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Natural History of Pathologically Organ-Confined (pT2), Gleason ≤ 6 Prostate Cancer Following Radical Prostatectomy

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Abstract

Objectives—Men with pathologically organ-confined (OC), Gleason score ≤ 6 prostate cancer (PCa) are considered to have an excellent prognosis following surgery as definitive monotherapy. We determined the incidence of biochemical recurrence (BR), local recurrence (LR), distant metastasis (DM) and prostate-cancer specific mortality (PCSM) among this low-risk cohort.

Methods—A retrospective search of our radical prostatectomy database identified 6,081 men with pathologically OC (pT2), Gleason score ≤ 6 PCa treated between 1983 and 2005. Of these, 2,551 (42%) had adequate follow-up information and were assessed for BR, LR, DM, and PCSM. Pathologic specimens of men who progressed were re-evaluated by an experienced genitourinary pathologist, and patients who were upgraded or upstaged (25) were excluded from further analysis resulting in a final study cohort of 2,526. Actuarial probabilities of BR and LR were estimated using the Kaplan-Meier method.

Results—With a median follow-up of 5.0 years (range 2–22), BR occurred in 13 patients (0.5%). The 5-, 10- and 15-year actuarial probabilities of BR were 0.3%, 0.9%, and 1.3%, respectively. Five patients (0.2%) developed LR, four of whom received salvage radiotherapy with subsequently undetectable PSA. The 5-, 10-, and 15-year actuarial probabilities of LR were 0.1%, 0.5%, and 0.5%, respectively. There were no DMs and no PCSMs.

Conclusions—With postoperative follow-up on over 2,500 patients with pathologically OC, Gleason score ≤ 6 PCa, BR and LR following RP were extremely rare and no patients experienced DM or PCSM.

Keywords

Prostatic neoplasms; prostatectomy; disease progression; prognosis

INTRODUCTION

Early detection of prostate cancer (PCa) resulting from prostate-specific antigen (PSA) screening has resulted in a significant stage migration. Currently, the majority of men are

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diagnosed with non-palpable, clinically-localized disease, approximately 10 years earlier than tumors detected by digital rectal examination alone.^{1, 2} As a consequence, the percentage of patients with pathologically organ-confined (OC) tumors has increased substantially.³ Previous studies have demonstrated that 4–32% of men with pathologically OC disease eventually recur following RP,^{4–9} though tumor recurrence for apparent OC disease is poorly understood.

Several series have identified independent predictors of recurrence in patients with OC PCa, namely preoperative PSA, clinical stage, pathological Gleason score and surgical margin status. Men with pathologically OC disease (pT2), Gleason score ≤ 6 and negative surgical margins are thus generally considered to have an excellent prognosis following surgery.

Utilizing the data from a high-volume, tertiary referral center, we determined the incidence of biochemical recurrence (BR), local recurrence (LR), distant metastasis (DM) and prostate-cancer specific mortality (PCSM) in this low-risk group. In cases of progression, RP histologic findings were re-evaluated by an experienced genitourinary pathologist.

MATERIAL AND METHODS

PATIENT POPULATION AND INCLUSION CRITERIA

A retrospective search of our RP database approved by the institutional review board identified cases of pathologically OC (pT2), Gleason ≤ 6 PCa. Between January 1983 and December 2005, 13,707 men underwent anatomic RP for clinically localized adenocarcinoma of the prostate at our institution. 6,081 (44.4%) were identified to have pathologically OC, Gleason ≤ 6 disease and met the following criteria based on their pathology report: 1) No Gleason pattern ≥ 4 ; 2) No extraprostatic extension (EPE), and no seminal vesicle or lymph node invasion; 3) Negative surgical margin status and no evidence of capsular incision (CI); and 4). No neoadjuvant or adjuvant therapy.

PATHOLOGIC EXAMINATION

RP specimens were serially sectioned, totally embedded, and processed as described previously.^{10, 11} The prostate, seminal vesicles, and lymph nodes were examined histologically in standard fashion to determine EPE status, surgical margin status, seminal vesicle involvement, and lymph node status. Positive surgical margin was defined as tumor extension to the inked edge of the tissue. Cases in which tumor extended to the inked margins in an area where benign prostatic acini also extended to the inked margins were considered to have a positive margin due to capsular incision.

POSTOPERATIVE EVALUATION AND STATISTICAL ANALYSES

Patients were followed postoperatively, either at our institution or by referring physicians, with serum PSA determinations and rectal examinations every 3 months for the first year, semiannually for the second year, and annually thereafter. BR was defined as a single PSA ≥ 0.2 ng/mL. No patient underwent adjuvant therapy before recurrence and therefore outcomes reflect cancer control rates with surgery as monotherapy. Following BR, imaging was performed at the discretion of the primary care physician. LR was determined by a palpable nodule or positive biopsy in the presence of an elevated PSA. DM was determined by a positive bone scan or other radiographic or histologic (tissue biopsy) evidence of distant failure.

