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PROSPECTIVE EVALUATION OF MEN WITH STAGE T1C ADENOCARCINOMA OF THE PROSTATE

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Abstract

Purpose—The pathological characteristics of stage Tlc cancers in the era of widespread prostate specific antigen (PSA) testing were determined, and the ability of pretreatment parameters to predict tumor significance in men with stage Tlc disease was evaluated.

Materials and Methods—Of 336 men with stage Tlc prostate cancer seen between 1994 and 1996, 240 (71.4%) were treated with radical prostatectomy, 20 (6%) with radiation therapy and 76 (22.6%) expectantly. Recommendations for treatment were based on previously determined criteria predictive of a significant stage Tlc cancer (more than 0.2 $cm.^3$: 1) PSA density 0.15 ng./ml./gm. or more, 2) Gleason score 7 or greater, 3) 3 or more cores involved with cancer, or 4) 50% or more involvement of any core with cancer. Pathological evaluation of prostatectomy specimens allowed classification of tumors as insignificant (confined tumor smaller than 0.2 $cm.^3$ with a Gleason score of less than 7), minimal (confined tumor 0.2 to less than 0.5 $cm.^3$ with a Gleason score of less than 7), moderate (0.5 $cm.^3$ or larger disease, or capsular penetration with a Gleason score of less than 7) and advanced (capsular penetration with a Gleason score of 7 or more, or positive margins, seminal vesicles or lymph nodes). Pathological characteristics of tumors in this series were compared to a previous series of 157 men with stage Tlc cancers who underwent radical prostatectomy between 1988 and 1992.

Results—Of 240 men who underwent radical prostatectomy tumors were insignificant in 40 (17%), minimal in 29 (12%), moderate in 124 (52%) and advanced in 47 (19%). An increase in organ confined cancers (51 to 72%) and a decrease in positive margins (17 to 8%) were noted when comparing stage Tlc series (1988 to 1992 versus 1994 to 1996) but the percentage of insignificant tumors remained stable (16 versus 17%) between series. Ultrasound and sextant biopsies were available for review in 72 cases (current series). If the pretreatment criteria used to recommend therapy suggested significant tumor (64 cases) then insignificant tumor was present in only 10 (16%). If pretreatment criteria suggested insignificant tumor (8 cases), insignificant or minimal tumor was present in 6 (75%) and moderate organ confined disease was present in 2 (25%). The absence of a lesion on ultrasound and measurement of total length of cancer within the biopsy specimen were not predictive of an insignificant tumor.

Conclusions—In a nonscreened population stage Tlc cancers are being discovered earlier with widespread PSA testing. Even with the detection of earlier cancers we demonstrated that it is possible to minimize the number of patients with small tumors who will undergo radical prostatectomy using pretreatment criteria to counsel men regarding appropriate management options.

Keywords

adenocarcinoma; prostatic neoplasms; pathology

The widespread use of prostate specific antigen (PSA) for prostate cancer detection has resulted in diagnosis and treatment earlier in the natural history of the disease.[1] Men who undergo routine PSA testing are most commonly diagnosed with nonpalpable prostate cancers that are discovered when disease is suspected based on a PSA elevation (stage Tlc). The majority of PSA detected prostate cancers would appear to be significant based on size, grade and extent.[2] However, some of these tumors are small and may pose no threat during the lifetime of the host. One would anticipate that widespread serial PSA testing would detect more of these smaller tumors, which are more likely to be organ confined.

Epstein et a1 described pretreatment criteria, based on PSA density and pathological findings on needle biopsy, that could be used to help identify men with the smallest tumors.[2] These criteria were identified retrospectively from a radical prostatectomy series of men with stage Tlc prostate cancer. We prospectively applied these criteria to help men with stage Tlc prostate cancer choose reasonable treatment options. We compared this contemporary series of stage Tlc prostate cancers to an older series[2] to determine the pathological characteristics of stage Tlc carcinoma in the era of widespread PSA testing, and we evaluated the ability of pretreatment parameters to predict tumor significance in men with stage Tlc disease.

