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# Does a Delay Between Diagnosis and Radical Prostatectomy Increase the Risk of Disease Recurrence?

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## Abstract

**BACKGROUND.—**Men diagnosed with clinically localized prostate carcinoma have several treatment options. The investigation of these options may delay the initiation of definitive therapy. In the current study, the authors evaluated whether time from biopsy to radical prostatectomy (RP) was predictive of postoperative biochemical disease recurrence (BCR).

**METHODS.—**A total of 3149 consecutive patients who underwent RP as their initial treatment for prostate carcinoma within a year of diagnosis were identified. The time between diagnosis and RP was entered as a predictor in a multivariate logistic regression model predicting BCR at 3 years, 5 years, 8 years, and 10 years. The year surgery was performed and the nomogram-predicted probability of recurrence, which incorporates stage of disease, Gleason grade, and prostate-specific antigen (PSA) level, were used as covariates.

**RESULTS.—**The authors found no clear evidence of a significant effect of delay to diagnosis on BCR. For those patients treated within 6 months (96% of the total sample) the odds ratio for each additional month of delay was 1.04, 1.07, 1.08, and 1.02, respectively, for 3-year, 5-year, 8-year, and 10-year BCR-free survival ($P > 0.2$ for all analyses). However, the 95% confidence intervals were wide and included the possibility that even a minor delay in surgery might have a large impact on the probability of BCR.

**CONCLUSIONS.—**The time between biopsy and surgery does not appear to have a large effect on the risk of disease recurrence. Counseling patients on the importance of avoiding undue delay to surgery must be based on clinical judgment, particularly with respect to modifying advice based on the patient's risk.

### Keywords

prostatic neoplasms; diagnosis; prostatectomy; pathology; recurrence; survival

Patients with newly diagnosed clinically localized prostate carcinoma must educate themselves about the disease, the available treatment modalities, and the potential impact of each treatment option on their survival and quality of life. They then must make a life-changing choice of

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treatment approach. This learning and decision-making process can take a considerable period of time for some patients. Moreover, factors such as clinician or institution schedules and insurance clearance may cause an additional delay between the time the diagnosis of prostate carcinoma is made and the time treatment is initiated.

Whether a delay in therapy for clinical localized prostate carcinoma has an adverse effect on outcome has been the subject of controversy.[1-4] In the current study, we examined the impact of the time elapsed from prostate biopsy to surgery on the risk of biochemical disease recurrence (BCR) by examining a large, consecutive cohort of patients.

## MATERIALS AND METHODS

### Patient Population

Between August 1987 and June 2002, we prospectively recorded information regarding 4460 consecutive patients who underwent radical prostatectomy (RP) for clinically localized prostate carcinoma. The procedures were either performed by a single surgeon at the Baylor College of Medicine ($n$ = 1162 patients) or by urologic surgeons at the Memorial Sloan-Kettering Cancer Center ($n$ = 3298 patients). Clinical, pathologic, and outcome data were uploaded to a multidisciplinary prostate carcinoma database by specialized research assistants. Institutional review board approval of the study was obtained prior to data analysis. Because this study was aimed at patients who elected to undergo RP as their initial treatment modality, we excluded 794 men who had received either prior radiation therapy ($n$ = 110 patients) or neoadjuvant hormonal therapy ($n$ = 684 patients). We also excluded 481 men with missing data and a small number of patients ($n$ = 36 patients) who underwent surgery > 12 months after diagnosis. Many of these patients underwent surgery 3 or 4 years after biopsy and their results did not appear to be applicable to the routine counseling of patients with early stage prostate carcinoma. Clinical stage of disease was determined according to the 1992 American Joint Committee on Cancer (AJCC) staging guidelines.[5] The time from first positive prostate biopsy to RP was recorded, and the serum prostate-specific antigen (PSA) level obtained before biopsy was used for analysis. All biopsy specimens were reviewed at the treating institution and a primary and secondary Gleason grade was assigned.

Postoperative follow-up included measurement of the serum PSA level and complete physical examinations at 3-month to 4-month intervals for the first 2 years after surgery and at 6-month intervals thereafter. The endpoint measured was BCR, which was defined as 2 postoperative PSA levels > 0.2 ng/mL, or the initiation of secondary therapy for carcinoma due to an increase in the PSA. No patient in our database experienced clinical disease progression without a prior elevation in PSA.

