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Delayed Versus Immediate Surgical Intervention and Prostate Cancer Outcome

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Abstract

For prostate cancer patients with small, lower-grade tumors, expectant management with delayed surgical intervention (active surveillance) is a rarely used therapeutic option because the opportunity for cure may be lost. We compared outcomes of 38 patients with small, lower-grade prostate cancer in an expectant management program who underwent delayed surgical intervention at a median of 26.5 months (95% confidence interval [CI] = 17 to 32 months; range = 12.0–73.0 months) after diagnosis with 150 similar patients who underwent immediate surgical intervention at a median of 3.0 months (95% CI = 2 to 4 months; range = 1.0–9.0 months) after diagnosis. Noncurable cancer was defined as adverse pathology associated with a less than 75% chance of remaining disease-free for 10 years after surgery. Noncurable cancer was diagnosed in nine (23%) of the 38 patients in the delayed intervention cohort and in 24 (16%) of the 150 men in the immediate intervention group. After adjusting for age and prostate-specific antigen (PSA) density (i.e., PSA value divided by prostate volume) in a Mantel–Haenszel analysis, the risks of noncurable cancer associated with delayed and immediate intervention did not differ statistically significantly (relative risk = 1.08, 95% CI = 0.55 to 2.12; $P = .819$, two-sided Cochran–Mantel–Haenszel statistic). Age, PSA, and PSA density were all statistically significantly associated with the risk of noncurable cancer ($P = .030$, .013, and .008, respectively; two-sided chi-square test). Thus, delayed prostate cancer surgery for patients with small, lower-grade prostate cancers does not appear to compromise curability.

Men screened for prostate-specific antigen (PSA) are diagnosed an estimated 10 years earlier in the natural history of prostate cancer than men diagnosed without PSA screening (1,2). Although earlier diagnosis may have contributed to a decline in prostate cancer mortality (3), it has also led to the diagnosis of some cancers that would not have been detected in the absence of screening (i.e., overdiagnosis) (1,4). Because overdiagnosis can lead to over-treatment, expectant management (or active surveillance) with delayed curative intent (i.e., surgery or radiation therapy) has been proposed as an alternative to immediate surgery for men with newly diagnosed prostate cancer with low-grade, low-stage disease in an effort to reduce unnecessary treatment for prostate cancer (5,6). However, this approach is rarely recommended to patients, presumably because of the concern that surveillance will compromise the ability to be cured later if definitive treatment is required (7). We tested the hypothesis that curability is not lost among patients with small, lower-grade prostate cancers enrolled in an expectant management program by comparing the rates of non-curable cancer

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among patients undergoing delayed curative surgery with those among patients undergoing immediate curative surgery.

At our institution, men suspected of having small, lower-grade prostate cancer have the option of entering an expectant management program (6) that has been approved by the institutional review board. Each year, our program has historically enrolled approximately 1% of the patients with newly diagnosed prostate cancer. Enrollment criteria are based on PSA density and the findings of a biopsy examination (6). Follow-up involves semiannual measurements of total and free PSA, a semiannual digital rectal examination, and an annual surveillance prostate biopsy examination. Curative surgery is triggered by the finding of adverse pathological features on an annual surveillance biopsy examination (i.e., a Gleason score of 7 or more with a Gleason pattern grade 4 or above, more than two cores that are positive for cancer, or more than 50% of any one core that is involved with cancer) or a patient's request for a change in management. In our program, total PSA changes have not triggered intervention.

Between January 1, 1995, and February 1, 2005, 320 men (median age = 65.4 years; range = 48.3–77.1 years) have been enrolled in the expectant management program. Ninety-eight of these 320 men have undergone curative intervention (either radiation or surgery) after an observation period of at least 12 months. Thirty-nine of these 320 men underwent radical prostatectomy; nine of these 39 men requested a change in management without a trigger for intervention. We excluded one patient who received neoadjuvant androgen deprivation therapy before curative intervention. Thus, the final delayed intervention cohort contained 38 men who underwent surgical intervention. The cohort was stratified by quartiles of age at diagnosis and total PSA at diagnosis; the resulting distribution was used for frequency matching to the immediate intervention cohort. From the database of 2266 consecutive prostatectomy patients treated at our institution between January 1, 1975, and December 31, 2004, there were 420 men who underwent immediate surgery and who would have been eligible for expectant management. We randomly selected 150 men from this group who were frequency matched at a 4: 1 ratio to the distribution of age and PSA in the delayed intervention cohort (see Table 1 for selection criteria); these 150 men constituted the comparison group in the analysis. Informed consent was not required because we did not use subject identifiers.

