Delay in surgical therapy for clinically localized prostate cancer and biochemical recurrence after radical prostatectomy

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Background: *In Canada, waiting times for cancer care have been increasing, particularly for patients with genitourinary malignancies. We examined whether delay from diagnosis for patients undergoing surgery for clinically localized prostate cancer affects cancer cure rates.*

Methods: *We conducted a historical cohort study among 645 patients who underwent radical prostatectomy between 1987 and 1997, using biochemical recurrence (PSA elevation) and metastasis as endpoints. We examined whether patients who underwent surgery ≥3 months (delayed surgery group) from the date of diagnosis had reduced recurrence-free survival, compared to patients who had surgery <3 months (early surgery group) from the date of diagnosis, adjusting for grade, stage and PSA level at diagnosis.*

Results: *The crude 10-year recurrence-free and metastasis-free survival rates for all patients were 71.1% (95% C.I.: 64.9% - 77.3%) and 95.3% (95% C.I.: 91.3% - 99.3%), respectively. Of the 645 patients, 189 (29.3%) had surgery ≥3 months after diagnosis. The median time from the date of diagnosis to surgery was 68 days (range 15 to 951 days). The 10-year recurrence-free survival was higher for patients who underwent early surgery (74.6%, 95% C.I.: 67.9% - 81.4%) compared to patients in the delayed surgery group (61.3%, 95% C.I.: 46.7% - 76.0%, p=0.05). The crude and adjusted hazard ratios for developing biochemical recurrence for patients in the delayed surgery group were 1.58 (95% C.I.: 1.0 – 2.4, p=0.04) and 1.46 (95% C.I.: 0.9 – 2.3, p=0.09), respectively, compared to patients who underwent early surgery.*

Conclusions: *There may exist a possible relationship between delays from diagnosis for radical prostatectomy and prostate cancer cure rates. These findings may have many biases that could not be properly accounted in this retrospective analysis and larger cohort analyses will be required to confirm these findings.*

Key Words: prostatic neoplasms, radical prostatectomy, treatment delay

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Introduction

Prostate cancer is the most common male malignancy and the second leading cause of male cancer deaths in Canada.[1] Since the introduction of serum prostate

specific antigen (PSA) to detect prostate cancer in 1987, both the incidence of prostate of cancer and the proportion of patients with early disease has increased.[2] As a result, the number of men undergoing treatment has also risen.[3]

Current treatment options for clinically localized prostate cancer include surgery and radiation. Large, population-based, observational studies show that these treatment modalities provide durable cancer control.[4-7] However, there can be significant morbidity associated with treatment.[8,9] Because there are no definitive studies that compare their efficacy, the patient must ultimately make the treatment decision after comparing the risks and benefits of each treatment option. This can result in treatment delay. Patients may seek further expert opinion or be initially reluctant to commit to a treatment decision. Another more alarming reason for treatment delays is long waiting lists for cancer treatment. Recently, Simunovic et al showed that many patients with cancer in Ontario experience significant delays for cancer management.[10] Patients diagnosed with a urologic malignancy wait a median of 64 days from the time of referral to the time of surgery.[10] Currently, the waiting list for patients to undergo radical prostatectomy at our institution can be as long as 3 months from the time of diagnosis.

To our knowledge, there are no studies that examine whether delays for prostate cancer treatment affect cancer cure rates. To determine the significance of treatment delays, we conducted a historical cohort study among patients who underwent radical prostatectomy, using time to cancer recurrence as an endpoint. Because a proportion of patients chose to undergo delayed curative therapy, we were able to examine the effects of delayed cancer care as a potential adverse prognostic factor.

Methods

Study subjects

The study subjects were drawn from a total sample of 871 consecutive men who underwent radical prostatectomy between 1987 to 1997 at Toronto General Hospital, University Health Network (Toronto, Ontario). Medical records were reviewed for all clinical data and follow-up information after approval from our institution's research ethics board. Each of the medical and electronic charts was systematically reviewed using standardized data entry forms by trained data abstractors and stored within a prostate cancer-specific database.

Of the 871 patients who underwent radical prostatectomy with or without pelvic lymphadenectomy for clinically localized prostate cancer, clinical data were not available on 22 patients. Because the purpose of the study was to examine factors that influence prostate cancer relapse among patients with localized prostate cancer, only patients without evidence of residual disease following surgery were included. Thus, patients whose postoperative PSA level did not decline to 0.1 ng/mL or who had cancer in the pelvic lymph nodes (89 patients), were excluded. Also, patients who received neoadjuvant hormone therapy were excluded since it required at least 3 months before undergoing surgery (115 patients), leaving 645 patients for analysis.

