0022-5347/02/1672-0528/0
THE JOURNAL OF UROLOGY®
Vol. 167, 528–534, February 2002
Printed in U.S.A.

CANCER CONTROL WITH RADICAL PROSTATECTOMY ALONE IN 1,000 CONSECUTIVE PATIENTS

GERALD W. HULL, FARHANG RABBANI, FARHAT ABBAS, THOMAS M. WHEELER,* MICHAEL W. KATTAN AND PETER T. SCARDINO†

From the Department of Urology, Medical University of South Carolina, Charleston, South Carolina, Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York, Department of Surgery-Urology, Aga Khan University, Karachi, Pakistan, and Department of Pathology, Baylor College of Medicine, Houston, Texas

ABSTRACT

Purpose: We analyzed the long-term progression-free probability after radical retropubic prostatectomy in a consecutive series of patients with localized prostate cancer.

Materials and Methods: From 1983 to 1998, 1,000 patients (median age 62.9 years, range 37.7 to 81.4) with clinical stage T1 to T2 prostate cancer were treated with radical retropubic prostatectomy and pelvic lymphadenectomy, without other cancer related therapy before recurrence. Mean followup was 53.2 months (median 46.9, range 1 to 170).

Results: Ten years after radical retropubic prostatectomy the mean probability ± 2 standard errors that patients remained free of progression and of any further treatment was 75.0% ± 3.7% and of metastasis 84.2% ± 4.4%. Mean actuarial cancer specific survival rate ± 2 standard error was 97.6% ± 1.7%. In a multivariate analysis pretreatment prostate specific antigen level ($p < 0.0001$), biopsy Gleason sum ($p < 0.0001$) and clinical stage ($p = 0.0071$) were independent prognostic factors for progression. After prostatectomy independent risk factors were Gleason sum in the prostatectomy specimen ($p = 0.0008$), extracapsular extension ($p = 0.0019$), seminal vesical involvement ($p < 0.0001$), lymph node metastasis ($p < 0.0001$) and surgical margin status ($p < 0.0001$). Margins were positive in 12.8% of cases. At 10 years postoperatively radical retropubic prostatectomy was effective for cancer confined to the prostate (92.2% progression-free probability) and also not confined (52.8%), including 71.4% progression-free probability for patients with only extracapsular extension and 37.4% with seminal vesicle invasion without lymph node metastasis.

Conclusions: Radical retropubic prostatectomy provided long-term cancer control in 75% of patients with clinically localized prostate cancer and was effective in the majority of those with high risk cancer, including T2c or biopsy Gleason sum 8 to 10, or PSA greater than 20 ng./ml. Further research should address identifying patients who can safely avoid aggressive therapy.

KEY WORDS: prostatectomy, survival, prostatic neoplasms, disease-free survival, probability

Most prostate cancer detected clinically by digital rectal examination or serum prostate specific antigen (PSA) level poses a substantial risk to the life and health of the patient. In a pooled analysis of 823 patients with clinical stage T1 to 2 Nx M0 prostate cancer managed conservatively Chodak et al reported the risk of metastasis at 10 years postoperatively as 19% for well, 42% moderately and 74% poorly differentiated cancer.[1] In a population based study of 767 similar patients diagnosed during the 1970s, and treated conservatively Albertsen et al assessed the probability of dying of cancer at 15 years as 4% to 7% for the Gleason sum 2 to 4 cancer, 6% to 11% 5, 18% to 30% 6, 42% to 70% 7 and 60% to 87% 8 to 10.[2] There will continue to be a need for reliable outcome data from large treatment series to document long-term cancer control rates, and provide more accurate information for prognostic models and medical decision making, even when randomized trials comparing different treatment modalities for localized prostate cancer are completed.[3–5]

We report a detailed analysis of long-term cancer control in a prospective series of 1,000 consecutive men with clinical stage T1 or T2 prostate cancer treated with bilateral pelvic lymphadenectomy and radical retropubic prostatectomy alone. This series includes 14 patients who agreed to radical prostatectomy ("intention to treat"), even if the operation was abandoned when metastasis was found in the dissected pelvic lymph nodes. No patient received adjuvant irradiation or hormonal therapy preoperatively. Adjuvant therapy postoperatively before documented recurrence was considered evidence of progression or metastasis with systemic therapy. Consequently, outcomes reflect cancer control rates with surgery as monotherapy.

Accepted for publication August 3, 2001.

*Financial interest and/or other relationship with Astra Zeneca Pharmaceuticals.

†Financial interest and/or other relationship with ProQuest, RITA, EDAP Technomed, Zeneca Pharmaceutical, UroMed and TAP Pharmaceuticals.

MATERIALS AND METHODS

Patient population. The study population includes all patients with clinically localized (stage T1 to 2 NX M0) adenocarcinoma of the prostate who agreed to be treated with radical retropubic prostatectomy and pelvic lymphadenectomy by 1 surgeon (P. T. S.) at Baylor College of Medicine between June 1983 and April 1998. Patients who received prior radiotherapy, cryotherapy or neoadjuvant hormonal therapy were excluded from the study, as were those with clinical stage T3 cancer, which was determined by digital rectal examination. A total of 986 patients underwent radical retropubic prostatectomy and pelvic lymphadenectomy. In 14 patients the prostatectomy was abandoned because the lymph nodes contained metastasis on frozen section exami-

nation. These 14 patients included in the analysis were considered to have metastasis at initiation of hormonal therapy.

