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PATTERN OF FAILURE AFTER RADICAL RETROPUBIC PROSTATECTOMY FOR CLINICALLY AND PATHOLOGICALLY LOCALIZED ADENOCARCINOMA OF THE PROSTATE: INFLUENCE OF TUMOR DEOXYRIBONUCLEIC ACID PLOIDY

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ABSTRACT

From 1966 to 1980, 315 patients underwent bilateral pelvic lymphadenectomy and radical retropubic prostatectomy without adjuvant treatment for clinically and pathologically localized adenocarcinoma of the prostate. Followup was 5 to 21 years, with a median of 8 years. The disease was pathological stage A in 24 patients (8%) and pathological stage B in 291 (92%). A total of 45 patients (14.2%) experienced progression. Over-all, 28 patients (8.9%) suffered local recurrence at a mean of 6.6 years postoperatively (median 5.5 years). Local recurrence was noted as late as 15 years postoperatively. Over-all, systemic progression was observed in 25 patients (8%) after a mean of 4.7 years (median 6 years). Eight patients (2.5%) experienced local and systemic failure. The projected local and systemic failure rates at 15 years were 22% and 15%, respectively. Disease-specific survival at 15 years was 93%, since only 11 patients (3.4%) died of prostate cancer. In an age-matched case control analysis, after all prognostic variables were analyzed (Mayo grade, Gleason score, capsule involvement, number of foci, volume of tumor and deoxyribonucleic acid tumor ploidy), progression was related to nondiploid deoxyribonucleic acid tumor ploidy (p less than 0.0004) as determined by flow cytometry in 63% of the patients who evidenced progression versus 8% of the nonrecurrent group. (*J. Urol., 142: 1262–1265, 1989*)

Traditionally, poor tumor differentiation, capsular penetration and large tumor bulk have been associated with poor prognosis after radical retropubic prostatectomy for localized adenocarcinoma of the prostate.[1–6] However, it is apparent that local and systemic failure occurs even when lesions are confined pathologically to the prostate in 10 to 26% of the patients.[3–6] In an attempt to improve upon the predictive value of histological factors for patients with organ-confined adenocarcinoma of the prostate, we studied 315 patients who underwent bilateral pelvic lymphadenectomy and radical retropubic prostatectomy for clinically and pathologically localized disease. A total of 38 patients who experienced progression along with 38 age-matched controls underwent a case-control analysis to evaluate the association of recurrence with histological parameters and with tumor deoxyribonucleic acid (DNA) ploidy.

MATERIALS AND METHODS

From July 1966 through December 1980 we identified 315 patients who underwent bilateral pelvic lymphadenectomy and radical retropubic prostatectomy for clinically and pathologically localized adenocarcinoma of the prostate without adjuvant therapy. Absence of metastases was established in all patients by negative results from preoperative radionuclide bone scanning, and radiological and biochemical studies, as well as examination of excised pelvic lymph nodes. For the purposes of this study a stage A1 lesion was defined as a clinically inapparent tumor found at resection for benign disease that was less than 1 cc in volume and well differentiated (Mayo grade 1 or 2). Stage A2 was a clinically inapparent tumor 1 cc or more in volume or any tumor of any volume that was poorly differentiated (grade 3 or 4). Stage B1 was an intracapsular lesion 2 cm. or less in greatest linear diameter and stage B2 was either an intracapsular lesion greater than 2 cm. in linear diameter or involving both lobes with or without invasion but not penetration of the prostate capsule.[4]

Patients were evaluated quarterly for 1 year postoperatively, biannually for 1 year and annually thereafter if there was no evidence of disease progression. These tests (almost always performed at our clinic) routinely included chest, pelvis and lumbar spine roentgenograms, hematology and chemistry groups, enzymatic acid phosphatase levels and tartrate inhibition fraction. Bone scanning was performed at least twice a year during the first 2 years and later annually or more often if indicated. Disease progression was judged to be present if there was biopsy proved local recurrence or if radionuclide bone scans and/or roentgenograms became positive, usually preceded or accompanied by an increase in the acid phosphatase level. An abnormal acid phosphatase level alone, that is without demonstrable concomitant visual or palpable pathological changes, was not considered to be consistent with progression of disease. Survival to progression (either local or systemic), over-all interval free of disease and cause-specific survival curves were constructed by the Kaplan-Meier method and compared with log-rank tests.[7] The closing date for observation was January 1, 1986.

