total of 290 (69%) patients received their treatment with the 20 MV photon beam. The remaining patients were treated with 6 to 15 MV photon beams. The four-field "box technique" was used in the treatment of 75% of patients with the remainder treated with a combination of fixed fields and bilateral arc rotation. Prior to 1992, radiation portals were shaped with the use of custom shields and in the most recent period with a multi leaf collimator. An average field size was 11x11 cm with an effective area of treatment about 90 cm^2. The volume of interest included the prostatic fossa and its immediate vicinity with no attempt being made to treat the regional lymphatics. Details of the radiation techniques used in this study as well as details on data analysis have been published [31, 32].

Results

The overall 5- and 10-year actuarial survival for RP+RT patients was 92 and 73%, respectively, which was very similar to the long-term survival obtained in RP patients, p=0.73 (Table V). The 5- and 10-year DFS for RP+RT patients was 69 and 52%, respectively and again there was no significant difference in DFS between to two treatment groups, p=0.19 (Table V). Likewise freedom from clinical recurrence was nearly identical for both treatment groups, p=0.19 (Table V). It is of interest to analyze DFS by pathological stage, and Gleason score (Table VI). The data are similar for both treatment groups. The 5- and 10-year DFS for patients with pT3a disease and those with Gleason score 2-6 was very good (Table VI). There was, however, a poor long-term DFS in patients with seminal vesicle involvement (pT3b) and in those with high (7-10) Gleason score. The 10-year probability of DFS (PSA<0.05 ng/ml) in patients with a high Gleason score and seminal vesicle involvement was only 11%. Freedom from any recurrence (no clinical recurrence and PSA <0.05 ng/ml) (FFR) by pathological stage and Gleason score was analyzed using the Cox model. The 10-year probability of FFR ranged from a high of 67% for pT3a, Gleason score 2-6 to a low of 11% for those with pT3b Gleason score 7-10 disease

Table V. Survival, freedom from clinical recurrence, clinical and chemical recurrence by treatment

Parameter	% 5-year	% 10-year	Median (years)	N Total	N Failure
Survival					
RP[1] + RT[2]	92	73	>10	423	71
RP	92	75	>10	199	20
Freedom from clinical recurrence					
RP + RT	91	84	>10	423	44
RP	92	91	>10	199	9
Freedom from clinical + PSA recurrence					
RP + RT	69	52	>10	423	132
RP	71	60	>10	199	35

[1] Radical prostatectomy
[2] Adjuvant radiotherapy

Table VI. Disease-free survival by pathological stage, Gleason score and treatment

Parameter	% 5-year	% 10-year	Median (years)	N Total	N-failure
pstage T3a					
RP[1] + RT[2]	78	60	>10	296	66
RP	76	63	>10	180	27
pstage T3b					
RP + RT	52	35	5.2	129	66
RP	32	–	4.4	17	8
Gleason score 2-6					
RP + RT	84	75	>10	169	31
RP	77	63	>10	93	15
Gleason score 7-10					
RP + RT	59	-	6.9	253	99
RP	61	-	-	101	20

[1] Radical prostatectomy
[2] Adjuvant radiotherapy

(Table VII). The mean and median time to clinical or chemical recurrence for all patients was 3.4 and 3.1 years, respectively. There was no significant difference in time to any recurrence between the two treatment groups.

Table VII. Freedom from any recurrence: Cox Model

pstage	Gleason	% 5 yr	C.I.	% 10 yr	C.I.
pT3a	2-6	82	75-90	67	54-81
pT3a	7-10	67	58-77	43	30-62
pT3b	2-6	81	69-95	64	45-91
pT3b	7-10	35	26-48	11	5-27

A total of 532 (85.5%) had preoperative PSA level available. The 2- and 5-year survival for patients with PSA <10 ng/ml was 97 and 91%, respectively. In the group of >10 and <25 ng/ml it was 99 and 94%, respectively and in those with PSA > 25 ng/ml it was 100 and 94%, respectively, p=0.81. Likewise, there was no significant difference in the incidence of freedom from clinical recurrence between the above preoperative PSA levels. It is of interest, however, that there was a difference in a probability of FFR with patients of <10 ng/ml having the 2- and 5-year FFR of 91 and 76%, respectively, as compared to 83 and 56%, respectively for those with PSA >25 ng/ml, p=0.02. Of the 142 patients who developed PSA recurrence in this study the 2- and 5-year survival was 93 and 78% respectively with a median survival of 7.5 years. The 2- and 5-year incidence of freedom from clinical recurrence in this group of patients was 77 and 59%, respectively with a median probability of 5.6 years. There was no difference in survival, FFR and the incidence of clinical recurrence by the treatment group (RP+RT vs. RP alone).