Median patient age was 62.9 years (range of 37.7 to 81.4). Only 5% of the patients were younger than 50 years and 84% were in their 60s or 70s, with 11% 70 years or older and 1.5% 75 years or older. Median PSA measured with the Hybritech assay (Hybritech Tandem R, Hybritech Beckman Coulter Corp., San Diego, California) was 6.8 ng./ml. (range 0 to 88.3). In 51.5% of the patients PSA was 4.0 to 9.9 ng./ml., with 27.1% having greater than 10 ng./ml.

Clinical stage, grade and PSA (table 1). Clinical stage was assigned preoperatively with the 1992 International Union Against Cancer TNM system.[6] All patients had a digital rectal examination and transrectal ultrasonography. Gleason grade in the diagnostic biopsy or transurethral prostatic resection specimen was assigned by 1 pathologist (T. M. W.). Impalpable cancer seen on ultrasound was classified as T1c but palpable tumors were subclassified, including T2a, b or c, with digital rectal examination and ultrasound results.[6,7] Because of the controversy about the accuracy of detecting extracapsular extension or seminal vesicle invasion with ultrasound,[7] sonographic data were not used to reclassify T2 cancer to T3. Preoperative PSA levels were not available in 103 of the patients, of whom 68 were treated before 1987. The PSA results obtained closest to the time of surgery were used for this analysis, and no PSA value within 3 weeks after biopsy was used. The presence of distant metastasis was excluded when clinically indicated by standard tests.

Operative technique. Pelvic lymph node dissection and modified anatomical radical retropubic prostatectomy were performed as described previously, with particular attention to achieving negative surgical margins.[8,9] The decision to resect 1 or both neurovascular bundles partially or completely was based on the size, location, and extent of the tumor on digital rectal examination and ultrasound, serum PSA level, grade and extent of cancer in the biopsy specimen, and proximity and adherence of the nerve to the prostate gland and cancer assessed intraoperatively.

Pathological findings. Every radical prostatectomy specimen was analyzed at Baylor College of Medicine by 1 pathologist (T. M. W.) with a protocol described previously.[10] A primary and secondary Gleason grade was assigned to the whole cancer in the specimen. Only patients with extension of cancer through the capsule into periprostatic soft tissue were considered to have extracapsular extension, either focal or established.[11] The presence of tumor cells at the inked margin of resection was considered a positive surgical margin. Pathological stage, which was available in 996 patients, was assigned according to the 1992 International Union Against Cancer TNM classification with 1 of 4 mutually exclusive groups: 1) pT2 N0, confined, 2) pT3a,b N0, extracapsular extension only, 3) pT3c N0, seminal vesicle involvement and 4) pT1 to 3 N+, lymph node metastasis.[6]

Followup. Clinical and pathological data were collected, and entered prospectively into a database that included demographic information, indication for prostatic biopsy, Gleason sum (primary and secondary grade) in the biopsy, all serum PSA levels, details of prior prostate or prostate cancer related therapy, a touch diagram of digital rectal examination results, results of transrectal ultrasound, clinical stage, and preoperative continence level and erectile function. Details of the operative findings, surgical procedure, intraoperative complications, transfusions, and immediate postoperative course were added at the time of hospitalization. Patients were followed every 3 months during year 1, every 6 months until year 5 and then annually. PSA levels were checked at each visit, and digital rectal examination was performed annually. Imaging studies were obtained only after biochemical or clinical evidence of disease recurrence.

Disease progression in all patients, including those with positive lymph nodes, was defined as occurring on the date of biopsy proved local recurrence, evidence of distant metastasis by bone scan or other tests, or persistently increased PSA to 0.4 ng./ml. or greater. Treatment failure and disease progression were also considered to have occurred on the date of initiation of adjuvant radiotherapy or hormonal therapy. Metastatic failure was considered to occur at the first clinical sign of metastasis or start of systemic adjuvant therapy. Followup ranged from 1 to 170 months (mean 53.2, median 46.9) in 989 patients, with no postoperative information on 11. Of these patients 372 (37.2%) were followed greater than 5 years and 56 (5.6%) greater than 10.

Statistical analysis. Clinical prognostic factors included clinical T stage, biopsy Gleason sum and serum PSA level. Pathological prognostic factors included Gleason sum in the radical retropubic prostatectomy specimen, extracapsular extension, positive margins, seminal vesical involvement and lymph node metastasis. End points used in the analysis included positive surgical margins, overall survival rate, cancer specific survival rate (free of death from a prostate cancer related cause), metastasis-free probability (free of clinical evidence of metastasis or systemic therapy) and progression-free probability (continuously undetectable serum PSA level, no clinical evidence of local or distant recurrence and no adjuvant therapy).

The actuarial probabilities, including mean $\pm$ 2 standard errors (SE) or 95% confidence interval (CI), were generated with the Kaplan-Meier method and compared using the log-rank test.[12,13] We used univariate and multivariate analyses to assess the prognostic significance of clinical and pathological parameters for predicting time to each cancer related end point. Cox proportional hazards analysis was used to obtain the maximum likelihood estimates of relative risk and 95% CI in multivariate analysis.[14] PSA levels were analyzed as $\log_2$ of the preoperative PSA ($\log_2$ [preoperative PSA]=ln[preoperative PSA/ln2]). This formula allowed us to evaluate the relative risk with each doubling of the preoperative PSA level. Biopsy and prostatectomy Gleason sum were classified as categorical variables, including Gleason sum 2 to 4, 5 to 6, 7 and 8 to 10. Statistical analysis was performed with commercial software.