METHODS

study groups

Between October 1994 and April 1996, 336 men with stage Tlc prostate cancer were seen by 2 of us (P. C. W. and H. B. C.). Stage Tlc adenocarcinoma of the prostate was defined as a nonpalpable prostate cancer detected by transrectal ultrasound directed prostatic biopsies regardless of the ultrasound findings. Of 336 men 240 (71.4%) with stage Tlc disease underwent radical retropubic prostatectomy (mean age 58 years), 20 (6%) were treated with radiation therapy (mean age 63 years) and 76 (22.6%) were treated expectantly (mean age 64 years). Recommendations for therapy were based on pretreatment criteria previously identified retrospectively to be predictive of a significant stage Tlc cancer (0.2 $cm.^3$ or larger): 1) PSA density 0.15 ng./ml./gm. or more, 2) Gleason score 7 or greater, 3) 3 or more cores involved with cancer, or 4) 50% or more involvement of any core with cancer.[2] Expectant treatment was presented as a reasonable option only if none of these conditions was present. Men believed to have significant tumors based on these criteria were counseled for treatment of prostate cancer. A previous series of patients with stage Tlc prostate cancer treated with radical prostatectomy between 1988 and 1992 was used as a comparison group.[2]

Serum PSA and prostate ultrasound data

In 238 of 240 patients (99%) serum PSA was measured preoperatively and at least 4 weeks after prostate needle biopsy using a monoclonal radioimmunoassay (Tandem-R*). PSA density was determined by dividing the serum PSA by the prostate volume on transrectal ultrasound at prostate biopsy. Of 138 ultrasound reports (58%) available for review from the 240 men who underwent radical prostatectomy 131 clearly documented the presence (58, or 44%) or absence (73, or 56%) of suspicious lesions and the location of ultrasound abnormalities.

Pathological evaluation

All prostate needle biopsies were reviewed by 1 pathologist (J. I. E.). Gleason score, Gleason pattern 4 or 5, number of cores involved with cancer, percentage of tumor involving the biopsy core, and total length of cancer in the biopsy cores were determined. Sextant biopsies were available for review in 72 cases together with the prostate volume measured

by ultrasound. These 72 cases were used to calculate the predictive value of pretreatment criteria with respect to tumor significance.

After radical prostatectomy the 240 specimens were processed as described previously to allow Gleason grading, pathological staging, designation of margin status, tumor mapping and calculation of tumor volume.[3-6] Pathological stage was described as organ confined, focal capsular penetration (a few neoplastic glands exterior to the prostate), established capsular penetration (more extensive extraprostatic spread), seminal vesicle invasion (tumor penetrating the muscular coat of the seminal vesicles) or lymph node involvement. Capsular margins of resection were designated as negative or positive.

The current definition of a significant cancer is imprecise, and must consider factors other than tumor size and grade. In our study the tumors from the 240 surgical specimens were classified into 1 of 4 categories as described Previously: 1) insignificant (confined tumor smaller than 0.2 $cm.^3$ with a Gleason score of less than 7), 2) minimal confined tumor 0.2 to less than 0.5 $cm.^3$ with a Gleason score of less than 7), 3) moderate (0.5 $cm.^3$ or larger disease, or capsular penetration with a Gleason score of less than 7) and 4) advanced (capsular penetration with a Gleason score of 7 or more, or positive margins, seminal vesicles or lymph nodes).[2] Recognizing that some investigators use a 0.5 $cm.^3$ cutoff point to define a tumor of significant size, we showed the data for insignificant and minimal tumor so that the results can be according to individual classifications. One surgical specimen with a capsular incision was designated as a minimal tumor with a positive margin.

Prediction of tumor significance using pretreatment criteria

To calculate positive and negative predictive values using pretreatment criteria minimal, moderate and advanced tumors were considered together as significant tumors and compared to insignificant lesions. The pretreatment criteria evaluated with respect to prediction of significant cancers were: 1) the presence or absence of a suspicious lesion on transrectal ultrasound among 131 men for whom this information was available; 2) the presence or absence of 3 mm. or more of cancer (or any Gleason grade 4 or 5) on any biopsy core among the 240 men who underwent radical prostatectomy, and 3) the presence of any or absence of all PSA density 0.15 ng./ml./gm. or more, Gleason score 7 or more, 3 or more cores involved with cancer, or 50% or more of any core involved with cancer among 72 men with sextant biopsies and ultrasound determined prostate size available for review. The positive predictive value refers to how often, when a pretreatment criterion predicted significant tumor, there was actually significant tumor within the radical prostatectomy specimen. The negative predictive value refers to how often, when a pretreatment criterion predicted insignificant tumor, insignificant tumor was actually present.

RESULTS

The pathological data for the 240 men who underwent radical prostatectomy are shown in table 1. The majority of men had moderately differentiated tumors that were posteriorly located (peripheral zone), organ confined and larger than 0.5 cm^3. The characteristics of stage T1c prostate cancers treated surgically between 1988 and 1992, and between 1994 and 1996 are compared in table 2. An increase in the number of organ confined tumors (51 versus 72%) and a decrease in the prevalence of positive surgical margins (17 versus 8%) were noted when comparing the old and new series. However, the incidence of men with insignificant tumors was similar between the series (16 versus 17%).