At the last follow-up of the 423 RP+RT patients, 353 (83.4%) were alive including 192 (45.4%) who had PSA <0.05 ng/ml and 6 patients with local recurrence. Comparison of treatment outcomes between the two treatment groups is shown in Table VIII. Ultimately, 13 (3%) patients had local recurrence in RP+RT group and 9 (4.5%) patients had a local recurrence in RP alone group (NS).

Treatment complications

Surgery

There was no surgical mortality recorded in this study. Major surgical complications were reported in 3.5% of patients and there was no significant difference in their incidence between the two treatment groups. All of these major complications occurred during or soon after prostatectomy and were successfully managed with an appropriate treatment in all cases. Relevant details on surgical complications have been published [33]. Minor surgical complications were seen in 9% of patients. Intraoperative blood transfusion was given in 2% an postoperative an additional 3%. The average hospital length of stay was 4 days. Continence was assessed at 1 year posttreatment and 80% of patients were fully continent in either treatment group. Mild stress incontinence was present in approximately 15% of patients with the remainder having various degrees incontinence. Very few (<3%) patients were fully incontinent and required a surgical procedure for correction. There was no difference in the incidence of incontinence or erectile function between patients treated with RP+RT and RP alone. Early and late assessment of sexual potency and incontinence have been published [34].

Adjuvant radiotherapy

Radiotherapy was very well tolerated treatment by the 423 study patients. Acute complications were common (66%) but mild and of no clinical significance. They consisted of symptoms and signs of proctitis in 35% with mild diarrhea in 29%, urinary obstructive and irritative signs and symptoms such as frequency, nocturia or dysuria in 35% and other acute toxicity in 3%. In most of these patients with acute toxicity no specific therapy was

Table VIII. Status of all patients at last follow-up

Status	RP[1] + RT[2]		RP		Total	
	N	%	N	%	N	%
Alive-clinical of disease						
PSA <0.05 ng/ml	192	45.4	106	53.3	298	47.9
PSA >0.05 ng/ml	61	14.4	21	10.6	82	13.2
PSA not available	59	14	27	13.6	86	13.8
Alive-clinical recurrence						
Local	6	1.4	5	2.5	11	1.8
Distant	15	3.6	2	1.0	17	2.7
Local + distant	1	0.2	0	0.0	1	0.2
Unknown	1	0.2	0	0.0	1	0.2
Alive-disease status unknown	18	4.3	17	8.5	35	5.6
Dead of other causes						
Local recurrence	5	1.2	3	1.5	8	1.3
Distant metastasis	14	3.3	2	1.0	16	2.6
Local + distant	1	0.2	0	0.0	1	0.2
Unknown	0	0.0	1	0.5	1	0.2
Dead of other causes						
PSA<0.05 ng/ml	33	7.8	13	6.5	46	7.4
PSA >0.05ng/ml	17	4.0	2	1.0	19	3.1

[1] Radical prostatectomy
[2] Adjuvant radiotherapy

required and the symptoms have not persisted much beyond the course of radiotherapy. None of these patients needed hospitalization to treat radiation related toxicity. No late toxicity of radiotherapy was reported in particular no urethral stricture or bowel injury, no increased incidence of erectile dysfunction or incontinence as compared to the 199 patients treated with RP alone.

Dicussion

In the absence of a randomized trial comparing outcomes in patients with pT3N0 disease treated with or without adjuvant radiotherapy is difficult and this study may be of help to clinicians who have to provide the patient with specific treatment recommendations. The study patients were selected for postoperative irradiation by our two urologists. Their selection process was based on well-recognized risk factors with RP+RT patients, as expected, to include those with worse prognostic factors than the patients in RP alone group. The strength of this study includes a treatment uniformity used in both surgery and radiotherapy over a long (>20 years) period of time and reported outcomes based on a relatively large number of patients. Additionally, the study patients were treated with RP+RT or RP alone without any other adjuvant treatment. Specifically, none of the patients received neoadjuvant or adjuvant hormonal therapy. The obvious weakness is a non-randomized nature of this report. Due to the complexity of designing such a randomized study for pT3N0 patients its phase in is not expected to be imminent.