RESULTS

Clinical stage and biopsy Gleason sum. Although the Gleason sum was 2 to 4 in 11.2% of cancers, 33 (30%) of these were

TABLE 1. *Clinical stage and Gleason sum in biopsy specimen*

Clinical Stage	Biopsy Gleason Sum				Total No. (%)
	No. 2–4 (%)	No. 5—6 (%)	No. 7 (%)	No. 8–10 (%)	
T1a	16 (47.1)	18 (52.9)	0	0	34 (3.4)
T1b	17 (30.9)	28 (50.9)	5 (9.1)	5 (9.1)	55 (5.6)
T1c	19 (5.8)	230 (70.1)	69 (21.0)	10 (3.0)	328 (33.2)
T2a	24 (13.4)	112 (62.6)	40 (22.3)	3 (1.7)	179 (18.1)
T2b	22 (8.1)	165 (60.9)	69 (25.5)	15 (5.5)	271 (27.5)
T2c	13 (10.8)	59 (49.2)	43 (35.8)	5 (4.2)	120 (12.2)
Totals	111 (11.2)	612 (62.0)	226 (22.9)	38 (3.9)	987

Stage or grade data are missing in 13 cases.

detected with transurethral prostatic resection, including T1a,b (table 1). Only 8.7% of T1c to T2c cancers were well differentiated, while 28.3% of these were Gleason sum 7 to 10. Nearly 85% of all cancers were "moderately differentiated," including Gleason sum 5 to 7. A third (33.2%) was impalpable cancer detected with needle biopsy, including T1c, and only 9% were detected with transurethral prostatic resection. Approximately 40% of the patients had extensive cancer, including clinical stage T2b or T2c.

Correlation of clinical features with final pathological stage and surgical margins. Greater than 40% of the cancers were not confined to the prostate, including pT3 or N1, and 25.2% had established extracapsular extension without seminal vesicle involvement or lymph node, 8.1% seminal vesicle invasion without lymph node and 6.9% lymph node metastasis (table 2). Increasing clinical stage, and higher biopsy Gleason sum and preoperative serum PSA level were each independently associated with a greater incidence of extracapsular extension ($p < 0.0001$) and lymph node metastasis ($p = 0.033$, 0.0014 and 0.0002, respectively). Only higher biopsy Gleason sum and preoperative PSA level were independently associated with a greater incidence of seminal vesicle involvement ($p < 0.0001$ and < 0.0001, respectively), and clinical stage was not ($p = 0.094$). In univariate analysis those patients in whom Gleason sum was 7 in the biopsy specimen had more advanced pathological features compared to Gleason sum 5 and 6 ($p < 0.0001$). Patients in whom Gleason sum was 8 to 10 cancer did not have significantly different pathological features than Gleason 7 ($p = 0.24$), perhaps because there were relatively few of the former. Overall, 12.8% of the patients had positive surgical margins. In a multivariate analysis PSA level ($p < 0.0001$) and biopsy Gleason sum ($p = 0.026$) predicted surgical margin status, and clinical stage did not.

Survival and progression. Only 11 (1.1%) patients died of prostate cancer during the analysis, and 40 (4.0%) died of other causes. Thus, cancer accounted for only 22% of all deaths. At 10 years postoperatively the overall actuarial probability of death from any cause was 13.4%, death from cancer 2.4% and metastasis 15.8%. The actuarial probability of remaining free of progression at 5 and 10 years postoperatively was 78% and 75%, respectively (table 3).

Data on progression were available in 989 patients, of whom 844 (85.3%) remained continuously free of disease and 145 (14.7%) had evidence of cancer recurrence after intended radical prostatectomy. Of these 145 patients 14 had positive lymph nodes (radical retropubic prostatectomy was abandoned) and treatment was considered an immediate failure. Two patients first presented with distant recurrence, including 1 before the PSA test was available. In the remaining 129 cases (89% of failures) an additional 30 were considered to have progressed, although recurrent cancer was not identified, including 28 at initiation of adjuvant radiotherapy and 2 considered as having progression and metastatic failure at initiation of androgen deprivation therapy. In most (52%) of the 175 patients in whom treatment was considered a failure evidence of progression was apparent within 1 year postoperatively. Only 9 (5.1%) cases progressed after 5 years.

TABLE 3. *Actuarial overall, cancer specific, and metastasis-free survival rates, and progression-free probabilities*

End Point	Mean ± 2 SE or 95 CI (No. pts. at risk)	
	5 Yrs.	10 Yrs.
Cancer specific	99.1 ± 0.78 (372)	97.6 ± 1.71 (55)
Metastasis-free	89.9 ± 2.29 (328)	84.2 ± 4.41 (47)
Progression-free	78.2 ± 3.10 (277)	75.0 ± 3.72 (40)
Overall	95.5 ± 1.71 (372)	86.6 ± 4.43 (56)

Prognostic factors for survival and progression. Considering the limited followup in our study, none of the clinical or pathological factors was a significant independent predictor of cancer specific survival (table 4). However, clinical stage ($p = 0.037$), Gleason sum in radical retropubic prostatectomy specimen ($p = 0.0001$), level of extracapsular extension ($p = 0.0028$), surgical margin status ($p = 0.0313$), seminal vesical involvement ($p = 0.0006$) and lymph node status ($p < 0.0001$) were all significant independent predictors of metastatic-free survival. Each clinical and pathological factor in table 4 was significantly associated with progression (figs. 1 and 2) in univariate analysis.