The primary outcome of this study was the proportion of patients with non-curable disease [i.e., <75% chance of remaining biochemical recurrence-free at 10 years after surgery (8)]. Table 1 shows the distribution of prognostic factors for the groups. We compared outcomes of 38 patients with small, lower-grade prostate cancer in an expectant management program who underwent delayed surgical intervention at a median of 26.5 months (95% con3 dence interval [CI] = 17 to 32 months; range = 12.0–73.0 months) after diagnosis with 150 similar patients who underwent immediate surgical intervention at a median of 3.0 months (95% CI = 2 to 4 months; range = 1.0–9.0 months) after diagnosis. Nine (23%) of the 38 patients in the delayed intervention group and 24 (16%) of the 150 men in the immediate intervention group had noncurable cancer at the time of surgery.

The relative risk (RR) was calculated in a Mantel–Haenszel analysis as the ratio of the proportion of patients with noncurable cancer in the delayed versus immediate intervention groups (nonad-justed RR = 1.48, 95% CI = 0.75 to 2.92; $P = .266$) (Table 2). After adjustment for age and PSA density at diagnosis, the risk of noncurable prostate cancer was not associated with the type of intervention (adjusted RR = 1.08, 95% CI = 0.55 to 2.12; $P = .819$) (Table 2). Additional adjustment for other potential confounding factors did not improve this estimate (data not shown). When the analysis was restricted to the 27 patients

in the delayed intervention group who met all of the criteria for the expectant management program, the results remained the same (data not shown). All statistical tests were two-sided.

Age, PSA, and PSA density were each statistically significantly associated with the presence of noncurable cancer when the median value was used as the cut-point (P = .030, .013, and .008, respectively; two-sided chi-square test) (Table 2). The maximum percentage of the biopsy core involved with cancer, the number of positive cores with cancer, year of surgery, and time between diagnosis and surgery were not associated with the risk of noncurable cancer (data not shown). These results remained the same when the analysis was restricted to those subjects in the delayed intervention group who met all of the criteria for the expectant management program (data not shown).

The safety of delayed surgical intervention has been suggested in a small case-control study that used surgical pathology as the end-point (9) and in another study that evaluated freedom from disease for more than 15 months aftersurgeryin17men(10).Ourdata suggest that the window of opportunity for cure appears to be maintained, despite a delay in surgical intervention averaging 2 years, if men are carefully selected at the time of initial diagnosis for the presence of small-volume, lower-grade cancer.

Our findings have two important implications. First, men who are diagnosed with early-stage, lower-grade prostate cancer should not be led to believe that they have an urgent situation that requires immediate treatment. Although they may ultimately decide on treatment, there is no apparent gain to making this management decision quickly with the belief that a delay will compromise cure. Second, when selected carefully by use of criteria that suggest the presence of small-volume, lower-grade cancer and then monitored with a rigorous protocol for disease progression, these patients appear to have the same risk of non-curable prostate cancer for at least 2 years after diagnosis as those patients who received immediate prostate cancer surgery. Our data thus suggest that this expectant management approach should be used more frequently, given that approximately 50% of men today are diagnosed with low-risk prostate cancer (11).

Potential limitations of this study include the small sample of men who underwent delayed surgical intervention and the use of a surrogate end-point for noncurability (i.e., surgical pathology consistent with a <75% chance of remaining biochemical recurrence-free at 10 years after surgery). With longer follow-up, we could find that a delay in surgical intervention compromises disease-free outcomes. However, given the minimal 5% overall improvement in cancer-specific survival at 10 years after diagnosis when comparing surgical treatment to no treatment among men with cancers not detected by screening (12), it seems unlikely that expectant management of low-risk, screen-detected cancers will place patients at undue risk of an adverse outcome. Thus, expectant management with curative intent appears to be a safe alternative to immediate treatment for a carefully selected group of patients with small-volume, lower-grade prostate cancer.

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Table 1

Distribution of prognostic factors in a cohort of patients with prostate cancer who were initially managed expectantly and subsequently underwent surgery (i.e., delayed intervention group) and in a cohort of patients treated with immediate surgery

	Study group		
Variable*	**Delayed intervention†**	**Immediate surgery‡**	***P* value§**
No. of patients	38	150	
Age at diagnosis, y			
Mean (95% CI)	61.2 (60.0 to 62.5)	60.8 (60.2 to 61.4)	.482
Median (range)	61.0 (52.0–70.0)	61.0 (52.0–70.0)	
PSA, ng/mL			
Mean (95% CI)	5.1 (4.6 to 5.7)	5.3 (5.0 to 5.6)	.632
Median (range)	4.9 (2.0–11.2)	5.0 (2.1–12.0)	
PSA density,// ng/mL/cm^3			
Mean (95% CI)	0.127 (0.108 to 0.146)	0.089 (0.084 to 0.094)	.001
Median (range)	0.11 (0.04–0.30)	0.09 (0.03–0.15)	
No. of cores positive for cancer			
Mean (95% CI)	1.3 (1.2 to 1.5)	1.4 (1.3 to 1.5)	.274
Median (range)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	
Maximum percent core involvement with cancer¶			
Mean (95% CI)	10.8 (6.3 to 15.4)	23.5 (21.2 to 25.8)	.001
Median (range)	5.0 (1.0–50.0)	20.0 (5.0–50.0)	
Time to treatment, mo#			
Mean (95% CI)	27.7 (22.7 to 32.6)	3.5 (3.3 to 3.8)	.001
Median (range)	26.5 (12.0–73.0)	3.0 (1.0–9.0)	

*PSA = prostate-specific antigen; CI = confidence interval.