The ability of pretreatment criteria to predict the significance of stage Tlc cancers is shown in table 3. A lesion on transrectal ultrasound and 3 mm. or more of cancer (or a Gleason pattern of 4 or 5) within any biopsy core were predictive of a significant tumor (positive

predictive value of 83 and 87%, respectively). However, the absence of these criteria was not predictive of an insignificant tumor (negative predictive value of 22 and 28%, respectively). The pretreatment criteria based on a combination of PSA density, Gleason score, number of cores involved with cancer and percentage of cancer within the core had the highest positive and negative predictive values of 84 and 63%, respectively. If these pretreatment criteria suggested significant tumor (64 cases), insignificant tumor was present in only 10 (16%). If these pretreatment criteria suggested insignificant tumor (8 cases), insignificant (5) or minimal (1) tumor was present in 6 (75%) and moderate organ confined tumor was present in 2 (25%). The characteristics of the 3 tumors (1 minimal and 2 moderate) that were predicted to be insignificant by these pretreatment criteria but that were not insignificant are shown in table 4. One of these lesions was a 3.2 $cm.^3$ well differentiated (Gleason score 4) transition zone tumor and all 3 were pathologically organ confined.

DISCUSSION

With the increasing use of PSA for early detection of prostate cancer, more nonpalpable tumors are being detected and treated. In a recent screening study 78% of cancers detected were nonpalpable (stage Tlc) and diagnosed because of a PSA elevation.[7] Prior studies demonstrated that the majority of stage Tlc cancers are significant in terms of size, grade and extent.[2,7] However, since PSA testing increases the lead time for cancer diagnosis[8] it might be anticipated that more small tumors will be detected and treated with widespread use of PSA for prostate cancer screening.

Epstein et al evaluated a nonscreened population of men with stage Tlc cancer who underwent radical prostatectomy, and found that 16% of tumors were smaller than 0.2 $cm.^3$ and that 10% were 0.2 to 0.5 cm^3.[2] Humphrey et al found that 32% of 100 cancers detected in a screening program, of which 78% were stage Tlc, were smaller than 0.5 $cm.^3$.[7] thus, a substantial percentage of tumors detected in the PSA era (20 to 30%) were smaller than 0.5 $cm.^3$ and may pose no immediate threat, particularly among older men. Identification of men with smaller tumors would be helpful in terms of recommending reasonable management options.

It has been suggested that measurement of the volume of cancer in the prostate biopsy specimen cannot reliably predict the actual volume of cancer in the prostate at radical prostatectomy.[9] Dietrick et a1 found that a core cancer length of 3 mm. or more on 1 or 2 needle biopsies reliably predicted the presence of cancers 0.5 cm^3 or large.[10] Epstein et a1 reported that a combination of pretreatment parameters (PSA density, Gleason score, total number of cores involved with cancer and the percentage of the cores involved) provided a means for assessing the significance of stage Tlc tumors.[2] A PSA density of 0.15 ng./ml./gm. or more, Gleason score 7 or greater, 3 or more cores involved with cancer, or 50% or greater involvement of any core with cancer was found retrospectively to be predictive of tumors 0.2 cm^3 or larger, whereas absence of these pretreatment criteria was predictive of a tumor smaller than 0.2 cm^3 (positive and negative predictive values 92 and 63%, respectively).

We prospectively applied the criteria suggested by Epstein et al[2] to recommend treatment options for 336 consecutive men with stage Tlc prostate cancer. Those with a PSA density of 0.15 ng./ml./gm. or more, Gleason score 7 or more, 3 or more cores involved with cancer, or 50% or greater involvement of any core with cancer were counseled for treatment of prostate cancer. If none of these conditions was present, expectant management was presented as an option. With this approach 22.6% of 336 consecutive men with stage Tlc prostate cancer were treated expectantly and the remainder were treated with radiation therapy (6%) or surgically (71.4%). Of 72 men treated surgically in whom we could

evaluate sextant biopsies and ultrasound determined PSA density before treatment these criteria had positive and negative predictive values of 84 and 63%, respectively (table 3). Three men with organ confined prostate cancer had tumors 0.2 $cm.^3$ or larger despite the prediction of insignificant cancer in 8 (table 4). Insignificant cancers were found in 10 of 64 cases (16%) that were predicted to be significant by pretreatment criteria. In comparison, a suspicious lesion on ultrasound was predictive of a significant cancer but absence of a lesion on ultrasound was not predictive of an insignificant tumor. Similarly, 3 mm. or more of cancer in the biopsy (or Gleason grade 4 or 5) was predictive of a significant tumor but the absence of this finding waa not predictive of an insignificant tumor.