Table 5 lists the risk ratio values for prognostic factors that differed significantly in univariate analysis. Of the clinical T stages progression rates for T1c and T2a cancers were similar. T1c cancer was significantly more favorable than T2b or T2c ($p < 0.0001$), and T2b and T2c did not differ ($p = 0.90$, tables 4 and 5). There were no differences between biopsy Gleason sums 2 to 4 and 5 to 6, or 7 and 8 to 10 ($p = 0.11$ and 0.06, respectively). In a multivariate analysis of clinical preoperative parameters T stage ($p = 0.007$), biopsy Gleason sum ($p < 0.0001$) and PSA level ($p < 0.0001$) were significant independent predictors of progression (table 6). However, there was no significant difference among any of the T2 substages, including T2a versus T2b ($p = 0.16$), T2a versus T2c ($p = 0.44$) and T2b versus T2c ($p = 0.59$). For each doubling of the serum PSA level the relative risk of progression increased 1.80 fold. When the pathological factors in the radical retropubic prostatectomy specimen were included in a multivariate analysis,

TABLE 2. *Association of clinical features with final pathological stage and surgical margin status*

	No.	No. pT2 N0 Confined (%)	No. pT3a,b N0 Extracapsular Extension, Only (%)	No. pT3c N0, Seminal Vesicle Invasion (%)	No. pT1-3 N +, Lymph Node Metastasis (%)	% Pos. Surgical Margins
Clinical stage:						
T1a	34	30 (88.2)	3 (8.8)	1 (2.9)	0	0
T1b	55	33 (60.0)	15 (27.3)	3 (5.5)	4 (7.3)	28.8
T1c	327	240 (73.4)	57 (17.4)	19 (5.8)	11 (3.4)	11.6
T2a	177	117 (66.1)	37 (20.9)	11 (6.2)	12 (6.8)	7.5
T2b	274	121 (44.2)	95 (34.7)	28 (10.2)	30 (10.9)	14.5
T2c	121	50 (41.3)	42 (34.7)	18 (14.9)	11 (9.1)	17.2
Overall %		(59.8)	(25.2)	(8.1)	(6.9)	12.8
Biopsy Gleason sum:						
2–4	111	84 (75.7)	20 (18.0)	3 (2.7)	4 (3.6)	12.7
5–6	613	410 (66.9)	145 (23.7)	31 (5.1)	27 (4.4)	10.8
7	229	86 (37.6)	75 (32.8)	39 (17.0)	29 (12.7)	14.0
8–10	38	11 (28.9)	10 (26.3)	8 (21.1)	9 (23.7)	38.9
Serum PSA (ng./ml.):						
0–3.9	190	141 (74.2)	38 (20.0)	5 (2.6)	6 (3.2)	5.3
4–9.9	460	308 (67.0)	105 (22.8)	28 (6.1)	19 (4.1)	9.2
10–19.9	164	80 (48.8)	49 (29.9)	17 (10.4)	18 (11.0)	19.5
20–49.9	68	14 (20.6)	25 (36.8)	15 (22.1)	14 (20.6)	29.2
50 or Greater	11	2 (18.2)	2 (18.2)	3 (27.3)	4 (36.4)	40.0

TABLE 4. *Actuarial cancer specific, metastasis-free and progression-free probability*

	No.	Mean % Cancer Specific ± 2 SE	Mean % Metastasis-Free ± 2 SE	Mean % Progression-Free ± 2 SE	
		10 Yrs.	10 Yrs.	5 Yrs.	10 Yrs.
Clinical stage:					
T1a,b	89	98.9 ± 2.37	94.2 ± 4.98	89.4 ± 6.55	89.4 ± 6.55
T1c	328	Not available	Not available	84.9 ± 6.61	Not available
T2a	179	97.9 ± 3.08	86.7 ± 6.02	82.2 ± 6.66	73.0 ± 12.6
T2b	274	95.9 ± 3.92	75.8 ± 9.23	67.2 ± 6.39	64.2 ± 7.00
T2c	122	97.5 ± 3.49	74.9 ± 11.3	69.9 ± 8.86	62.6 ± 11.5
Gleason Sum:					
2–4	111	100	94.7 ± 4.57	89.4 ± 5.96	87.8 ± 6.66
5–6	617	97.6 ± 2.67	88.8 ± 4.80	84.0 ± 3.72	78.9 ± 5.55
7	229	99.2 ± 1.63	58.3 ± 26.95	59.9 ± 8.31	55.9 ± 10.8
8–10	38	81.6 ± 17.6	57.6 ± 21.2	48.7 ± 17.4	40.5 ± 20.5*
Preop. PSA (ng./ml.):					
0–3.9	192	98.8 ± 2.37	94.7 ± 4.72	90.9 ± 4.86	89.2 ± 5.72
4–9.9	461	100	92.3 ± 3.80	86.9 ± 3.94	84.0 ± 5.45
10–19.9	164	95.0 ± 6.91	82.4 ± 8.27	69.3 ± 8.70	69.3 ± 8.70
20–49.9	68	96.3 ± 5.08	73.9 ± 11.8	50.2 ± 13.2	46.4 ± 14.2
50 or Greater	11	Not available	Not available	28.6 ± 42.7	Not available
Pathological stage:					
Confined	593	99.8 ± 0.3	97.8 ± 1.82	94.9 ± 2.78	92.2 ± 3.88
Extracapsular extension alone	251	97.1 ± 4.04	84.7 ± 7.57	76.3 ± 6.27	71.4 ± 7.49
Seminal vesicle invasion	81	94.6 ± 6.21	56.9 ± 20.9	37.4 ± 11.6	37.4 ± 11.6
Pos. lymph nodes	71	90.0 ± 9.60	29.6 ± 20.3	18.5 ± 10.2	7.41 ± 11.5
Surgical margin:					
Neg.	857	98.2 ± 1.72	88.1 ± 3.74	84.6 ± 3.00	80.8 ± 4.08
Pos.	126	94.3 ± 5.90	65.8 ± 19.1	41.6 ± 10.3	36.4 ± 11.4

* Longest followup in this group is 102.4 months.