Of the 6,081 men who met the inclusion criteria, 2,551 (42%) had more than one year of follow-up information and were assessed for the four progression outcomes: BR, LR, DM, and PCSM. The pathologic specimens of men who developed BR were re-evaluated by an experienced genitourinary pathologist (JIE) in an unblinded fashion. Pathologic review confirmed the initial

postoperative grade and stage in 13 (34.2%). The other 25 men had the following: Gleason 3 +4=7 (7); Gleason 4+3=7 (3); tertiary pattern 4 (6); areas of ductal carcinoma (1); Gleason 2 +4=6 (1); Gleason 3+4=7 with EPE (4); Gleason 3+3=6 with EPE (2); capsular incision into cancer (1). Patients who were upgraded or upstaged on pathologic re-valuation (25) were excluded from further study resulting in a final study cohort of 2,526.

All statistical analyses were performed using STATA 9.2 (Stata Corp., College Station, Texas). The study cohort of 2,526 patients were stratified into groups of low-, intermediate-, or high-risk for BR following RP as previously described by D'Amico.¹² We compared the clinical and pathologic variables for patients with and without progression (see Table 1) using the Fisher's exact test for categorical variables (age at time of surgery by decade, preoperative PSA, biopsy Gleason score, 1992 AJCC TNM clinical stage, race, D'Amico risk classification, and type of surgery) and the Wilcoxon rank-sum (Mann-Whitney) test for continuous variables (total follow-up years without censoring for disease progression). Preoperative PSA levels were not available in 83 of the patients, of whom 76 were treated before 1988. Six patients did not have biopsy Gleason score available. The Kaplan-Meier method was used to estimate the actuarial probabilities of BR and LR. Because of the small number who experienced disease progression, univariate and multivariate analyses for the prediction of disease progression were not conducted.

RESULTS

Clinical and pathologic characteristics of our final study cohort are summarized in Table 1. Of the 2,526 patients, 2,422 (95.9%) underwent radical retropubic prostatectomy (RRP) and 104 (4.1%) had a laparoscopic radical prostatectomy (LRP). The median age was 58 years (range, 33 to 75; mean $\pm$ SD, 57.0 $\pm$ 6.6). The median preoperative serum PSA level was 5.2 ng/mL (range, 0.1 to 69; mean $\pm$ SD, 5.8 $\pm$ 4.0). The majority of the patients presented with nonpalpable tumors (71.4%), PSA $\leq$ 10 ng/mL (90.3%), biopsy Gleason $\leq$ 6 (94.9%) and were Caucasian (92.2%). Stratification using the D'Amico risk classifications resulted in low-, intermediate-, and high-risk for BR in 1,883 (80.1%), 416 (17.7%), and 52 (2.2%), respectively.

All patients had more than 1 year of follow-up information available (range, 2–22 years). Fifty-two percent (1,322/2,526) had 5 years or more of follow-up and 18% (449/2,526) had 10 years or more. With a median overall follow-up of 5.0 years, 13 patients (0.5%) had a BR whereas 2,513 remained disease-free. The mean ($\pm$ SD) and median times to progression were 6.8 ($\pm$ 5.5) and 5 years, respectively (range, 2–16 years). The mean ($\pm$ SD) and median preoperative PSA was 5.8 ($\pm$ 4.0) and 5.2 ng/mL in patients without progression versus 5.7 ($\pm$ 4.0) and 4.7 ng/mL in patients with progression ($p=0.8$), respectively. None of the clinical and pathologic variables assessed was found to differ significantly between the two groups (Table 1).

A total of 5 men (0.2%) had a LR, 4 of whom received salvage radiotherapy and subsequently had an undetectable PSA. No patients developed DMs. Overall, 77 patients (3%) died, all dying from other causes of whom 1 (0.04%) previously had a BR. There were no PCSMs.

Kaplan-Meier survival analysis for time to BR demonstrated that the 5-, 10- and 15-year actuarial probabilities of BR were 0.3% (95% confidence interval [CI], 0.2–.7%), 0.9% (CI, 0.4–1.8%), and 1.3% (CI, 0.6–2.8%), respectively. The 5-, 10-, and 15-year actuarial probabilities of LR were 0.1% (CI, 0.01–0.4%), 0.5% (CI, 0.1–1.6%) and 0.5% (CI, 0.1–1.6%), respectively.

