Delay From Biopsy to Radical Prostatectomy Influences the Rate of Adverse Pathologic Outcomes

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BACKGROUND. We sought to determine maximum wait times between biopsy diagnosis and surgery for localized prostate cancer, beyond which the rate of adverse pathologic outcomes is increased.

METHODS. We retrospectively reviewed 4,610 patients undergoing radical prostatectomy between 1990 and 2011. Patients were stratified by biopsy Gleason score and PSA value. For each stratification, χ^2 analysis was used to determine the smallest 15-day multiple of surgical delay (e.g., 15, 30, 45…180 days) for which adverse pathologic outcomes were significantly more likely after the time interval than before. Adverse outcomes were defined as positive surgical margins, upgrading from biopsy, upstaging, seminal vesicle invasion, or positive lymph nodes.

RESULTS. Two thousand two hundred twelve patients met inclusion criteria. Median delay was 64 days (mean 76, SD 47). One thousand six hundred seventy-five (75.7%), 537 (24.3%), and 60 (2.7%) patients had delays of <=90, >90, and >180 days, respectively. Twenty-six percent were upgraded on final pathology and 23% were upstaged. The positive surgical margin rate was 24.2% and the positive lymph node rate was 1.1%. Significant increases in the proportion of adverse pathological outcomes were found beyond 75 days in the overall cohort ($P = 0.03$), 150 days for patients with Gleason <=6, and PSA 0–10 ($P = 0.038$), 60 days for patients with Gleason 7 and PSA >20 ($P = 0.032$), and 30 days for patients with Gleason 8–10 and PSA 11–20 (0.041).

CONCLUSION. In low-risk disease, there is a considerable but not unlimited surgical delay which will not adversely impact the rate of adverse pathologic features found. In higher risk disease, this time period is considerably shorter. *Prostate 9999: XX–XX, 2015.*

KEY WORDS: **prostatectomy; surgical pathology; time-to-treatment**

INTRODUCTION

For patients with organ-confined disease, it has been demonstrated that radical prostatectomy (RP) reduces all-cause mortality, death from prostate cancer, and distant metastasis versus watchful waiting [1]. With the introduction of prostate-specific antigen (PSA) screening, there has been a stage migration to a lower stage disease [2,3] and few men now present with palpable disease on clinical exam [4]. However, this trend toward earlier detection has not prevented large numbers of patients from experiencing biochemical recurrence following "curative" therapy. Eleven

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percent of patients currently experience a biochemical recurrence (BCR) [5], as compared with 14% in the pre-PSA era [6].

It is known that a certain percentage of cancers will be upgraded and upstaged on final pathology. In the SPCG-4 trial, only 32% of final pathology Gleason scores were in concordance with transrectal ultrasound (TRUS) biopsy scores; 30% of specimens were one step higher, and 28% two or more steps higher [1]. Additionally, we have previously shown that in our Columbia University cohort of patients the concordance of Gleason scores between biopsy specimens and final pathology is 0.33 (55%) and the highest value that has been reported in the literature for any cohort is 45% [7]. Some of this is due to the imperfect sensitivity and specificity of the TRUS biopsy [8] and the inherent sampling error of the test, particularly in low-volume cancer [9,10]. However, some of these discrepancies are likely due to progression of the disease [11–13].

While prostate cancer is among the slower-growing and more indolent cancer types, the natural history of untreated prostate cancer has not been thoroughly elucidated. A population-based, prospective cohort study conducted in Sweden with over 30 years of follow-up demonstrated that local progression and distant metastasis can eventually occur in localized prostate cancer, even among low-risk men [14]. This could be partially attributable to a process of dedifferentiation and histological progression over time, which has been implicated in various studies [15–20]. Delay from diagnosis to surgery may allow time for this process to occur. This could partially explain the upstaging this is commonly observed, and potentially contribute to the frequency of BCR.

Many factors may cause delays between diagnosis of prostate cancer and definitive treatment. With the recent centralization of radical prostatectomies, these procedures are increasingly performed at high-volume institutions by a small proportion of surgeons [21]. This undoubtedly increases the wait time for surgery at the high volume centers. With the widespread detection of less aggressive cancers, clinicians may lack urgency promoting definitive treatment. Patients are often given time to weigh their options and seek out several opinions, particularly due to the availability of many different treatment modalities. Patients have been known to have great difficulty making prostate cancer treatment decisions given the perceived uncertainty about the ideal treatment, and, therefore, seek out many different opinions [22,23].