### Statistical Analysis

Multivariable regression models were used to evaluate the effect of time from biopsy to diagnosis, as a continuous variable, on BCR. We used year of biopsy and the nomogram-predicted probability of 5-year recurrence-free survival as covariates. The nomogram is a multivariate model incorporating biopsy Gleason score, prebiopsy serum PSA level, and clinical stage of disease. Use of the nomogram prediction as a covariate thereby controls for disease severity. The nomogram we used has been validated in a large, international dataset of patients with prostate carcinoma.[6]

For a Cox proportional hazards approach, in which the dependent variable is time to BCR, the choice of the start date is a key problem. Measuring time from diagnosis is unsound because some patients who are treated early may develop disease recurrence before patients who are treated later are even at risk. Such an analysis will be biased in favor of delayed surgery.

Measuring time from surgery has countervailing biases. Although patients with early surgery are followed longer, which can cause bias if the hazard (i.e., the risk of developing disease recurrence within the next day) changes over time, conversely, it may be that, for some patients, the time of BCR is not strongly dependent on surgery and is approximately fixed in time relative to diagnosis. For example, if a patient had a small and slow-growing metastasis at a site distant to the prostate, this would eventually grow large enough to secrete measurable amounts of PSA, leading to an identifiable BCR. In this case, using time from surgery might bias the results in favor of early surgery.

As a result of such considerations, several investigators have advocated a landmark analysis.[2] In this analysis, time to disease recurrence is measured from a fixed point, such as 6 months, after diagnosis. Patients are excluded if they are treated after the landmark time. To prevent negative time-to-treatment failure, patients also are excluded if they develop disease recurrence or are censored before the landmark. However, this method may bias results in favor of early surgery because patients who develop disease recurrence rapidly would be excluded if they underwent early surgery, but not if surgery was delayed.

We sought a method of analysis that would 1) avoid evaluating patients for BCR before others were at risk (such as in a Cox model measuring time from diagnosis); 2) avoid following patients for different lengths of time depending on delay to surgery (such as in a Cox model measuring time from surgery); and 3) avoid excluding differential proportions of BCRs depending on delay to surgery (such as in the landmark analysis). Therefore, we analyzed the binary endpoint of disease recurrence within *n* years of surgery. Patients were eligible for analysis if they had been treated at least *n* years previously and had either experienced a BCR or were known to be free of BCR at *n* or more years of follow-up. We chose *n* years of 3 years, 5 years, 8 years, and 10 years and performed analyses both for the entire group and excluding the minority of patients (120 patients; 4%) who underwent surgery after 6 months. All statistical analysis was performed using Stata 8 software (Stata Corporation, College Station, TX).

Our chosen analysis is subject to one of the biases discussed earlier; when measuring time from surgery, earlier treatment appears to be of benefit if the time of BCR is independent of surgery. However, this problem would affect only the binary endpoint of *n* year survival in the relatively unlikely event that BCR occurred close to *n* years. For example, let us examine 2 patients undergoing RP at 1 month and 5 months, respectively, after diagnosis. Both have a slow-growing metastasis distant to the prostate and will develop disease recurrence at 26 months after diagnosis regardless of the time of surgery. In the Cox analysis, the patient with earlier surgery would have an apparent 4-month increase in BCR-free survival. In an analysis of BCR at 5 years, both patients would be treated as failures and there would be no bias. It is only if *n* were 2 years that there would be bias, with only the later-treated patient considered to have developed a BCR. Therefore, we believe that the bias associated with our analysis is moderate.

## RESULTS

Overall, 3149 patients met the criteria for inclusion in the current study. Clinical and pathologic features of the patients from the overall cohort are shown in Table 1. For illustrative purposes, we also show data for the subgroups of patients who underwent RP ≤ 3 months and those who underwent RP > 3 months after biopsy.

Table 2 shows the principal results regarding the effects of treatment delay. The odds ratios for all analyses were close to 1, and none were found to be statistically significant. The increase in odds for every additional month of delay was smaller for the entire group than when patients with a delay > 6 months were excluded. This may result from the small number of patients with extreme delay to surgery; only 20 patients in the current study waited > 9 months to

undergo RP and none experienced a BCR. These outlying observations have an undue influence on the estimate for an increase in the odds of BCR per each month of additional delay.