COMMENT

The current study represents the largest series to date to report the natural history of pathologically OC (pT2), Gleason $\leq$ 6 PCa following RP. With follow-up on over 2,500

patients, BR and LR were very uncommon (10-year actuarial probabilities of 0.9% and 0.5%, respectively) and no patients developed systemic disease or died of PCa. This study validates our overall impressions for the very low-risk cohort of patients with pathologically OC, Gleason ≤ 6 disease with negative surgical margins: 10. A very small proportion develop BR; 20. The few who experience BR usually have PSA-only relapses without clinical evidence of disease progression; and 30. No patients develop DMs and/or die of PCa. As approximately 45% of patients who currently undergo RP at our institution have this pathologic stage and grade, this study will reassure these patients that they are virtually cured with surgery as monotherapy.

Our study only evaluated men who underwent RP at our institution. As we cannot assess how many of the men in our cohort would not have progressed had they declined active intervention, we cannot precisely surmise the extent of over-treatment. Tumor volume measurement of RP specimen is not routinely performed at our institution since it is technically demanding, time-consuming, often inaccurate, and likely fails to provide additional information beyond that of Gleason score and margin status.¹³ As an alternative, we determined the number of men in our study that would be predicted to have insignificant tumors (tumor volume $\leq 0.5\text{cm}^3$) using the PSA and needle biopsy criteria established by Epstein et al.¹⁴ In this manner, we estimated that only 268 men (10.6%) in our study had insignificant tumors at the time of surgery. We also determined the number of men who would be considered to be the safest candidates for expectant management with curative intent (EMCI). As described by Warlick et al, men 65 years or older with clinical T1c disease, PSA density $<0.15\text{ ng/mL/cm}^3$, and favorable biopsy characteristics per the Epstein criteria (biopsy Gleason score ≤ 6 , no more than 2 positive cores, and no more than 50% involvement of any single core)¹⁴ are the safest candidates for EMCI.¹⁵ Only 35 men (1.4%) in our patient cohort met all of these criteria.

In addition, despite the protracted natural history previously defined for low-risk PCa, the younger age of our patient cohort favors definitive management (69% were 60 years old or younger). In men with a long life-expectancy, even a low-risk tumor may ultimately progress. Of the 2,526 patients, there were only 9 men (0.4%) above age 70 years who were low-risk by the D'Amico criteria and thus few would have been counseled for expectant management. Consequently, though the extent of over-treatment cannot be precisely determined, the clinical and pathological characteristics of this cohort suggest that it is quite low.

The 10-year actuarial probability of BR reported herein is significantly lower than in previous studies which have demonstrated BR rates of 5–32% in men with pathologically OC, Gleason ≤ 6 disease.^{4,5,7–9,16} Major limitations of these previous studies include smaller cohorts, shorter follow-up, and the fact that most authors did not exclude patients with positive surgical margins due to capsular incision. In our more contemporary study, we specifically excluded men with positive surgical margins due to capsular incision and included the largest series to date with extended follow-up. Our patients were typically younger (mean age of 57 years compared to 58–66 years), had a lower clinical stage (non-palpable disease in 71% compared to 17–63%), and a lower preoperative PSA (90% $\leq 10\text{ ng/mL}$ versus 62–78%) than these other cohorts.^{4,5,7,9,16} All these factors (i.e., patient selection and inclusion criteria) may contribute to the lower actuarial probability of BR in our study. On the other hand, we defined BR as a single serum PSA value $\geq 0.2\text{ ng/mL}$, whereas others used higher cutoffs which may have underestimated BR.¹⁶

It was our hypothesis that men with pathologically OC, Gleason ≤ 6 would not progress such that to verify that under-staging, under-grading and false negative surgical margin status did not result in an overestimation of disease progression, we retrospectively re-evaluated the pathologic specimens of patients who experienced BR. Of the 38 patients that were re-evaluated, only 13 (34%) were confirmed to have OC, Gleason score ≤ 6 with negative surgical

margins. A total of 18 were upgraded and 6 upstaged, and 1 was found to have positive surgical margins due to CI. This re-evaluation indicates that Gleason score shift may also be contributing to our improved clinical outcomes over time, a statistical artifact known as the Will Rogers phenomenon.¹⁷ A separate pathology paper will depict the pathologic specimens of the confirmed patients.

One potential criticism of our study is that we did not re-evaluate the pathologic specimens of patients who did not progress (2,513) and may therefore be underestimating the progression rates. Given the size of this cohort, complete pathologic review was deemed logistically unfeasible. If we assume that 10% of the non-progressors would have been excluded had we reviewed all the pathologic specimens, the actuarial probabilities of BR and LR would not have changed significantly as the overall cohort is so large. To test this, we randomly excluded 250 men who did not progress and the 10-year actuarial probabilities of BR and LR minimally increased (by 0.13% and 0.08%, respectively).