Clinical follow-up varied by the individual surgeon, but in general, it consisted of four assessments in the first year after surgery, two assessments in the second year and one assessment every year thereafter. At each follow-up, patients had a clinical evaluation, a PSA test, and radiographic studies if indicated.

Outcome measures

The primary endpoint was biochemical disease recurrence which was defined as a PSA elevation of at least 0.2 ng/mL on two consecutive measurements. The secondary endpoint was the detection of metastasis. Prostate cancer specific mortality was not examined due to few events occurring during the time period of the study. Biochemical recurrence has been shown to be an excellent prognostic indicator for the development of metastasis, with a median time to metastasis from the first elevation of PSA of 8 years.[11] The date of recurrence was the time of the first PSA recording of ≥0.2 ng/mL. Prostate cancer metastasis was diagnosed radiographically or by biopsy of a suspicious organ site. Patients underwent radionuclide bone scans, computed tomography or ultrasonography for clinical suspicion of metastasis, including rising PSA levels. The date of metastasis was the date of the first positive diagnostic test.

Data analysis

Crude rates of disease relapse and metastasis were calculated using the Kaplan-Meier method.[12] The effect of delayed therapy was examined by Cox proportional hazard modeling. Potential confounding variables in the multivariate model included histologic grade, pathologic stage, and PSA level at diagnosis. These factors have been consistently demonstrated in large observational cohort studies to be the most important prognostic factors for prostate cancer recurrence following surgery.[5,13] Patients were

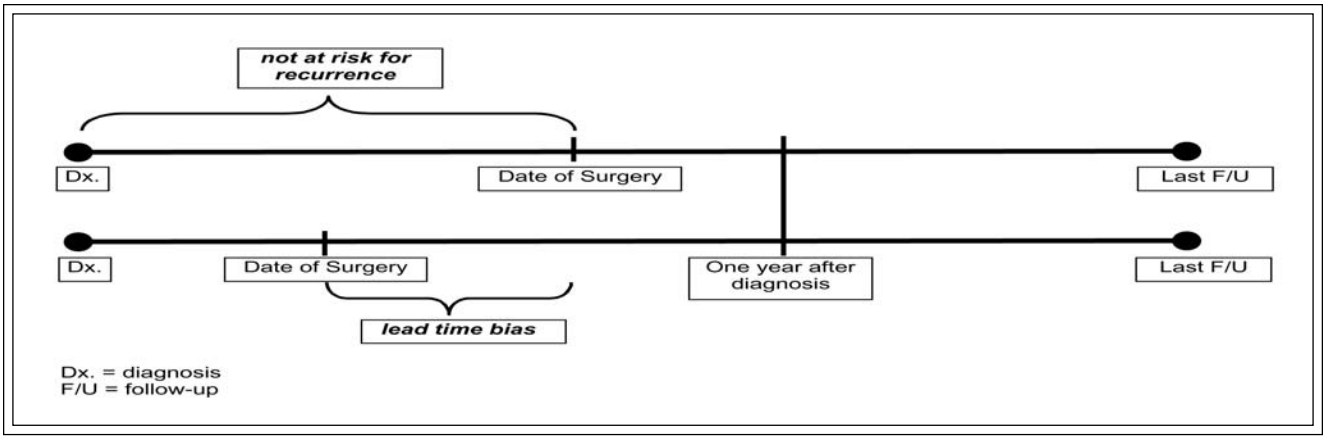

Figure 1. Summary of biases related to differential time exposure in the comparative survival models when using PSA relapse as an endpoint.

considered to be at risk from the date of diagnosis until the date of recurrence, or until the date of the last PSA test. However, by using the date of diagnosis as the start date, patients who had delayed treatment would not be at risk for developing a PSA recurrence before having surgery, introducing a bias in favor of the delayed surgery group Figure 1. Using the date of surgery as the start date would also introduce a lead-time bias in favor of the early treatment group, since there would be shorter follow-up in the delayed surgery group Figure 1. To address these two biases, we performed another analysis where patients were considered at risk for recurrence from one year after the date of diagnosis. In this analysis, we excluded men who had delayed treatment beyond one year after the date of diagnosis and men who developed a PSA recurrence after surgery within one year from the date of diagnosis Figure 1. This resolves the biases related to differential time exposure in the comparative survival models, but assumes that the recurrence rate is independent of the time elapsed since diagnosis and surgery.