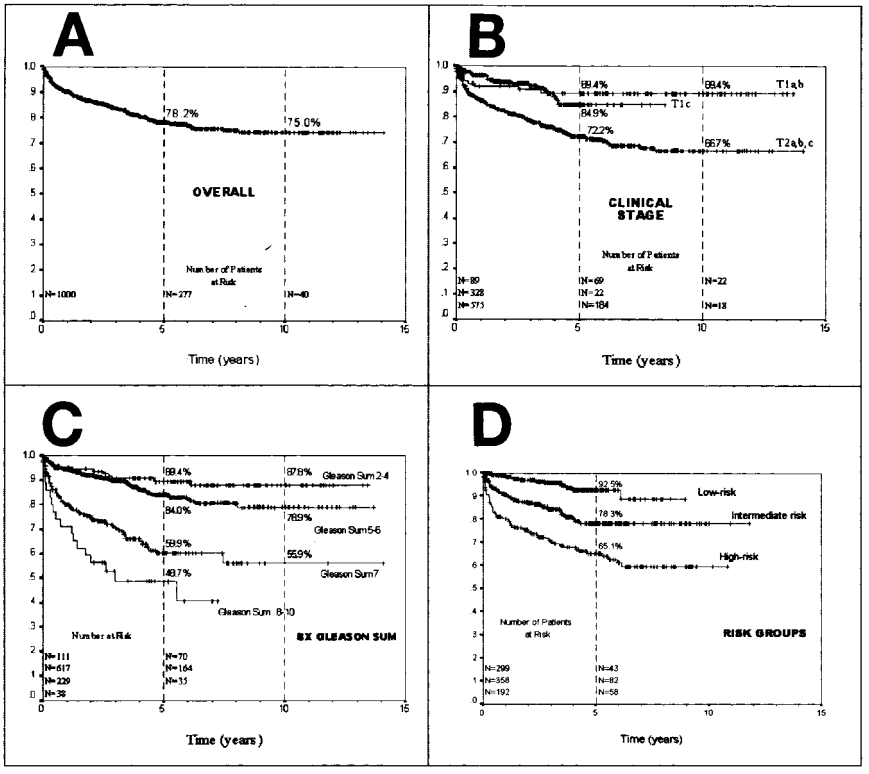

FIG. 1. Progression-free probability curves. *A*, all patients. *B*, clinical stage. *C*, biopsy (*BX*) Gleason sum. *D*, preoperative risk groups. Low risk is defined as clinical stage T1c or T2a, and Gleason sum 2 to 6 and PSA 10 ng./ml. or less. Intermediate risk is clinical stage T2b or Gleason sum 7 or PSA 10.1 to 20 ng./ml., and high risk is T2c or Gleason sum 8 to 10 or PSA greater than 20 ng./ml.[15] Number of patients at risk is shown on horizontal axis.

only the pathological factors, Gleason sum in the radical retropubic prostatectomy specimen ($p=0.0008$), level of extracapsular extension ($p=0.002$), surgical margins ($p<0.0001$), seminal vesical involvement ($p<0.0001$) and lymph node metastasis ($p<0.0001$) were significant independent predictors of progression. Clinical stage, preoperative PSA level and biopsy Gleason sum were not.

Risk stratification. The 849 patients with all data available, including clinical stage (excluding T1a,b), biopsy Gleason sum and PSA level, were stratified into 3 risk groups, as suggested by D'Amico et al,[15] and the 5-year progression-free probabilities were calculated (fig. 1, *D*). In low (PSA 10 ng./ml. or less, and clinical stage T1c or T2a and Gleason sum 6 or less), intermediate (PSA 10.1 to 20 ng./ml. or clinical stage

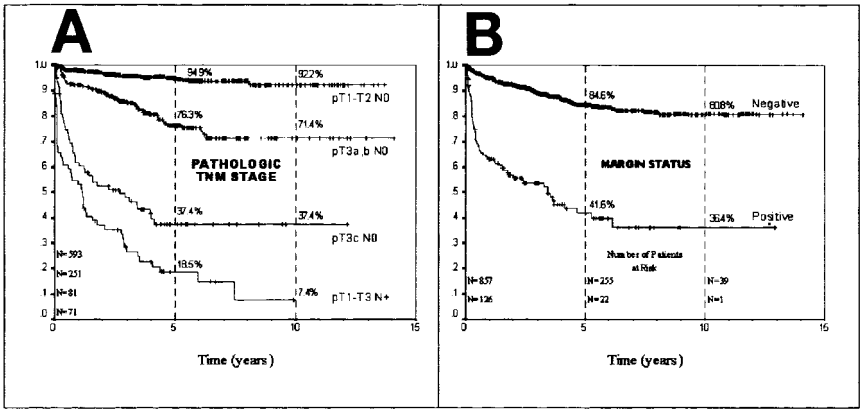

FIG. 2. Progression-free probability curves. *A*, pathological stage. *B*, surgical margin status

TABLE 5. *Univariate analysis of risk of progression based on preoperative clinical and pathological parameters*

	Relative Risk (95% CI)	p Value
Preop. clinical parameters		
Stage T1c vs.:		<0.0001
T1a,b		0.28*
T2a		0.15*
T2b	2.91 (1.84–4.58)	<0.0001
T2c	3.02 (1.81–5.04)	<0.0001
Biopsy Gleason sum:†		<0.0001
2–4 vs. 5–6		0.15*
5–6 vs. 7	2.93 (2.10–4.11)	<0.0001
5–6 vs. 8–10	4.90 (2.89–8.32)	<0.0001
Log_2 (preop. PSA)	2.07† (1.67–2.57)	<0.0001
Pathological parameters		
Prostatectomy specimen Gleason sum		<0.0001
2–4 vs. 5–6		0.95*
5–6 vs. 7	5.79 (3.69–9.08)	<0.0001
7 vs. 8–10	2.40 (1.64–3.51)	<0.0001
5–6 vs. 8–10	13.88 (8.20–23.5)	<0.0001
Extracapsular extension:		<0.0001
Focal vs. none	3.62 (2.22–5.91)	<0.0001
Established vs. none	9.80 (6.61–14.52)	<0.0001
Focal vs. established	2.70 (1.81–4.05)	<0.0001
Pos. vs. neg. surgical margins	5.97 (4.36–8.16)	<0.0001
Seminal vesicle involvement present vs. absent	8.04 (5.90–10.95)	<0.0001
Lymph node metastasis present vs. absent	8.97 (6.36–12.65)	<0.0001

* Not statistically significant ($p > 0.05$).