†Criteria for entry into the expectant management program are based on PSA density (PSA before diagnosis divided by prostate volume determined by transrectal ultrasound measurement) and needle biopsy findings in patients with nonpalpable prostate cancers (stage T1c) as follows: PSA density ≤ 0.15 ng/mL/cm^3 and favorable biopsy characteristics (Gleason score of 6 or less with no Gleason pattern grade of 4 or above, no more than two cores positive for cancer, and no more than 50% of any one core involved with cancer). Twenty-seven of the 38 patients in the expectant management cohort met all of the entry criteria for expectant management that were based on PSA density and favorable biopsy findings, whereas 11 patients met all criteria with the exception of a PSA density of more than 0.15 ng/mL/cm^3 (range = 0.16–0.3).

‡A database of consecutive patients undergoing radical prostatectomy at our institution (between January 1, 1975, and December 31, 2004) was used to select a group of control patients who underwent immediate intervention. After excluding patients operated on before 2001 who lacked details of their prostate needle biopsy results and patients with incomplete data, we had a cohort of 2266 patients. When we applied the criteria used to define eligibility for the expectant management program (PSA density and prostate needle biopsy findings) to these 2226 patients, we obtained data for 420 patients who underwent surgery at the time of diagnosis. We randomly selected patients from these 420 patients and frequency matched them by age at diagnosis and PSA level to the delayed intervention cohort at a ratio of 1: 4 patients in the delayed intervention cohort to patients in the immediate intervention cohort; 150 patients were so matched to the 38 men who underwent delayed intervention in the expectant management program.

§Clinical parameters of subjects in the delayed intervention cohort and the immediate intervention cohort were compared by use of *t* tests or chi-square tests for continuous variables and categorical variables, respectively.

[//]PSA density for delayed intervention group was the PSA level (before biopsy diagnosis) divided by the prostate volume obtained from transrectal ultrasound measurement. PSA density for the immediate intervention group was the PSA level (before biopsy diagnosis) divided by the weight of the surgical specimen.

[¶]Maximum percentage of biopsy core involved with cancer.

[#]Time from diagnosis to surgical intervention.

Table 2

Risk of noncurable prostate cancer in the delayed intervention cohort of patients who were initially managed expectantly and then underwent surgery compared to the immediate surgery cohort*

	Nonadjusted		Adjusted‡	
Comparison†	RR (95% CI)§	*P* value‖	RR (95% CI)§	*P* value‖
Delayed versus immediate intervention	1.48 (0.75 to 2.92)	.266	1.08 (0.55 to 2.12)	.819
Age: 63–70 y versus 52–62 years	1.96 (1.06 to 3.63)	.030	n.d.¶	n.d.
PSA density: ≥0.10 versus <0.10 ng/mL/cm^3	2.21 (1.16 to 4.24)	.013	n.d.	n.d.
PSA: >6.0 versus ≤6.0 ng/mL	2.27 (1.24 to 4.17)	.008	n.d.	n.d.

*Noncurable cancer, defined as a less than 75% chance of biochemical freedom from disease at 10 years after surgery (8), was stage pT2 (organ confined) if the Gleason sum was ≥7 (4 + 3) and/or the surgical margins were positive, stage pT3aN0 (extraprostatic extension) if the Gleason sum was ≥7 and/or surgical margins were positive, and any stage higher than pT3a regardless of grade or margin status or any N^+ stage.

†PSA = prostate-specific antigen.

‡Adjusted for age and PSA density.

§Proportion of men with noncurable tumors in the delayed intervention cohort divided by the proportion with noncurable tumors in the immediate intervention cohort. The Mantel–Haenszel procedure was used to obtain estimates of relative risks (RRs) and 95% confidence intervals (CIs), adjusted for potential confounding factors at diagnosis including age, PSA, PSA density, number of positive cores, maximum percentage of a core positive for cancer, year of diagnosis, and year of surgery.

‖Two-sided *P* values were derived from Cochran–Mantel–Haenszel statistics.

¶n.d. = Not done. Adjusted analyses were not performed for these risk factors because they were not the major focus of the study.