Within the Cox model, histologic grade, pathologic stage and serum PSA were considered as categorical variables Table 1. The effect of delayed therapy was examined in two approaches. First, we considered it

TABLE 1. **Methods of microvascular reconstruction employed**

Prognostic factor	**Distribution (n=645)**
Histologic grade:	
Gleason score 2-6	229 (35.5%)
Gleason score 7	350 (54.3%)
Gleason score 8-10	66 (10.2%)
Clinical stage:	
T1	297 (46.1%)
T2	348 (53.9%)
Pathologic stage:	
Organ confined	266 (41.3%)
Extracapsular extension	322 (49.9%)
Seminal vesicle involvement	57 (8.8%)
PSA level at diagnosis (ng/mL)*	
<4.0	111 (19.0%)
4.1–10.0	279 (47.7%)
10.1–20.0	135 (23.0%)
>20.0	60 (10.3%)

* Based on total sample size of 585 who underwent a PSA test prior to surgery.

as a dichotomous variable: a) patients who underwent surgery <3 months after the time of diagnosis (early surgery group); and b) patients who underwent surgery ≥3 months after the time of diagnosis (delayed surgery group). We chose 3 months as the cut-off since this time delay reflects our current surgical waiting time for patients to undergo surgery at our institution. We also examined the effect of delayed therapy by categorizing this variable according its quartile distribution. The time between the date of diagnosis and surgery were collapsed into four categories. Statistical analyses were performed using the SAS System V8e (Carey, North Carolina).

Results

The mean age at diagnosis of the 645 patients was 62.6 (range, 39.2 – 74.5 years). The distributions of grade, stage and PSA are described in Table 1. The crude 5- and 10-year biochemical recurrence-free survival rates were 79.1% (95% C.I.: 75.3% – 82.9%) and 71.1% (95% C.I.: 64.9% - 77.3%), respectively. The crude 10-year metastasis-free survival rate was 95.3% (95% C.I.: 91.3% - 99.3%). The mean follow-up time was 4.0 years (range, 0.4 – 11.7 years). Of the 645 patients, 111 developed PSA relapse leaving 534 (82.8%) still at risk for recurrence. Only nine patients were diagnosed with systemic metastasis. Grade, stage and serum PSA level of diagnosis were found to be important independent prognostic factors for prostate cancer recurrence Table 2.

Of the 645 patients, 189 (29.3%) had surgery later than 3 months after diagnosis. Of these patients, 42 had surgery more than 6 months after diagnosis, and 13 had surgery more than one year after diagnosis. We did not examine these subgroups separately,

TABLE 2.

Covariate	Crude hazard ratio	95% C.I.	p-value	Adjusted	95% C.I.	p-value
Treatment time (from 1 year after diagnosis)						
<3 months	1.00			1.00		
≥3 months	1.61	1.1–2.4	0.02	1.46	0.9-2.3	0.09
Histologic grade*						
Gleason score 2-6	1.00			1.00		
Gleason score 7	3.15	1.9-5.3	0.0001	2.68	1.4-5.1	0.0001
Gleason score 8-10	7.55	4.1-14.0	0.0001	5.21	2.5-11.0	0.002
Pathologic stage*						
OC	1.00			1.00		
ECE	2.62	1.6-4.3	0.0001	2.14	1.2-3.9	0.03
SVI	4.48	2.4-8.2	0.0001	2.29	1.1-4.9	0.01
PSA level at diagnosis* (ng/mL)						
<4.0	1.00			1.00		
4.1-10.0	1.96	1.1-3.4	0.02	1.87	0.9-4.1	0.13
10.1-20.0	3.12	1.7-5.6	0.0002	1.91	0.9-4.4	0.12
>20.0	5.16	2.8-9.6	0.0001	2.55	1.1-6.1	0.04
Treatment time (from date of surgery)						
<3 months	1.00			1.00		
≥3 months	1.61	1.1-2.4	0.02	1.48	0.9-2.2	0.06
Treatment time (from date of diagnosis)						
<3 months	1.00			1.00		
≥3 months	1.47	1.0-2.2	0.05	1.36	0.9-2.1	0.14

*Adjusted hazard ratios based on sample size of 526 patients and using the start date from one year after the date of diagnosis.