Several previous studies have attempted to address the impact of waiting on outcomes, but published results are in conflict. Various studies have found that time from biopsy to RP did not influence the probability of BCR, even in higher risk patients [24–30]. Similarly, a recent analysis of our Columbia University cohort from 1990–2007 with patients stratified into delay groups of <60, 60–90, >90 days showed that a delay of >60 days did not correlate with worse BCR-free survival [31]. Conversely, studies by Nam et al. and O'Brien et al. showed a negative impact from prolonged time between diagnosis and surgery. Patients in these cohorts experienced worse outcomes, even in D'Amico low-risk men, with a surgical delay of 6 months or more [32,33]. Abern et al. showed an adverse effect on BCR risk of delays >9 months in intermediate-risk but not low-risk men [34]. Nguyen showed that a treatment delay of >2.5 months led to higher BCR rates in high-risk men treated with external beam radiation therapy [35].

In some cohort studies, multivariate logistic regression analysis may fail to prove associations between wait times and poor pathologic outcomes due to confounding variables or other false predictors and their interactions. However, the continuous reporting of conflicting results in high-quality studies warrants a different analytical approach to the available data. Most statistical models compare associations between outcomes and wait times of a single, arbitrary length. Our goal in this analysis was, for given combinations of preoperative PSA values and Gleason scores, to establish exact wait time cut points beyond which there is a worse pathologic outcome.

MATERIALS AND METHODS

The IRB-approved Columbia University Urologic Oncology retrospective database was queried to identify all patients who underwent RP from 1990 to 2011. We identified 4,610 patients. Demographic, clinical, and pathologic data were collected. Patients on active surveillance protocols were excluded (n = 250). Patients who underwent neoadjuvant hormone or radiation treatment were excluded (n = 256). Patients with an unknown date of TRUS biopsy (n = 604), an unknown Gleason score on biopsy (n = 968), insufficient clinical and pathological stage data to determine upstaging (n = 1,352), or unknown preoperative PSA were also excluded (n = 638) (numbers reported for groups are not mutually exclusive). Pathologic characteristics of the excluded cohort had some differences (mean age: 60.3 vs. 60.8, $P < 0.02$; biopsy Gleason sum 0–6: 41.8% vs. 51.2%, Gleason 7: 41.6% vs. 39.2%, Gleason 8+: 16.5% vs. 9.6%, $P < 0.01$ for biopsy Gleason distribution; cT1 disease: 57.0% vs. 65.4%, cT2: 37.0% vs. 32.7%, cT3: 5.9% vs. 1.7%, $P < 0.01$ for cT distribution), but in other respects were similar to the cohort in the final analysis (positive margin rate: 26.9% vs. 24.2%, pT3 disease:

25.6% vs. 24%, PSA 10–20: 16.0% vs. 14.8%, PSA over 20: 5.7% vs. 4.6%, $P = \text{NS}$).

Time to surgery was calculated based on the difference between the date of diagnosis on TRUS biopsy and the date of surgery. Cut point analysis was performed by testing for significant differences in the proportion of adverse pathologic outcomes above and below intervals of 15 days (e.g. 15, 30, 45…180) until the groups became small. The lowest cut point for which a statistically significant proportional difference in adverse outcomes was obtained is reported. Significant cut points were determined using a χ^2 statistic with a *P*-value of less than 0.05. In other words, each subgroup was first divided into those with a surgical delay $\leq$15 days and those with a delay >15 days, and a χ^2 test was carried out to assess for a significant difference in the rate of adverse pathological outcomes between these groups. If a significant difference was found, the procedure was stopped and 15 days was reported as the cut point. If no significant difference was found, the subgroup was re-apportioned into two different groups: those with surgical delay $\leq$30 days and those with delay >30 days, and the statistical test was repeated. The procedure was repeated until either a significant cut-point was found or until the groups became prohibitively small. Adverse pathologic outcome was defined as either surgical margins positive for cancer, upgrading from TRUS biopsy, upstaging, seminal vesicle invasion, or positive lymph nodes on pathology. Preoperative stage in our database is based on clinical reports and imaging results. All statistical analysis was performed using STATA v11.0 (StataCorp, Texas, USA).

RESULTS

Of the original cohort of men identified, 2,212 met our inclusion criteria. The demographics, clinical, and pathologic characteristics of our cohort can be found in Tables I, II, and III, respectively. The majority of the men were White, with a mean pre-operative PSA of 8, and a majority were intermediate risk by D'Amico criteria. Of the entire cohort, 537 (24.3%) men waited greater than 90 days and 60 (2.7%) waited greater than 180 days. The mean time from diagnosis to surgery was about 76 days (SD 47.3) with a median of 64 days (interquartile range [IQR] 48–90).

On final pathology, the majority of men were Gleason 3 + 4 (43.6%) with 66.1% having pT2 disease. In the cohort, we found that 26% of men were upgraded on final pathology and 23% were upstaged. The positive surgical margin rate was 24.2% and the positive lymph node rate was 1.1%. 85.3% of patients underwent lymph node dissection.