All stage A tumors were initially diagnosed by examination of transurethrally resected prostatic chips. Among the 90 cases selected for closer analysis, prostatic tissue preserved in formalin and stored in the tissue registry was totally embedded for microscopic study.

All radical prostatectomy specimens were examined by the pathologist immediately after resection in the fresh state using gross inspection as well as multiple frozen sections. All surgical margins were checked, including the urethra, prostatic apex, bladder neck, prostatic capsule, and periprostatic tissue posteriorly and around the seminal vesicles. Multiple sections from the prostate were examined by frozen section and later by

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routine paraffin sections, and tumor volume, location, Mayo grade and Gleason score were recorded. All lymph nodes from the lymphadenectomy were examined by frozen section and again later by paraffin section. Metastases were recorded in the pathology report by number of involved lymph nodes and by location.

Because of the time that would be required for pathological review of all 315 patients 90 were selected for closer analysis. They were derived from a group that included all 45 patients with progression (local and/or systemic) of disease and 45 matched controls without evidence of disease progression. The matching criteria were patient age, year of operation and followup interval for the control longer than the progression interval for the patient. For 3 patients the age requirement had to be relaxed to find a control. The age differences of these pairs were 1.6, 3.7 and 6.1 years. In 6 patients adequate tissue for review was not available and in 1 patient followup was deemed unreliable, leaving 38 age-matched pairs for the study. Paraffin-embedded blocks and available slides were reviewed by the study pathologist (G. M. F.) in a blind fashion. The parameters studied were Mayo grade, Gleason score, tumor volume (less than 3, 3 to 10 and greater than 10 cc), unifocal versus multifocal, status of capsule (not involved, invaded but not penetrated) and DNA tumor ploidy determined by flow cytometry. Nuclear DNA tumor ploidy was determined by the Hedley and Vindeløv technique for analyzing paraffin-embedded archival material.[8, 9] This method has been reported by Winkler and associates for prostate tumor at our institution.[10] Classification of tumor DNA histograms was divided into DNA diploid and DNA nondiploid (DNA tetraploid and DNA aneuploid patterns). Statistical analysis of these parameters was performed with McNamar's method.[11]

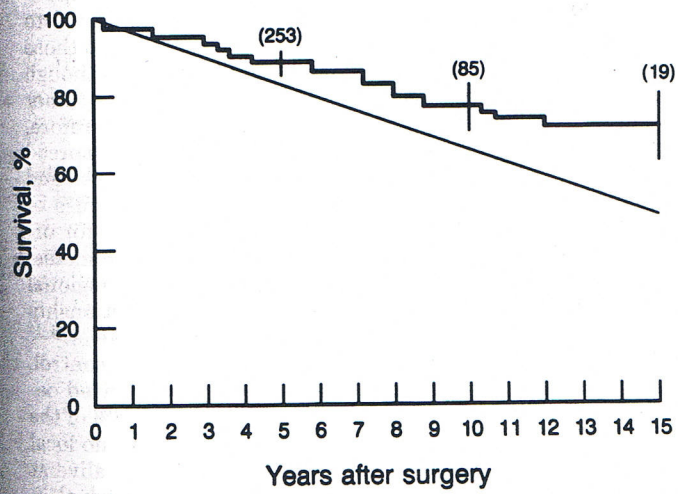

FIG. 1. Over-all observed survival (▬) for 315 patients who underwent radical retropubic prostatectomy for localized (stage pT2 or less) prostate cancer compared to expected survival (—) of age-matched cohort seen during same interval (1966 to 1980).