### Other Analyses

We investigated whether the other statistical methods discussed earlier led to the biases anticipated. We first used time from diagnosis in a Cox model, with adjustment for the year of surgery and predicted the 5-year recurrence-free survival. This resulted in an apparent protective effect of increasing time between biopsy and RP. The hazard ratio (HR) for each additional month of delay was 0.96 (95% confidence interval [95% CI], 0.9 -1.03; $P = 0.3$). The bias in favor of late surgery was because of the occurrence of early BCRs; approximately 10% of BCRs occurred before 3 months and 25% occurred before 6 months. With the time from surgery as the dependent variable, an increased time from biopsy to RP again appeared to be nonsignificantly protective (HR of 0.98; 95% CI, 0.91-1.04 [$P = 0.5$]). Such a result might be explained by the longer follow-up of the patients treated earlier. This effect was greater than we had anticipated; by linear regression, every additional day between biopsy and surgery was associated with 3.7 fewer days of follow-up ($P < 0.0005$), presumably because delay to surgery had been increasing over time ($P < 0.0005$). We also conducted a landmark analysis, in which 6 months after diagnosis was selected as the landmark. A total of 120 patients were excluded for surgery occurring after 6 months and 204 were excluded for BCR or censoring before 6 months. There was a strong suggestion of harm from delaying surgery (HR of 1.09; 95% CI, 0.99 -1.19 [$P = 0.066$]). However, this effect might well be explained in terms of differential exclusion of BCRs. For the purposes of illustration, we divided the data by whether patients were treated within or after 3 months from biopsy. There were 398 BCRs in the early-surgery group, 107 (27%) of which were excluded. In comparison, only 12 of the 86 BCRs reported in the latersurgery group (14%) were excluded ($P = 0.012$ by the chi-square test). Nevertheless, similar to the primary analyses, none of these alternative methods of analysis detected very large effects of delay on outcome.

## DISCUSSION

Several studies of various malignancies have examined the oncologic effects of delay to therapy and have reported conflicting results. Although the prognostic significance of treatment delays in head and neck carcinoma[7] have been demonstrated, to our knowledge delays in therapy for carcinomas of the breast[8] and colon[9] have not been shown to have a significant impact on survival. Studies evaluating the impact of the interval from diagnosis to the primary therapeutic intervention in patients with prostate carcinoma are limited and controversial.[1-4] A deleterious effect of longer intervals from biopsy to radiation therapy, particularly for men with high-risk disease, was reported by Nguyen et al.[1] With regard to surgery, reports differ concerning whether an increased time from diagnosis to RP increases the risk of BCR.[2-4] Khan et al. reported no significant impact for a delay from biopsy to RP on BCR after patients were stratified according to clinical stage of disease, serum PSA level, and biopsy Gleason score.[4] Moul et al. reported no clear overall impact, but found that longer intervals between diagnosis and prostatectomy were significantly deleterious for highrisk patients.[3] These results were consistent with those of Nam et al., who reported a statistically significant 14% reduction in the probability of 10-year recurrence-free survival for those patients undergoing RP > 3 months after diagnosis compared with those undergoing RP before 3 months.[2] However, time to RP was found to no longer be statistically significant after adjustment for histologic grade, pathologic stage of disease, and serum PSA level at the time of diagnosis.[2]

We have two general criticisms of the prior literature regarding prostate carcinoma. First, there appears to have been inadequate attention to the differential biases associated with alternative methods of analysis. For example, Nam et al. argued that the landmark analysis they used was superior to measuring time from diagnosis because some patients who were treated early

developed disease recurrence before patients who were treated later were at risk for BCR.[2] However, these authors appear not to have considered the differential exclusion of BCRs in early surgery versus delayed-surgery patients. This acts as a bias in favor of early surgery and, indeed, the authors reported that delayed surgery was associated with an increased risk of BCR. Our second criticism of the literature is the rather tabula rasa approach to the data, without sufficient emphasis on cancer biology. In our view, the risk of oncologic failure must be increasing monotonically with delay to surgery; for every day that passes, an event such as a mutation or shedding of a metastatic cell must occur in at least one patient in a large population. Therefore, we see no justification for the null hypothesis that a delay to surgery has no effect on outcome, unless one assumes either that surgery is ineffective or that cancer does not progress. Hence the question is not *whether* a delay to surgery affects outcome, but by *how much* a certain length of delay increases risk.

In the current study, we found no clear evidence that an increased time between biopsy and surgery was associated with a significantly poorer outcome. This suggests that any effect of a treatment delay is moderate, at least for a time period up to 6-12 months. Such a finding might be explained in terms of the relatively slow progression of prostate carcinoma. For example, the study by Epstein et al. demonstrated little evidence of a worsening in tumor grade in the short term (< 18 mos) after biopsy.[10] Nonetheless, our main estimates indicate a small, but relevant, harm from delay. Let us use as an example, a patient with a 20% chance of developing a BCR at 5 years. Given an odds ratio of 1.07 per month, an additional 3-month delay in surgery would increase the risk of 5-year BCR to 23.4%. Moreover, even with this large dataset, the 95% CIs are wide and include the possibility that even a minor delay in surgery might have a large impact on patient risk. If we take the upper bound of the 95% CI (an odds ratio of 1.21), such a delay would increase the risk of BCR to 30.7%. The comparable figure for a patient at high risk (e.g., 50%) is 64%.