TABLE I. Overall Cohort Demographics

Demographics	
Race/ethnicity (%)	
White	1371 (62.0)
Black	317 (14.3)
Hispanic	215 (9.7)
Other	308 (13.9)
Mean age (SD)	60.77 (7.2)
Time to surgery, days	
Mean (SD)	75.68 (47.3)
Median (IQR)	64 (48–90)
≤90 (%)	1675 (75.7)
>90 (%)	537 (24.3)
>180 (%)	60 (2.7)

The results of the cut point analysis can be found in Table IV. For the entire cohort, we found a significantly higher proportion of adverse pathologic features at delays greater than 75 days ($P = 0.03$). The cohort was then analyzed stratified by TRUS Gleason grade and pre-operative PSA. For patients with Gleason score $\leq$6 and PSA of <10, a significant cut point in adverse pathologic features was seen at 150 days ($P = 0.038$) and a cut point approached significance at 105 days in patients with a PSA 11–20 ($P = 0.056$). For patients with Gleason score 7 and a PSA of >20, a significant difference in the proportion of adverse pathologic features was observed at 60 days ($P = 0.032$). For patients with high grade cancer on TRUS biopsy ($\geq$8) and a PSA of 11–20, a significant cut point was observed at 30 days ($P = 0.041$). For all other Gleason score and PSA

TABLE II. Overall Cohort Clinical Characteristics

Clinical characteristics	
Mean preoperative PSA (SD)	7.94 (7.81)
Clinical stage (%)	
cT1	1210 (65.4)
cT2	605 (32.7)
cT3	32 (1.7)
TRUS Gleason score (%)	
≤6	1132 (51.2)
7	867 (39.2)
≥8	213 (9.6)
D'Amico risk group (%)	
Low	726 (34.9)
Intermediate	1133 (54.6)
High	216 (10.4)

TABLE III. Overall Cohort Pathologic Characteristics

Pathologic characteristics	
Pathologic Gleason score (%)	
≤6	622 (30.2)
3 + 4	908 (43.6)
4 + 3	320 (15.4)
≥8	231 (11.1)
Pathologic stage (%)	
pT2	1462 (66.1)
pT3	532 (24.1)
pT4	39 (1.8)
Positive surgical margin (%)	535 (24.2)
Positive lymph nodes (%)	25 (1.1)
Median Follow-up, months (IQR)	39 (12–82)

combinations, significant cut points in adverse pathologic features were not able to be determined, likely due to sample size limitations.

DISCUSSION

This study set out to definitively establish, for various combinations of Gleason scores and PSA values, cut points for surgical delay beyond which the risk of adverse pathologic outcomes would be affected. We attempted to create an analysis with practical application, such that when a patient with a given Gleason score and PSA value and the intention to undergo definitive therapy consults with his urologist, a maximum wait time can be established. There has been much debate in the literature about the significance of wait times for prostate cancer treatment, summarized in a recent review article [36]. The adverse effect of wait time on oncologic and survival outcomes has been shown for breast, bladder, rectal, lung, and head and neck cancers [37–43]. However, several studies of the effect of surgical delay on oncologic outcomes following RP have shown negative findings [26–30]. We thought a novel statistical approach to establish a clear impactful cut point of delay times for men with various preoperative risk profiles was warranted given the conflicting results previously published.

Selection of patients for active surveillance is a crucial task, as not all patients should delay intervention. Tosoian et al., Dall'Era et al., and Berglund et al. all found that optimal criteria for a delayed curative intervention protocol included stage ≤T2a, PSA ≤10, and Gleason ≤3 + 3 [44–46]. While our study excluded all patients that were on active surveillance in order to remove those that are unlikely to progress, presumably a non-insignificant proportion of the low-risk patients could have been candidates for active surveillance but chose to have surgery instead.

In our analysis of a similar low-risk group of patients of Gleason ≤6 PSA <10, we found a difference in adverse pathological outcomes with a delay to surgery of 5 months. Accordingly, O'Brien et al. found a similar delay of greater than 6 months in D'Amico low-risk patients had worse 5-year BCR-free survival

TABLE IV. Cut-Point Analysis

Cut-point analysis for adverse pathologic events

Group	Number of patients	Cut-point (days)	*P*-value
All patients	2212	75	0.030
TRUS Gleason ≤6			
PSA 0–10	978	150	0.038
PSA 11–20	121	105	0.056
PSA >20	33	45	0.124
TRUS Gleason 7			
PSA 0–10	729	105	0.258
PSA 11–20	98	60	0.151
PSA >20	40	60	0.032
TRUS Gleason 8–10			
PSA 0–10	149	75	0.876
PSA 11–20	36	30	0.041
PSA >20	28	30	0.259