A comparison of our series to a series of men with stage Tlc cancer who were treated surgically between 1988 and 1992[2] suggested an increase in the detection of early cancers manifested by an increase in the prevalence of organ confined disease and a decrease in the positive margin rate (table 2). Despite the detection of earlier cancers in our series, the incidence of men with insignificant tumors (smaller than 0.2 $cm.^3$) remained stable at 16 to 17%. Given the negative predictive value of the criteria used to counsel men in our series, it would be anticipated that among the 76 men treated expectantly 48 (63%) would actually have insignificant and 28 (37%) would have significant tumors. Thus, if these men had undergone radical prostatectomy the incidence of men with insignificant tumor in our series would almost double (28 instead of 16%). On the other hand, we may be following 28 men with tumors that are significant and potentially life threatening. However, given the natural history of prostatic cancer, these tumors will most likely be detected as significant lesions, while still organ confined, by our current followup protocol of biannual PSA measurements and annual sextant biopsies.

CONCLUSIONS

We demonstrated in a nonscreened population that stage Tlc cancers are being discovered earlier, with an increase in organ confined tumors and a decrease in positive margins, without an increase in radical prostatectomy for insignificant tumors if appropriate candidates for expectant management are identified. The pretreatment criteria based on PSA density and pathological findings in sextant biopsies would appear to be useful in counseling men with stage Tlc cancer regarding treatment options.

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Table 1

Pathological data for 240 surgical cases

Observation	No. Pts. (%)
Pathological stage:	
Organ confined	173 (72)
Focal capsular penetration	30(12)
Established capsular penetration	28(12)
Seminal vesicle or lymph node involvement	9 (4)
Tumor location:	
Posterior (peripheral zone)	143(60)
Anterior (transition zone)	58(24)
Lateral (peripheral zone)	6 (2)
Anterior and posterior (transitional and peripheral zones)	33(14)
Tumor vol. (cm.3):	
Lees than 0.2	43(18)
More than 0.2–0.5 or less	37 (15)
More than 0.5–less than 1.0	51 (21)
1.0–Less than 4.0	98(41)
4.0 or More	11 (5)
Gleason score:	
3–4	12 (5)
5–6	160 (67)
7	60(35)
8–9	8 (3)

Table 2
Comparison of surgically treated stage Tic cancers from 2 series

Observations	Epstein et al (1988-1992)[2]	Present Study (1994-1996)
No. radical prostatectomy	157	240
Mean age (yrs.)	61	58
Mean PSA (ng./ml.)	10.4	9.4
% Organ confined cases	51	72
% Pos. margins	17	8
No. pathological features (%):		
Insignificant	26(16)	40 (17)
Minimal	15 (10)	29 (12)
Moderate	58 (37)	124 (52)
Advanced	58 (37)	47 (19)

Table 3

Pretreatment prediction of tumor significance

Pretreatment Criterion*	No. Tumor Category				% Pos. Predictive Value	% Neg. Predictive Value
	Insignificant	Minimal	Moderate	Advanced		
Transrectal ultrasound:						
Neg.	16	8	39	10	83	22
Pos.	10	5	31	12		
Ca size (mm.VGleason pattern 4 or 5: Less than 3 on 1 core/none	15	7	28	4	87	28
3 or More on any core/any	25	22	96	43		
PSA density/pathological findings on needle biopsy Less than 0.15/good	5	1	2	0	84	63
0.15 or More/poor	10	6	34	14		

*Positive—suspicious lesion. Negative—no suspicious lesion. Good pathological findings refer to a Gleason score of less than 7, fewer than 3 cores involved with cancer and less than 50% involvement of any core with cancer. Poor pathological findings refer to a Gleason score of 7 or more, 3 or more cores involved with cancer, or 50% or more involvement of any core with cancer.

Table 4

Characteristics of pathologically organ confined tumors predicted to be insignificant by pretreatment criteria but were not insignificant

Case No.	Pretreatment PSA (ng./ml.)	Gland Vol. (cm.3)	PSA Density (ng./ml./gm.)	Tumor Vol. ($cm.^3$)	Tumor Zone	Gleason Score of Final Pathological Specimen
1	4.7	59	0.08	0.3		g
2	8.2	63	0.13	3.2	Transition	4
3	7.9	54	0.146	1.3	Peripheral	6

Prediction based on PSA density, Gleason score, number of cores involved with cancer and percentage of core involved with cancer.