† Each doubling of the preoperative PSA level (1 unit increase in log_2 preoperative PSA level) resulted in an increased relative risk of progression of 2.07.

TABLE 6. *Multivariate analysis of risk of progression*

	Relative Risk (95% CI)	p Value
Preop. clinical parameters		
Clinical stage:		0.0071
T1a,b vs. T1c		0.60*
T1c vs. T2a		0.10*
T1c vs. T2b	2.47 (1.52–4.03)	0.0003
T1c vs. T2c	1.91 (1.06–3.42)	0.0304
Biopsy Gleason sum:†		<0.0001
2–4 vs. 5–6		0.15*
5–6 vs. 7	2.60 (1.75–3.87)	<0.0001
5–6 vs. 8–10	3.21 (1.72–5.97)	0.0002
Log_2 (preop. PSA)	1.80† (1.44–2.24)	<0.0001
Clinical, pathological parameters		
Clinical stage		0.15*
Biopsy Gleason sum		0.12*
Log_2 preop. PSA		0.52*
Prostatectomy specimen Gleason sum:		0.0008
2–4 vs. 5–6		0.97*
5–6 vs. 7	2.48 (1.34–4.58)	0.0038
5–6 vs. 8–10	4.55 (2.19–9.42)	<0.0001
Extracapsular extension:		0.0019
Focal vs. none	2.17 (1.20–3.92)	0.011
Established vs. none	2.72 (1.56–4.74)	0.0004
Focal vs. established		0.13*
Pos. vs. neg. surgical margins	4.37 (2.90–6.58)	<0.0001
Seminal vesicle involvement present vs. absent	2.61 (1.70–4.01)	<0.0001
Lymph node metastasis present vs. absent	3.31 (2.11–5.20)	<0.0001

* Not statistically significant ($p > 0.05$).

† Each doubling of the preoperative PSA level (1 unit increase in log_2 preoperative PSA level) resulted in an increased relative risk of progression of 1.80.

T2b or Gleason sum 7), and high risk patients (PSA greater than 20 ng./ml., or clinical stage T2c or Gleason sum 8 to 10) the 5-year progression-free probabilities were 92.5%, 78.3% and 65.1%, respectively.

DISCUSSION

Our consecutive series of patients treated with radical prostatectomy alone confirms the ability of this operation to provide excellent long-term cancer control in those with clinically localized cancer.[16–18] Although not a controlled trial, this prospective study provides reliable outcomes data for patients and for prognostic subsets that can be used in prognostic models and for medical decision making for those diagnosed with localized prostate cancer. Our series differs in several ways from other recently reported large series.[16–18] All 14 patients were analyzed as "intention to treat," regardless of whether radical retropubic prostatectomy was abandoned when lymph node metastasis was found. Also, 30 patients receiving adjuvant external beam radiotherapy or hormonal therapy after radical retropubic prostatectomy were considered to have progression or metastasis (if systemic therapy) at initiation of such treatment. Although adjuvant therapy was used in only 4% of patients in the Catalona and Smith series,[17] they were excluded from the study of Pound et al[16] who reported a total exclusion of 4.5%, including 1.2% with no postoperative PSA level, 1.4% with adjuvant radiotherapy, 0.6% with hormone therapy and 0.5% with lymph node metastasis. In the Mayo Clinic series 26% of patients received adjuvant therapy, yet treatment was not considered to have failed until biochemical or clinical recurrence.[18] Consequently, our report provides a more conservative estimate of the efficacy of radical retropubic prostatectomy as monotherapy, yet confirms the high rate of cancer control achieved with surgery alone.

The overall actuarial progression-free probability in our series was 75% at 10 years postoperatively. Few patients died of prostate cancer within 10 years of radical retropubic prostatectomy, except those in whom Gleason sum was 8 to 10 tumors who had a mean cancer specific survival probability $\pm$ 2 SE of 82% $\pm$ 18% at 102 months. These results further confirm the favorable 10-year cancer specific survival probabilities in poorly differentiated cancer treated with surgery

reported by Lu-Yao and Yao (67%, 95% CI 62% to 71%)[19] and Gerber et al (77%, 95% CI, 65 to 86).[20] These results appear substantially better than the extrapolated data on the 10-year cancer specific survival rate of only 22% to 44% in patients with high grade cancer managed conservatively,[2] and better than the 34% 10-year cancer specific survival rate and 26% 10-year metastatic-free probability reported by Chodak et al.[1]

We reported previously that poorly differentiated cancer that is confined to the prostate pathologically is highly likely to be controlled with radical prostatectomy.[21,22] Further evidence of the efficacy of surgery in poorly differentiated cancer was the 57.6% ± 21% 10-year metastasis-free survival rate for high grade cancer in this series, similar to the results of the multi-institutional analysis of surgery in similar patients by Gerber et al (52%, 95% CI 38% to 64%).[20] Additionally, in our series radical retropubic prostatectomy provided excellent cancer control in patients with advanced clinical stage or high preoperative PSA. At 10 years postoperatively the probability of freedom from progression was 64% in clinical stage T2b and 63% in T2c, 69% with a PSA 10 to 20 ng./ml. and 46% with a PSA 20 to 50 (table 4).