RESULTS

Mean age at diagnosis of the 315 patients was 62.5 years (range 38 to 80 years). With the initial pathology report, of the 315 cancer patients 18 (5.7%) had pathological stage A1, 6 (1.9%) stage A2, 139 (44%) stage B1 and 152 (48.3%) stage B2 disease. Patients were followed for 5 to 21 years (median followup 8 years). A total of 45 patients (14.2%) experienced progression. The over-all survival at 15 years was 71% (fig. 1). The disease-specific survival at 15 years was 93% (fig. 2, *A*) and the survival free of disease was 70% (fig. 2, *B*). Projected survival curves to local and systemic recurrence are depicted in figure 3.

Over-all, 28 patients (8.9%) suffered local recurrence at a mean of 6.6 years (range less than 1 to 15 years, median 5.5 years) postoperatively. Local recurrences were seen as late as 15 years postoperatively and 8 of the recurrences (28%) were seen after 10 years (table 1). Systemic progression was observed in 25 patients (8%) at a mean of 4.7 years (range 4 to 15 years, median 6 years). Eight patients (2.5%) suffered local and systemic failure. At local recurrence 6 patients received radiation therapy: 1 is alive with stable metastases and 5 have no evidence of disease. The remaining 22 patients received hormonal manipulation in the form of diethylstilbestrol therapy (3 mg. or less orally daily) or bilateral orchiectomy. Of these 22 patients 11 are alive with no evidence of disease, 4 are alive with stable metastases, 3 died of metastatic prostate cancer and 4 died of other causes. Therefore, in 8 patients who suffered local recurrence systemic disease eventually was detected and of these 3 died of prostate cancer. All 25 patients who failed initially with systemic disease were treated with early hormonal therapy and 8 died of prostate cancer. Of the remaining 17 patients 9 are without evidence of disease, 5 have stable metastases and 3 died of other causes.

The prostatectomy specimens of 38 patients who suffered progression and 38 age-matched controls underwent DNA ploidy flow cytometric evaluation, along with pathological review (table 2). Of the 6 prognostic variables (Mayo grade, Gleason grades, multiplicity of tumor foci, tumor volume, capsule involvement and DNA tumor ploidy) only tumor ploidy was at all significant (table 3). There were no aneuploid patients in the nonrecurrent group. Of the 24 nondiploid patients in the recurrent group 15 (63%) failed systemically and the remaining 9 (38%) locally. In the diploid group 8 patients (57%) failed locally and 6 (43%) systemically.

DISCUSSION

We focus on identifiable factors about the biology of prostate cancer that would place patients at increased risk for failure of definitive treatment of pathologically localized disease. Many clinicopathological studies have shown the importance of tumor

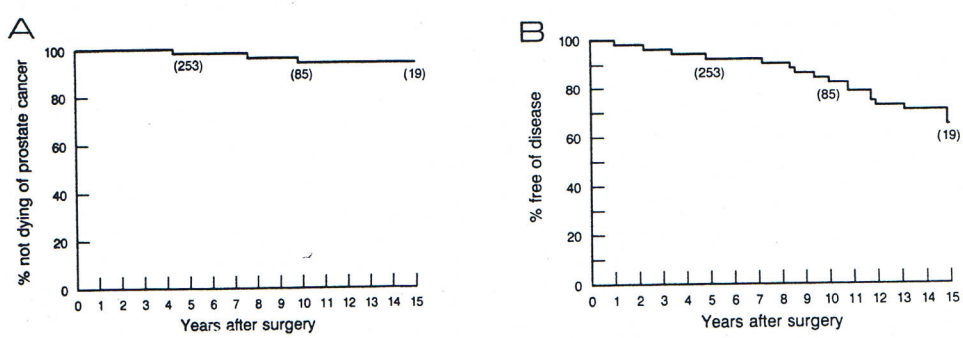

FIG. 2. Survival of 315 patients who underwent radical retropubic prostatectomy for localized (stage pT2 or less) prostate cancer (1966 to 1980). *A*, cause-specific survival. *B*, survival free of disease.