Patients were divided by Gleason score and pre-operative PSA value. Within each stratification, χ^2 analysis was used to test for a higher proportion of adverse pathological outcomes for patients with a biopsy-to-surgery delay above the cut-point. Analysis began at a putative cut-point of 15 days and progressed upward in increments of 15 days until significance ($P < 0.05$) was reached or until sample sizes became prohibitively small.

rates when compared to men treated within 6 months [33]. Further, evidence supporting the danger of long wait times for some men with low-risk disease can be found in the Scandinavian Prostate Cancer Group-4 study. In a cohort of low-risk patients (PSA <10 and Gleason <=7), the Gleason grading of the operative specimens was compared with the preoperative grading of the core biopsy specimens. Of the seven men who underwent surgery and subsequently died from prostate cancer, six had tumors that were upgraded to a score of 7 or 8 from a score of 6 or lower [1]. Furthermore, Holmstrom et al. reported more frequent upgrading after deferred radical prostatectomy in Swedish men with low or intermediate-risk disease [47]. This further supports the argument that long delays in intervention for prostate cancer may be harmful even in this relatively slow-growing tumor type.

In an expanded low-risk cohort study by Freedland et al., outcomes were compared between patients who waited longer than 180 days and those who waited a shorter amount of time. They found an increased risk of BCR, but interestingly no increased risk of worse pathologic findings (extracorporeal extension, positive margins, positive nodes) [48]. Pathologic outcomes were pooled in our analysis, and, therefore, a direct comparison to the present study is difficult. However, we did find a significant adverse pathological outcomes difference in a low-risk cohort with a similarly long wait time of 150 days.

A limitation of some of the above studies is that they focus on those extremely low-risk patients who might otherwise be candidates for active surveillance. It is important not to ignore treatment delays for other cancer patients of higher Gleason grade or PSA value. Patients with all different grades are delaying treatment for sometimes long periods, with potentially deleterious results, as evidenced by our cohort. Similarly, Abern et al. found that men with intermediate-risk disease by D'Amico criteria experienced significantly higher rates of BCR when the delay from diagnosis to RP was greater than 9 months [34]. In the radiation literature, worse BCR has been associated with delay to curative radiation therapy >2.5 months in high-risk patients [35]. Similarly, the present study found worse outcomes for Gleason 7, PSA >20 patients who delayed for 60 days or greater. It is paramount that we establish an accepted amount of time to wait until intervention for intermediate- and high-risk patients which will not affect pathologic outcomes. We could then provide patients with a known window in which to gather opinions from other physicians and confer with friends and family members.

We were able to identify significantly worse pathologic outcomes in our high-risk group of patients after 30 days, which is well within the traditionally cited wait time of 28–42 days after TRUS biopsy before surgery. This is a notably short amount of time, and may reflect the generally higher proportion of positive margins and upstaging seen on pathology with these high-risk patients. Fundamentally, the TRUS biopsy is a snapshot in the growth of a cancer. Higher grade cancers may be more unstable and quicker to manifest pathological changes compared to lower-grade cancers. These observations reinforce an untested but widely held understanding that there is more temporal urgency to treat high-grade cancers versus those of lower risk potential.

There are several limitations to our study that warrant discussion. First, it is retrospective in nature and, therefore, there may be confounding variables that are unaccounted for. Second, we lack sufficient follow-up information to assess the impact of wait time on disease specific or overall survival. Third, while our cohort was large, and a significant number of patients waited longer than 90 days, as the time increased the number of patients became smaller and the comparisons less conclusive. Lastly, because our methodology was based on a stratified analysis rather than a multivariate analysis, we were limited in the number of variables that could be accounted for. We stratified the cohort based on biopsy Gleason score and preoperative PSA level, but stratification of additional dimensions, such as race, would have resulted in groups with increasingly small sample sizes and less meaningful results. However, previously published analyses of our institution's data have found associations between race and surgical delay, as well as between race and adverse pathological outcomes [49,50]. A large, prospective study would be the optimal way to further investigate this topic while avoiding these limitations.

CONCLUSIONS

Through our analysis of a large heterogeneous population of patients who underwent RP, we found that the rate of adverse pathologic outcomes is significantly affected after certain wait times. For patients with low-grade cancers, wait times may extend up to 150 days without significant impact on outcomes. Conversely, for patients with high-grade disease, wait times as short as 30 days may have an impact on rates of upgrading, upstaging, and positive surgical margins. While most prostate cancers remain indolent, pathologic features may be worse with significantly long delays in treatment.

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