The use of adjuvant RT in pT3N0 patients has been reported by a number of medical centers [36-44]. The reported treatment results have been excellent in terms of a sharp reduction in the expected incidence of local tumor recurrence. The main difference between the present study and other reports in the literature is the radiation technique used in our study. Radiation dose in our study ranged from 45 to 54 Gy with a median dose of 48 Gy. This is in contrast to the other reports where the minimum radiation dose was 64 Gy [44]. Additionally, in our study the treated volume was small (prostatic fossa and its immediate vicinity) as opposed to whole pelvis to 40-45 Gy with a boost to a smaller volume in other published studies. In spite of these differences in treatment techniques, the results of our study are equal or better to the other published data. This is particularly evident in our patient treatment tolerance with virtually no clinically important acute toxicity and no late toxicity being noted as opposed to other reports [44]. There is a strong support for the use of approximately 45 Gy in patients with microscopic residual disease [45]. It is believed, there is a misunderstanding between two important terms or definitions, which include microscopic

Table IX. Ranking of important prognostic factors – multivariate analyses

Prognostic factor for	P-value
Survival	
Gleason score	0.00002
Pathological stage	0.09
Preoperative PSA	0.34
Clinical recurrence	
Gleason score	0.13
Pathological stage	0.002
Preoperative PSA	0.54
Clinical + chemical recurrence	
Gleason score	0.0002
Pathological stage	<0.00001
Preoperative PSA	0.31

proven or strongly suspected microscopic residual disease following prostatectomy vs. macroscopic residual disease or recurrent disease manifested by postoperative rise in PSA level. In the latter, we would also recommend higher (64 Gy) radiation dose while in the former such a high dose is not necessary.

Somewhat of a surprise in our study was a lack of correlation between preoperative serum PSA level and survival, especially in those patients with PSA>25 ng/ml. Such patients are generally expected to have a high probability of extracapsular disease with frequent lymph node involvement or even distant metastasis, which are known to compromise survival. There was, however, a strong predictive value of PSA>10 ng/ml on disease free survival.

Conclusions

Patients treated with surgery alone had significantly lower risk factors than those receiving RP+RT combination yet there was no significant difference in survival, disease free survival and the incidence of local failure between the two treatment groups. Adjuvant radiotherapy was well tolerated without clinically important toxicity. We hypothesize that moderate dose of adjuvant radiotherapy following radical prostatectomy helped to equalize risk factors in patients with pT3N0 disease. Patients with seminal vesicle involvement and Gleason score 7-10 disease have a low (11%) probability of 10-year disease free survival as compared to the patients presenting with lower Gleason score and no seminal vesicle involvement. This group of high-risk patients should be targeted for a trial of systemic management in addition to the local adjuvant radiotherapy.

Supported in part by the Albert & Elaine Borchard Foundation, Inc.