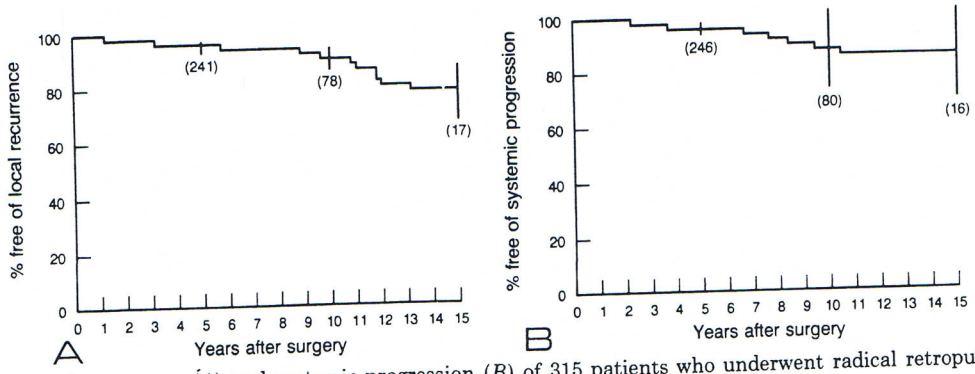

FIG. 3. Survival to local recurrence (*A*) and systemic progression (*B*) of 315 patients who underwent radical retropubic prostatectomy for localized (stage PT2 or less) prostate cancer.

TABLE 1. *Interval to recurrence in 45 patients who failed definitive treatment (bilateral pelvic lymph node dissection and radical retropubic prostatectomy) with clinically and pathologically confined adenocarcinoma of the prostate*

Yrs.	Local Recurrence No. (%)	Systemic Recurrence No. (%)
≦5	13 (46)	11 (44)
6–10	7 (25)	13 (52)
11–15	8 (29)	1 (4)
Totals*	28	25

* Eight patients suffered local and systemic failure.

TABLE 2. *Pathological variables and DNA tumor ploidy determined by flow cytometry for 76 patients who underwent bilateral pelvic lymph node dissection and radical retropubic prostatectomy without adjuvant treatment for clinically and pathologically confined adenocarcinoma of the prostate*

	Group 1 No. (%)	Group 2 No. (%)	P Value
Mayo grade:			
1–2	23 (61)	28 (74)	0.30
3–4	15 (39)	10 (26)	
Gleason score:			
3–5	13 (34)	15 (39)	0.36
6–9	25 (66)	23 (61)	
Tumor vol. ($cm.^3$):			
<3	30 (79)	28 (74)	
3–10	7 (18)	9 (24)	0.99
>10	1 (3)	1 (3)	
Multifocal:			
No	28 (74)	27 (71)	0.99
Yes	10 (26)	11 (29)	
Capsular invasion:			
Yes	25 (66)	17 (45)	0.48
No	13 (34)	21 (55)	
DNA tumor ploidy:			
Diploid	14 (37)	35 (92)	
Tetraploid	13	3	0.0004
Aneuploid	11 24 (63)	0 3*(8)	

Group 1—38 patients who experienced progression (local/systemic), group 2—38 age-matched controls who did not experience progression.
* Followup for these 3 patients is 14, 12 and 7 years.

TABLE 3. *Association of various prognostic variables of 38 case/control pairs who underwent bilateral pelvic lymph node dissection and radical retropubic prostatectomy for clinically and pathologically confined adenocarcinoma of the prostate*

Factor	Odds Ratio*	38 Case/Control Pairs	
		Mean	P Value
Grade 3–4 vs. 1–2	10/5 = 2	1.1	0.30
Gleason grade 6–9 vs. 3–5	12/7 = 1.7	0.84	0.36
Vol. >3 vs. <3 ($cm.^3$)	5/6 = 0.83	0	1.0
Nondiploid vs. diploid	17/1 = 17	12.5	0.0004
Capsular involvement (yes vs. no)	11/7 = 1.6	0.5	0.48
Foci ≧1 vs. 1	7/8 = 0.88	0	1.0