It is often stated that radical prostatectomy is an excellent form of therapy for cancer confined to the prostate. Yet, 71.4% of our patients with extracapsular extension, without seminal vesicle involvement or nodal metastasis, and 37.4% with seminal vesicle invasion, without nodal metastasis, remained free of progression at 10 years (fig. 2, *A*), which was similar to results reported by others.[16,18] In fact, greater than half our patients with cancer no longer confined to the prostate remained free of progression at 10 years postoperatively (fig. 3).

Although preoperative PSA levels and biopsy Gleason sum were strong independent predictors of progression in our series, clinical stage was a weak predictor. In fact, there was no difference in progression rates for the various T2 substages in multivariate analysis, including T2a versus T2b ($p=0.16$), T2a versus T2c ($p=0.44$) and T2b versus T2c ($p=0.59$). When clinical and pathological parameters were included in the multivariate analysis, Gleason sum in the prostatectomy specimen, surgical margin status and pathological stage were each strong independent predictors of progression. In fact, surgical margin status was among the most powerful predictors of progression. Patients with positive margins were greater than 4 times more likely to have recurrent cancer per year than those with negative margins (table 6).

Several recent publications have analyzed the results of surgery by stratifying patients into risk groups based on clinical stage, biopsy Gleason sum and preoperative serum PSA level.[15,23] For example, Kupelian et al reported radical retropubic prostatectomy cancer control rates at 5 years of 80% for low risk (PSA less than 10 ng./ml. and Gleason sum less than 7) and 34% for high risk patients (all others).[23] However, in their surgical cases the rate of positive surgical margins was remarkably high (49%). When we stratified our patients with the same categories, the 5-year freedom from progression was 92.1% for low and 66.2% high risk patients. In the 2 series, as well as others, margin status was a powerful independent risk factor for progression. Therefore, the marked difference in cancer control rates between our series and Kupelian et al[23] is likely related to our lower rate (12.8%) of positive margins. The difference in positive margin rates was striking for the low (7.7% in our present series versus 39% Kupelian et al) and high (18% versus 59%) risk groups.

D'Amico et al performed a similar risk stratified analysis comparing radical prostatectomy, external beam radiotherapy and brachytherapy with or without neoadjuvant androgen deprivation.[15] There were 3 risk groups in that study, including low risk cases that were defined as clinical stage T1c or T2a, Gleason sum 2 to 6 in the biopsy specimen and PSA 10 ng./ml. or less. Intermediate risk included those patients with stage T2b or Gleason sum 7 or PSA 10.1 to 20 ng./ml. High risk was stage T2c or Gleason sum 8 to 10 or PSA greater than 20 ng./ml. We grouped our patients similarly (fig. 1, *D*). In low risk patients the 5-year progression-free probability was 92.5%, similar to the results of all 4 treatments in the D'Amico et al series.[15] However, 78.3% of the intermediate and 65.1% of the high risk patients in our series were free of progression at 5 years postoperatively, results that appear substantially better than any treatment options reported by D'Amico et al. Our results suggest that they underestimated the efficacy of surgery for intermediate and high risk cancers. Although the rate of positive margins was not reported by them, it is possible that our low rate of positive margins explains the superior results. Positive margins are far too common (range 24% to 42%) in modern surgical series and have been shown to affect prognosis adversely in most series.[9,23–26] Positive margins can be minimized by meticulous preoperative planning and attention to technique during the operation.[8,9,27]

We recognize important limitations of our study. Although the data were collected prospectively, this study was not randomized comparing radical retropubic prostatectomy to other treatment modalities for localized prostate cancer. Our series reflects the efforts of 1 surgeon and 1 pathologist at 1 institution. The outcomes achieved may not be generally applicable, although the overall results are similar to those reported by Pound et al,[16] and Catalona and Smith.[17] Finally, mean followup in our series was only 53.2 months. Further evaluation is needed to confirm the long-term cancer specific survival and metastatic progression rates.

The validity of our results is supported by several findings. The progression-free survival curves appear to plateau after 5 years, the 95% CI is relatively narrow at 10 years and only 5% of the treatment failures occurred after 5 years, although we analyzed 12,140 patient-months of followup beyond 5 years. Nevertheless, a recent report with longer observation demonstrated that 23% of treatment failures occurred after 5 years,[28] although some patients in that series received adjuvant therapy, and treatment was not considered a failure until the disease progressed. Adjuvant therapy may not prolong survival substantially, but it may delay apparent progression.

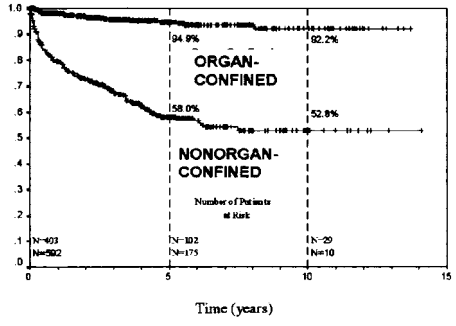

FIG. 3. Progression-free probability in patients with cancer confined to prostate in radical prostatectomy specimen or not confined, including those with extracapsular extension, seminal vesicle involvement or lymph node metastasis.

CONCLUSIONS

Our results in a consecutive series of 1,000 patients confirm the long-term efficacy of surgery alone for clinical stage T1 to T2 prostate cancer. Surgery was remarkably effective, even in high risk patients.[15] Favorable rates of cancer control in our series may be related to the low rate of positive surgical margins, emphasizing the importance of complete excision when prostate cancer is treated surgically.