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References

1. Jemal A, Thomas A, Murray T et al. Cancer statistics 2002. *Ca Cancer J Clin* 2002; 52: 23-47.
2. Moller Jensen O, Esteve J, Moller H et al. Cancer in the European Community and its member states. *Eur J Cancer* 1990; 26: 1167-1256.
3. Mettlin C, Murphy GP, Menck H. Trends in treatment of localized prostate cancer by radical prostatectomy: Observations from the commission on cancer national cancer database, 1985-1990. *Urology* 1994; 43: 488-492.
4. Krongrad A, Lai H, Lamm SH, et al. Mortality in prostate cancer. *J Urology* 1996; 156: 1084-1091.
5. Catalona WJ. Surgical management of prostate cancer. Contemporary with anatomic radical prostatectomy. *Cancer* 1995; 75: 1903-1908.
6. Oefelein MG, Smith ND, Grayhack JT, et al. Long-term results of radical retropubic prostatectomy in men with high grade carcinoma of the prostate. *J Urology* 1997; 158: 1460-1465.
7. Shipley WU, Thames HD, Sandler HM et al. Radiation therapy for clinically localized prostate cancer. A multi-institutional pooled analysis. *JAMA* 1999; 281: 1598-1604.
8. Hanlon AL, Watkins Bruner D, Peter R et al. Quality of life study in prostate cancer patients treated with three-dimensional conformal radiation therapy: Comparing late bowel and bladder quality of life symptoms to that of the normal population. *Int J Radiation Oncology Biol Phys* 2001; 49: 51-59.
9. Burman C, Chuhi C-S, Kutcher G et al. Planning, delivery, and quality assurance of intensity-modulated radiotherapy using dynamic multileaf collimator: A strategy for large-scale implementation for the treatment of carcinoma of the prostate. *Int J Radiation Oncology Biol Phys* 1997; 39: 863-873.
10. Chuba PJ, Moughan J, Forman JD et al. The 1989 patterns of care study for prostate cancer: Five-year outcomes. *Int J Radiation Oncology Biol Phys* 2001; 50: 325-334.
11. Rosen MA, Goldstone L, Lapin S et al. Frequency and location of extracapsular extension and positive surgical margins in radical prostatectomy specimens. *J Urology* 1992; 148: 331-337.
12. Weldon VE, Tavel FR, Neuwirth H et al. Patterns of positive specimen margins and detectable prostate specific antigen after radical perineal prostatectomy. *J Urol* 1995; 153:1565-1569.
13. Epstein JI. Incidence and significance of positive margins in radical prostatectomy specimens. *Urologic Clinics of North America* 1996; 23: 651-663.
14. Epstein JI, Carmicheal M, Partin AW et al. Is tumor volume an independent predictor of progression following radical prostatectomy? A multivariate analysis of 185 clinical stage B adenocarcinomas of the prostate with 5 years of follow up. *J Urology* 1993; 149: 1478-1481.
15. Epstein JI, Carmichael M, Walsh PC. Adenocarcinoma of the prostate invading the seminal vesicle: Definition and relation of tumor volume, grade and margins of resection to prognosis. *J Urology* 1993; 149: 1040-1045.
16. Theiss M, Wirth MP, Manseck A et al. Prognostic significance of capsular invasion and capsular penetration in patients with clinically localized prostate cancer undergoing radical prostatectomy. *Prostate* 1995; 27: 13-17.
17. Jones EC. Resection margin status in radical retropubic prostatectomy specimens: Relationship to type of operation, tumor size, tumor grade, and local extension. *J Urol* 1990; 144: 89-93.
18. Bostwick DG, Monitoroni R. Evaluating radical prostatectomy specimens: Therapeutic and prognostic importance. *Virchows Arch* 1997; 430: 1-16.
19. Mc Neal JE, Villers AA, Redwine EA et al. Capsular penetration in prostate cancer: Significance for natural history and treatment. *Am J Surg Path* 1990; 14: 240-247.
20. Ohori M, Wheeler TM, Kattan MW et al. Prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urology* 1995; 154: 1818-1824.
21. Carter GE, Lieskovsky G, Skinner DG et al. Results of local and/or systemic adjuvant therapy in the management of pathological stage C or D1 prostate cancer following radical prostatectomy. *J Urology* 1989; 142: 1266-1271.
22. Lowe BA, Lieberman SF. Disease recurrence and progression in untreated pathologic stage T3 prostate cancer: Selecting the patient for adjuvant therapy. *J Urology* 1997; 158:1452-1458.
23. Pound CR, Partin AW, Eisenberger MA et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999; 281: 1591-1597.
24 Van Poppel H, Vanuytsel L, Petrovich Z et al. Is postoperative irradiation after radical prostatectomy necessary? *Eur J Cancer* 1999; 35: 1763-1766.
25. Petrovich Z, Lieskovsky G, Freeman J et al. Surgery with adjuvant irradiation in patients with pathologic stage C *adenocarcinoma* of the prostate. *Cancer* 1995; 76: 1621-1628.
26. Petrovich Z, Lieskovsky G, Langholz B et al. Adjuvant radiotherapy in patients with pathologic stage C (pT3N0) *adenocarcinoma* of the prostate. *Urology* 1999; 53:1184-1193.
27. Petrovich Z, Lieskovsky G, Langholz B et al. Radical prostatectomy and postoperative irradiation in patients with pathological stage C (T3). *Int J Radiat Oncol Biol Phys* 1998; 40: 139-147.
28. American Joint Committee on Cancer. Prostate. In Fleming ID, Cooper JS, Henson DE et al. AJCC Cancer Staging Manual, 5th. Ed. Philadelphia: Lippincott-Raven; 1997, 219-224.
29. Freeman JA, Lieskovsky G, Cook DW et al. Radical retropubic prostatectomy and postoperative adjuvant radiation for pathological stage C (PCN0) prostate cancer from 1976 to 1989: Intermediate findings. *J Urology* 1993; 149: 1029-1034.
30. Freeman JA, Lieskovsky G, Grossfeld G et al. Adjuvant radiation, hormone and chemotherapy in pathological stage D1 *adenocarcinoma* of the prostate. *Urology* 1994; 44: 719-725.