* Odds of progressive disease calculated with McNamar's method.[11]

grade, tumor bulk, capsular involvement or perforation as important independent variables in terms of local recurrence and survival from prostate cancer.[1–6] What is not easily understood is the failure of radical prostatectomy for apparent pathologically organ-confined disease after radical retropubic prostatectomy. The incidence of local recurrence after prostatectomy from series with up to 15 years of followup varies from 10 to 26%.[1–6] Jewett and associates believed the cause of local failure to be incomplete resection of disease, and on review of 21 local therapeutic failures they upstaged 43% when examination of a larger number of sections revealed partial or complete capsular penetration.[1] Therefore, we insist that data should be reported according to pathological rather than clinical staging because of the significant clinical staging errors. For example, we found among 1,102 patients with clinical stages B and B2 disease that only 49% should have pathologically localized cancer (unpublished data). Myers and Fleming noted a shorter interval to local progression with capsular perforation as opposed to those with only partial invasion but capsular invasion, although related to systemic failure (probably because of large tumor bulk), was not associated with higher local failure.[8] Therefore, local failure must be due to unrecognized periprostatic spread or disruption of capsular tissue that is involved by cancer and unresected at radical retropubic prostatectomy. The cause of systemic failure after radical retropubic prostatectomy for organ-confined disease must be due to undetected micrometastases at operation, or dissemination from unrecognized regional or local recurrence. Few studies have addressed the relationship among local control, disseminated disease and survival.[11–13] Kuban and associates found a relationship among local control, systemic recurrence and survival in patients who received definitive radiation.[12] Distant metastases developed in 68% of the patients who failed local control compared to 37% with no local disease. Survival was significantly affected, with 86% alive at 5 years with locally controlled tumor versus 56% survival in those with locally recurrent disease.[12] Indeed, disseminated disease eventually was discovered in 8 patients from this study who experienced local recurrence and 3 died of prostate cancer.

There is little clinical information to predict the risk of local and systemic failure after radical retropubic prostatectomy for histologically confined cancer. The need for prolonged followup has been demonstrated by Culp, who reported that 15% of the patients did not experience local failure until after 10 years.[3] This has been reaffirmed in our study, since 29% of the local failures were detected after 10 years. In an attempt to improve upon the predictive value of histological factors on local and distant failure for organ-confined prostate cancer, we obtained objective information of DNA tumor ploidy by flow cytometry. Analysis of tumor nuclear DNA content by flow cytometry has been demonstrated to be useful to predict the clinical course of patients with various urological malignant lesions.[14] A few studies in which the Hedley method[9] of analyzing nuclear DNA content of adenocarcinoma of the prostate by extracting nuclei from formalin-fixed archival pathological material have been

published. These studies confirm that patients with a DNA diploid ploidy pattern have a better prognosis than patients with a nondiploid ploidy pattern.[14–18] It is apparent from this study that the DNA ploidy pattern uncovered some important prognostic information that is blind to histological examination for organ-confined prostate cancer. It particularly is noteworthy that traditional histological factors, such as tumor grade, tumor volume and capsular involvement, did not demonstrate predictive power for failure compared to tumor DNA ploidy pattern.

No other treatment surpasses radical retropubic prostatectomy in terms of nonprogressive and disease-specific survival for organ-confined prostate cancer.[5] Radical prostatectomy for localized prostate cancer is associated with a projected cancer death rate of only 7% at 15 years. However, it is apparent that local failure is not rare after radical prostatectomy and it may occur even when tumor reportedly is confined to the prostate by histological examination. A surprisingly high projected local recurrence rate of 22% at 15 years may respond to earlier adjuvant treatment in patients at risk for recurrence. A nondiploid tumor DNA ploidy pattern is a powerful predictor for ultimate local or systemic failure, as found in 63% of our patients who failed.

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