The current study was not randomized. Therefore, there may be differences between patients who underwent early compared with those who underwent late surgery that are not captured by our covariates. That said, a trial randomizing patients to immediate versus delayed surgery will never be conducted; an estimate of the effects of delay can come only from a carefully analyzed cohort study.

An additional limitation of the current study is that the sample was comprised of patients at one of two academic medical centers in which the delay to surgery was relatively moderate. It is unclear the extent to which the current study findings are applicable to nonacademic centers or sites in which longer delays are common.

## Conclusions

In the current study, we were unable to identify effects of treatment delay that we presume are moderate, using methods that we know to carry inherent biases. In the absence of clear data, we believe that patient counseling regarding the impact of any delay to surgery must be based on clinical judgment. Prostate carcinoma is not a rapidly progressing tumor and therefore it appears inappropriate to rush patients into decision-making and treatment. Nonetheless, undue delay in treating the disease clearly is inadvisable. Moreover, it would be reasonable to modify advice based on patient risk, perhaps encouraging early surgery for those patients at high risk while allowing more flexibility for those considered to be at low risk. In our opinion, such an approach is more justified than accepting the null hypothesis that delay has no effect.

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## TABLE 1

Patient Demographics

| | Overall cohort | Surgery ≤ 90 days after biopsy | Surgery > 90 days after biopsy |
|---|---|---|---|
| No. of patients | 3149 | 2258 | 891 |
| Median age at biopsy in yrs (interquartile range) | 61 (56-65) | 61 (56-65) | 61 (56-65) |
| Median prebiopsy serum PSA level in ng/mL (interquartile range) | 6.3 (4.6-9.6) | 6.6 (4.7-10.0) | 5.9 (4.5-8.6) |
| Biopsy Gleason score | | | |
| 6 | 2192 (70%) | 1517 (67%) | 675 (76%) |
| 7 (3 + 4) | 570 (18%) | 425 (19%) | 145 (16%) |
| 7 (4 + 3) | 224 (7%) | 183 (8%) | 41 (5%) |
| 8-10 | 163 (5%) | 133 (6%) | 30 (3%) |
| Clinical classification | | | |
| T1a/b | 73 (2%) | 41 (2%) | 32 (4%) |
| T1c | 1295 (41%) | 844 (38%) | 451 (51%) |
| T2a | 759 (24%) | 562 (25%) | 197 (22%) |
| T2b | 313 (10%) | 254 (11%) | 59 (7%) |
| T2c | 607 (19%) | 472 (21%) | 135 (15%) |
| T3 | 81 (3%) | 67 (3%) | 14 (2%) |
| Median nomogram-predicted probability of 5-yr disease progression-free survival (interquartile range) | 84% (71-90%) | 82% (68-89%) | 86% (77-91%) |
| Time to surgery | | | |
| < 1 mo | 233 (7%) | | |
| 1-2 mos | 985 (31%) | | |
| 2-3 mos | 1040 (33%) | | |
| 3-4 mos | 496 (16%) | | |
| 4-5 mos | 188 (6%) | | |
| 5-6 mos | 87 (3%) | | |
| 6-9 mos | 100 (3%) | | |
| 9-12 mos | 20 (1%) | | |

PSA: prostate-specific antigen.

**TABLE 2**

Effect of Delay to Surgery on Odds Ratio of Biochemical Disease Recurrence

| | Surgery within 6 mos of diagnosis | | | | Surgery within 12 mos of diagnosis | | | |
|---|---|---|---|---|---|---|---|---|
| **BCR at** | **BCRs (%)** | **OR per month of delay** | **95% CI** | ***P* value** | **BCRs (%)** | **OR per month of delay** | **95% CI** | ***P* value** |
| 3 yrs | 324/2192 (15) | 1.04 | 0.92-1.18 | 0.5 | 332/2262 (15) | 1.00 | 0.92-1.10 | 1 |
| 5 yrs | 359/1577 (23) | 1.07 | 0.94-1.21 | 0.3 | 369/1625 (23) | 1.03 | 0.94-1.12 | 0.6 |
| 8 yrs | 344/913 (38) | 1.08 | 0.93-1.25 | 0.3 | 350/933 (38) | 1.02 | 0.91-1.14 | 0.7 |
| 10 yrs | 273/546 (50) | 1.02 | 0.85-1.22 | 0.9 | 278/559 (50) | 0.95 | 0.83-1.09 | 0.5 |

BCR: biochemical disease recurrence; OR: odds ratio; 95% CI: 95% confidence interval.