31. Yamada AH, Lieskovsky G, Petrovich Z et al. Results of radical prostatectomy and adjuvant therapy in the management of locally advanced, clinical stage TC prostate cancer. *Am J Clin Oncol* 1994; 17: 277-285.
32. Petrovich Z, Lieskovsky G, Langholz B et al. Radiotherapy following radical prostatectomy in patients with adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1991; 21: 949-954.
33. Petrovich Z, Lieskovsky G, Langholz B et al. Post-operative radiotherapy in 423 patients with pT3N0 prostate cancer. *Int J Radiat Oncol Biol Phys* 2002; 53: 600-609.
34. Petrovich Z, Lieskovsky G, Stein JP et al. Comparison of surgery alone with surgery and adjuvant radiotherapy for pT3N0 prostate cancer. *BJU International* 2002; 89: 604-611.
35. Formenti SC, Lieskovsky G, Skinner D et al. Update on impact of moderate dose of adjuvant radiation on urinary continence and sexual potency in prostate cancer patients treated with nerve-sparing prostatectomy. *Urology* 2000; 56: 453-458.
36. Anscher MS, Robertson CN, Prosnitz LR. Adjuvant radiotherapy for pathologic stage T3/4 adenocarcinoma of the prostate: Ten-year update. *Int J Radiation Oncology Biol Phys* 1995; 33: 37-43.
37. Buskirk ST, Schild SE, Durr ED et al. Evaluation of serum prostate-specific antigen levels after postoperative radiation therapy for pathologic stage T3, N0 prostate cancer. *Mayo Clin* 1996; 71: 242-248.
38. Choo R, Hruby G, Hong J et al. Positive resection margin and/or pathologic T3 *adenocarcinoma* of the prostate with undetectable postoperative prostate-specific antigen after radical prostatectomy: To irradiate or not? *Int J Radiation Oncology* 2002; 52: 674-680.
39. Gibbons RP, Cole BS, Richardson RG et al. Adjuvant radiotherapy following radical prostatectomy: Results and complications. *J Urology* 1986; 135: 65-58.
40. Schild SE, Wong WW, Grado GL et al. The results of radical retropubic prostatectomy and adjuvant therapy for pathologic stage C prostate cancer. *Int J Radiation Oncology Biol Phys* 1996; 34: 535-541.
41. Shevlin BE, Mittal BB, Brand WN et al. The role of adjuvant irradiation following primary prostatectomy, based on histopatholic extent of tumor. *Int J Radiation Oncology Biol Phys* 1989; 16: 1425-1430.
42. Zietman AL, Coen JJ, Shipley WU et al. Adjuvant irradiation after radical prostatectomy for adenocarcinoma of prostate: Analysis of freedom from PSA failure. *Urology* 1993; 42:292-299.
43. Syndikus I, Pickles T, Kostashuk E et al. Postoperative radiotherapy for stage pT3 carcinoma of the prostate: Improved local control. *J Urology* 155:1983-1986, 1996.
44. Crane CH, Rich TA, Read PW et al. Preirradiated PSA predicts biochemical disease-free survival in patients treated with postprostatectomy external beam irradiation. *Int J Radiation Oncology Biol Phys* 1997; 39:681-686.
45. American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statements on radiation therapy of prostate cancer: Guidelines for prostate re-biopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. *J Clin Oncol* 1999; 17: 1155-1163.
46. Withers HR, Suwinski R. Radiation dose response for subclinical metastases. *Sem Radiat Oncol* 1998; 8: 224-228.

Paper received: 15 October 2002
Accepted: 30 October 2002