TABLE 3.

Prognostic factor	Early surgery (n=456)	Delayed surgery (n=189)	p-value
Histologic grade:			
Gleason score 2-6	171 (37.5%)	58 (30.7%)	0.26
Gleason score 7	240 (52.6%)	110 (58.2%)	
Gleason score 8-10	45 (9.9%)	21 (11.1%)	
Clinical stage:			
T1	215 (47.1%)	82 (43.4%)	0.38
T2	241 (52.9%)	107 (56.6%)	
Pathologic stage:			
Organ confined	181 (39.7%)	85 (45.0%)	0.46
Extracapsular extension	234 (51.3%)	88 (46.5%)	
Seminal vesicle involvement	41 (9.0%)	16 (8.5%)	
PSA level at diagnosis* (ng/mL)			
<4.0	91 (22.1%)	20 (11.5%)	0.003
4.1-10.0	196 (47.7%)	83 (47.7%)	
10.1-20.0	81 (19.7%)	54 (31.0%)	
>20.0	43 (10.5%)	17 (9.8%)	

* Based on total sample size of 585 with 174 and 411 undergoing immediate and delayed surgery, respectively. PSA data was not available on 60 patients.

because of limited sample size and follow-up. The median time from the date of diagnosis to surgery was 68 days (range 15 to 951 days). When we examined the proportion of patients who had delayed surgery by arbitrarily defined time periods for year of surgery, the highest proportion of patients (37.4%) had delayed surgery in the most contemporary time period of 1995 to 1997, compared to earlier time periods of 1987 to 1990 (20.9%) and 1991 to 1994 (26.7%, p=0.005) Figure 2. There were no significant differences in the distribution of grade and clinical stage between the early and delayed surgery group Table 3. However, for patients with a PSA level of >10 ng/mL, 40.8% had delayed surgery compared to 30.2% who had early surgery (p=0.003).

Using the date of diagnosis as the start date, the crude 10-year biochemical recurrence-free survival was higher for patients in the early surgery group (74.6%, 95% C.I.: 67.9% - 81.4%) compared to patients in the delayed surgery group (61.3%, 95% C.I.: 46.7% - 76.0%, p=0.05) Figure 3. Among the delayed surgery

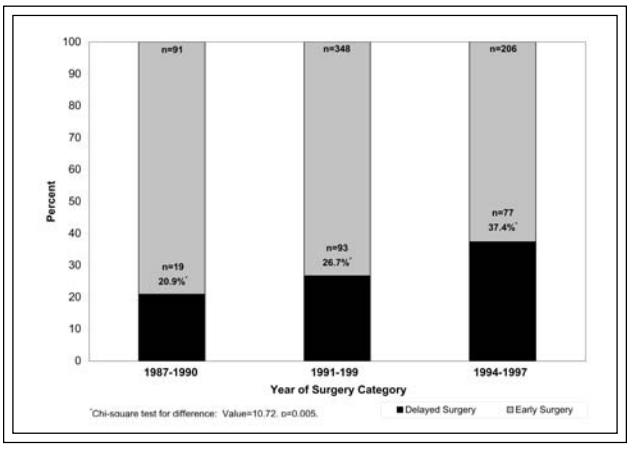

Figure 2. Proportion of patients who underwent delayed surgery by arbitrarily defined time periods.

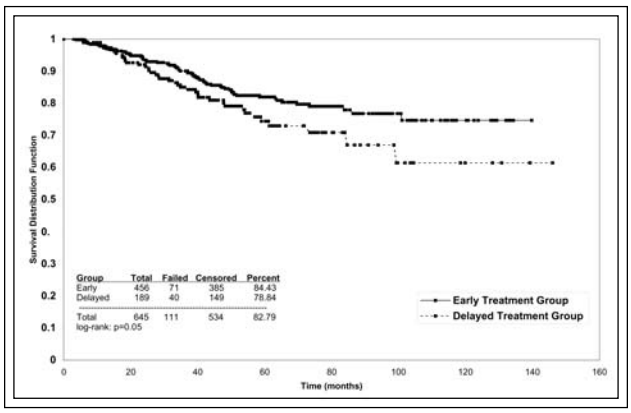

Figure 3. Kaplan-Meier recurrence-free survival stratified by time to treatment

TABLE 4.