REFERENCES

1. Chodak, G. W., Thisted, R. A., Gerber, G. S. et al: Results of conservative management of clinically localized prostate cancer. N Engl J Med, **330:** 242, 1994
2. Albertsen, P. C., Hanley, J. A., Gleason, D. F. et al: Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA, **280:** 975, 1998
3. Wilt, T. J. and Brawer, M. K.: The Prostate Cancer Intervention Versus Observation Trial (PIVOT). Oncology (Huntingt), **11:** 1133, 1997
4. Kattan, M. W., Cowen, M. E. and Miles, B. J.: A decision analysis for treatment of clinically localized prostate cancer. J Gen Intern Med, **12:** 299, 1997
5. Kattan, M. W., Eastham, J. A., Stapleton, A. M. et al: A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst, **90:** 766, 1998
6. Ohori, M., Wheeler, T. M. and Scardino, P. T.: The New American Joint Committee on Cancer and International Union Against Cancer TNM classification of prostate cancer. Clinicopathologic correlations. Cancer, **74:** 104, 1994
7. Rifkin, M. D., Zerhouni, E. A., Gatsonis, C. A. et al: Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. Results of a multi-institutional cooperative trial. N Engl J Med, **323:** 621, 1990
8. Stapleton, A. M. F. and Scardino, P. T.: Nerve-sparing radical retropubic prostatectomy. In: Atlas of Clinical Urology. The Prostate. Edited by J. D. McConnell and P. T. Scardino. Philadelphia: Current Medicine, vol. 2, p. 11.1, 1999
9. Eastham, J. A. and Scardino, P. T.: Radical prostatectomy for clinical stage T1 and T2 prostate cancer. In: Comprehensive Textbook of Genitourinary Oncology, 2nd ed. Edited by N. J. Vogelzang, P. T. Scardino, W. U. Shipley et al. Philadelphia: Lippincott Williams & Wilkins, p. 722, 2000
10. Wheeler, T. M.: Anatomy and pathology of prostate cancer. In: Comprehensive Textbook of Genitourinary Oncology, 2nd ed. Edited by N. J. Vogelzang, P. T. Scardino, W. U. Shipley et al. Philadelphia: Lippincott Williams & Wilkins, p. 587, 2000
11. Wheeler, T. M., Dillioglugil, O., Kattan, M. W. et al: Clinical and pathological significance of the level and extent of capsular invasion in clinical stage T1–2 prostate cancer. Hum Pathol, **29:** 856, 1998
12. Kaplan, E. L. and Meier, P.: Nonparametric estimation from incomplete observations. J Amer Stat Ass, **53:** 457, 1958
13. Peto, R., Pike, M. C., Armitage, P. et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer, **35:** 1, 1977
14. Cox, D. R.: Regression models and life tables. J R Stat Soc [Ser B], **34:** 187, 1972
15. D'Amico, A. V., Whittington, R., Malkowicz, S. B. et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA, **280:** 969, 1998
16. Pound, C. R., Partin, A. W., Epstein, J. I. et al: Prostate-specific antigen after anatomic radical retropubic prostatectomy. Patterns of recurrence and cancer control. Urol Clin North Am, **24:** 395, 1997
17. Catalona, W. J. and Smith, D. S.: Cancer recurrence and survival rates after anatomic radical retropubic prostatectomy for prostate cancer: intermediate-term results. J Urol, **160:** 2428, 1998
18. Zincke, H., Oesterling, J. E., Blute, M. L. et al: Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. J Urol, **152:** 1850, 1994
19. Lu-Yao, G. L. and Yao, S. L.: Population-based study of long-term survival in patients with clinically localised prostate cancer. Lancet, **349:** 906, 1997
20. Gerber, G. S., Thisted, R. A., Scardino, P. T. et al: Results of radical prostatectomy in men with clinically localized prostate cancer. JAMA, **276:** 615, 1996
21. Balaji, K. C., Wheeler, T. and Scardino, P.: Poorly differentiated prostate cancers (PCa) on prostatic biopsy detected by elevated PSA alone are more likely to be organ-confined than those detected by abnormal digital rectal examination (DRE) resulting in better progression free probability (PFP). Proc ASCO, suppl., **18:** 318a, 1999
22. Ohori, M., Goad, J. R., Wheeler, T. M. et al: Can radical prostatectomy alter the progression of poorly differentiated prostate cancer? J Urol, **152:** 1843, 1994
23. Kupelian, P., Katcher, J., Levin, H. et al: External beam radiotherapy versus radical prostatectomy for clinical stage T1–2 prostate cancer: therapeutic implications of stratification by pretreatment PSA levels and biopsy Gleason scores. Cancer J Sci Am, **3:** 78, 1997
24. Abbas, F. and Scardino, P. T.: Why neoadjuvant androgen deprivation prior to radical prostatectomy is unnecessary. Urol Clin North Am, **23:** 587, 1996
25. Weider, J. A. and Soloway, M. S.: Incidence, etiology, location, prevention and treatment of positive surgical margins after radical prostatectomy for prostate cancer. J Urol, **160:** 299, 1998
26. Grossfeld, G. D., Chang, J. J., Broering, J. M. et al: Impact of positive surgical margins on prostate cancer recurrence and the use of secondary cancer treatment: data from the CaPSURE database. J Urol, **163:** 1171, 2000
27. Klein, E. A., Kupelian, P. A., Tuason, L. et al: Initial dissection of the lateral fascia reduces the positive margin rate in radical prostatectomy. Urology, **51:** 766, 1998
28. Pound, C. R., Partin, A. W., Eisenberger, M. A. et al: Natural history of progression after PSA elevation following radical prostatectomy. JAMA, **281:** 1591, 1999