Our study has the potential limitations and biases inherent to all retrospective studies. Though the data represent disease progression outcomes after RP from a single, high-volume, academic institution over 23 years involving several surgeons, the potential for selection bias remains. In addition, despite the large number of men studied, the patient cohort may not be representative of the U.S. general population diagnosed with PCa. For example, only 4.6% of the patients in this study were African-American.

To definitively determine clinical progression rates (i.e., LR/DM) would require 10 or even 15-year follow-up. However, postoperative serum PSA monitoring is broadly accepted as a surrogate for disease recurrence. To this end, we utilized a stringent and therefore very sensitive definition of BR (a single serum PSA value ≥ 0.2 ng/mL). While a longer duration of follow-up may lead to the discovery of DMs or PCSMs, given the extremely low actuarial probabilities of BR using this conservative definition, they will likely remain exceptionally infrequent.

Recurrence following RP with pathologically OC PCa with negative surgical margins remains poorly understood. In these cases, when PSA persistently remains or becomes detectable, it is generally assumed that there was either sub-clinical metastasis at the time of surgery or a false-negative surgical margin.¹⁸ Others have suggested that spillage of cancer cells in the secretions from the cut distal urethra at surgery could result in local recurrence, as these malignant cells can be identified in the prostatic washings from men with pathologically OC PCa via cytology.¹⁹ The timing as well as the mechanism(s) by which systemic disease develops in these patients remain unclear. Our study, focusing on patients with OC, Gleason ≤ 6 and negative margins, demonstrates that essentially none of these men develop systemic disease and thus reinforces the general perception that pathologic grade is the most important factor for predicting outcome following RP in pathologically OC disease.

CONCLUSIONS

In the modern era when PCa is treated by the anatomic approach to radical prostatectomy with negative surgical margins, and the tumor is organ-confined and lacks high grade elements, it is effectively cured.

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Table 1

Clinical and Pathological Characteristics of Patients with Organ-Confined, Gleason ≤ 6 Prostate Cancer by Progression Status following Radical Prostatectomy

Parameter	Entire cohort, No. (%)	Progressors, No. (%) [*]	Non-Progressors, No. (%) ^{**}	p value
No. of patients	2,526	13	2,513	
Follow-up, years				0.98 ^a
Mean $\pm$ SD	6.0 $\pm$ 4.3	6.8 $\pm$ 5.4	6.0 $\pm$ 4.2	
Median (Range)	5(2–22)	6.5(2–16)	5(2–22)	
Year of surgery				0.09 ^b
1983–1990	258(10.2)	4(30.8)	254(10.1)	
1991–1998	940(37.2)	4(30.8)	936(37.3)	
1999–2005	1,328(52.6)	5(38.5)	1,323(52.7)	
Age at surgery, years				0.59 ^b
≤ 55	975(38.6)	4(30.8)	971(38.6)	
56–5	1,322(52.3)	7(53.9)	1,315(52.3)	
> 65	229(9.1)	2(15.4)	227(9.0)	
Type of Surgery				0.58 ^b
RRP	2,422(95.9)	13(100)	2,409(95.9)	
LRP	104(4.1)	0	104(4.1)	
Race				0.43 ^b
White	2,325(92.2)	12(92.3)	2,313(92.2)	
Black	115(4.6)	0	115(4.6)	
Other	82(3.3)	1(7.7)	81(3.2)	
PSA				0.90 ^b
≤ 4	776(31.8)	4(36.4)	772(31.7)	
4.1–10	1,431(58.6)	6(54.6)	1,425(58.6)	
> 10	236(9.7)	1(9.1)	235(9.7)	
Biopsy Gleason score				0.47 ^b
≤ 6	2,391(94.9)	11(91.7)	2,380(94.9)	
7	122(4.8)	1(8.3)	121(4.8)	
8–10	7(0.3)	0	7(0.3)	
1992 AJCC clinical stage				0.36 ^b
T1a-c	1,802(71.4)	7(53.9)	1,795(71.5)	
T2a/b	683(27.1)	6(46.2)	677(27.0)	
T2c/T3	40(1.6)	0	40(1.6)	
D'Amico risk class				1.0 ^b
Low Risk	1,883(80.1)	9(90.0)	1,874(80.1)	
Intermediate Risk	416(17.7)	1(10.0)	415(17.7)	
High Risk	52(2.2)	0	52(2.2)	

^{*} Pts with progression: 2 missing preoperative PSA; 1 missing biopsy Gleason score

^{**} Pts without progression: 4 unknown race; 81 missing preoperative PSA; 5 missing biopsy Gleason score; 1 clinical stage D0

^a Wilcoxon rank-sum

^b Fisher's exact