Surgical waiting time by quartiles	Crude hazard ratio	95% C.I.	p-value	Adjusted hazard ratio*	95% C.I.	p-value
<43 days	1.00			1.00		
43-68 days	0.82	0.5-1.4	0.47	0.71	0.4-1.3	0.25
69-97 days	0.92	0.5-1.6	0.76	0.88	0.5-1.6	0.66
>97 days	1.42	0.9-2.3	0.15	1.25	0.7-2.1	0.39

*Adjusted by grade, stage and PSA level.

group, 40 of 189 patients (21.2%) experienced a recurrence, compared to 71 of 456 (15.6%) patients in the early surgery group. The crude 10-year metastasis-free survival was also higher in the early surgery group (97.5%, 95% C.I.: 93.7% - 99.9%) compared to the delayed surgery group (88.1%, 95% C.I.: 76.7% - 99.6%, p=0.009). Using the least biased approach where the initial start date was at one year after diagnosis, the crude hazard ratio for developing biochemical recurrence for patients in the delayed surgery group was 1.58 (95% C.I.: 1.0 – 2.4, p=0.04) compared to patients who underwent early surgery. After adjusting for grade, stage and PSA, the hazard ratio for developing biochemical recurrence for patients in the delayed surgery group was 1.46 (95% C.I.: 0.9 – 2.3, p=0.09) compared to patients who underwent immediate surgery. The mean follow-up times between the immediate (41.5 months) and delayed (37.3 months) surgery groups were not significantly different (p=0.11).

Because we found a significant relationship between patients who had delayed therapy and their PSA level at diagnosis Table 3, we stratified patients into two groups according to their PSA level and examined the effect of delayed therapy using the time from one year after diagnosis as the start date. Patients were grouped into either a low PSA (<10 ng/mL) or high PSA (≥10 ng/mL). For patients in the low PSA group, the adjusted hazard ratio for recurrence for patients in the delayed treatment group was 1.70 (95% C.I.: 0.9 – 3.2, p=0.11), compared to patients in the immediate treatment group (adjusted for grade and stage). For patients in the high PSA group, the adjusted hazard ratio for recurrence for patients in the delayed treatment group was 1.44 (95% C.I.: 0.8 – 2.7, p=0.24), compared to patients in the immediate treatment group.

To examine whether there was an incremental increase in risk for relapse due to increasing treatment time from diagnosis, we collapsed the surgical waiting times by their quartile distribution and examined their relationship with PSA relapse rates. Although there were no statistically significant differences between the quartile groups, the hazard ratio for biochemical recurrence for patients in the highest quartile of surgical waiting times compared to the lowest quartile was in the same direction Table 4.

Discussion

This is the first report that has demonstrated a possible trend towards lower cancer cure rates because of delays in the treatment for prostate cancer. Patients who wait more than 3 months from the time of diagnosis have a possible 1.5-fold increase in risk for developing cancer recurrence compared to patients who undergo early surgery, after adjusting for grade, stage and PSA. Freedland et al examined patients who underwent serial PSA measurements for a minimum of 12 months before surgery and did not find an association between PSA doubling times and the risk of recurrence.[14] However, they did not specifically correlate the time between diagnosis and surgery to recurrence.

The biologic mechanism to explain our observation is unclear. It is well understood that the time to progression from clinically localized prostate cancer to the diagnosis of metastatic disease requires many years.[4,15] Thus, the impact of a 3 month delay to surgery does not appear to be consistent with the long observed natural history of the disease. Also, after adjusting for grade, stage and PSA, the statistical significance of the delayed treatment variable is lost. The effect of delayed therapy may further be a reflection of its association with a higher PSA level Table 3. After stratifying by PSA level, the effect of delayed therapy appeared to be important for patients in the low PSA group (<10 ng/mL), although the statistical significance was also lost (p-value=0.11). This is likely due to a loss in power from stratifying by PSA

level. Nevertheless, it seems reasonable that the best time for cancer cure is at its earliest stage of progression.

Another biologic explanation could be related to the degree of psychosocial stress that men might experience from treatment delays. Although there are no reports examining the prognostic significance of stress with prostate cancer, there has been a strong association between psychosocial stress and breast cancer survival.[16,17] Watson et al showed that women with signs of significant depression or feelings of helplessness had a 1.55 to 3.59 fold increase in risk for breast cancer death, after adjusting for the established prognostic factors for breast cancer.[16] Treatment delays may be identifying a group of men who experience more stress and anxiety over the treatment decision.

On the other hand, it is important to recognize that the effect of treatment delay may purely be due to chance. Because the p-values of the hazard ratios ranged from 0.02 for the crude value and 0.14 for the adjusted value, there is a strong possibility that there truly is no difference between the early and delayed treatment groups. Also, because there was no significant relationship between incremental increases in delay time (by quartiles) and PSA relapse, the effects of shorter or longer delays do not appear to be consistent. However, the point estimate in the hazard ratio for recurrence for patients in the fourth quartile was consistent with the findings when the delayed treatment variable was treated dichotomously. This is likely due to the observation that the group in the fourth quartile consisted of patients with a treatment delay of greater than 97 days, similar to the cut-off of 3 months when this variable was handled dichotomously. It did not reach significance because of a lack of power since only the fourth and first quartile groups were compared. Further, when using metastasis as an endpoint, patients who had delayed treatment had a significantly higher progression rate compared to patients who had early treatment, despite the low sample size.

It is also important to acknowledge that the reasons for treatment delays were likely due to a variety of factors that were not uniformly recorded in the medical charts. In addition to waiting lists for surgery, some reasons included psychosocial factors such as a reluctance to decide a treatment plan, anxieties related to the surgical procedure, factors related to the patient's employment, or the patients' desire to seek further opinions. Another factor could be delays in undergoing further staging tests. Regardless of the reason, these treatment delays have provided a unique opportunity to examine the effect of waiting times on prognosis.

Recent data has shown increasing waiting times for cancer treatment after being diagnosed with cancer.[10,18,19] However, what remains uncertain is how these delays for cancer care affect cure rates. In the study by Simunovic et al., determining whether wait times for treatment had a negative impact on prognosis was evaluated only by expert opinion and not objectively.[10] Reports examining the prognostic importance of treatment delays for other primary cancers, including breast and colon cancer have not shown a significant impact on survival.[20,21] In contrast, treatment delays for certain head and neck, and lung malignancies have shown a detrimental effect on cancer survival.[22,23]

There were no significant differences in the distribution of grade or stage among patients who had delayed or early treatment. However, more patients with a PSA of greater than 10 ng/mL had delayed surgery. A possible explanation of this finding was that these patients underwent further staging procedures, including radionuclide bone scan or computed tomography, which might have delayed their surgery. Patients with PSA values of >10 ng/mL and a Gleason score of 8 or more have a 20% to 30% chance of having metastatic disease.[24]

It is also interesting to observe that more patients had delayed surgery (37.4%) between 1994 and 1997 compared to earlier time periods (20.9% to 26.7%). Despite the fact that the reasons for delayed treatment varied between patients, more patients may have had to wait for surgery because of healthcare restraints, in the more contemporary time period. Another factor could be due to the sharp increase of prostate cancer incidence in the more recent time periods which could have contributed to the increasing demand for radical prostatectomy.[1]

The use of serum PSA as a surrogate endpoint for clinical recurrence and prostate cancer mortality is widely accepted and has been used in other studies.[13,25,26] Patients with PSA-detected recurrence eventually develop local or distant recurrence, if untreated, and fewer than 3% of patients who develop clinical recurrence maintain undetectable PSA values.[13,27,28] The hazard ratios for biochemical recurrence according to grade, stage and serum PSA at diagnosis are consistent with the outcomes of other large case series.[13,25,29] Although it is reasonable to use PSA defined recurrence as a surrogate endpoint, we could not completely resolve the biases associated with using the date of diagnosis or surgery Figure 1. Further, because we used biochemical survival as an endpoint, we could not include the 89 patients we initially excluded because their PSA did not reach

undetectable levels or had lymph node positive cancer. These patients would be considered as immediate events at time zero by the Kaplan-Meier method and would not provide meaningful data. A future study using prostate cancer-specific mortality will be required to overcome these issues, particularly for the 89 excluded patients. We did not provide any crude comparisons in their surgical delay times for this group since prostate-specific survival as an endpoint was beyond the scope of the study.

Given the limitations of this study, it is important to recognize that these findings should not be considered as conclusive evidence to avoid treatment delays. Certainly the long natural history of the disease is not consistent with our findings. However, even if cancer cure rates were not affected, the significant psychosocial stresses related to waiting for cancer treatment would be a compelling reason alone for timely cancer care.[30] □

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