Impact of active surveillance on pathology and nerve sparing status

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SUSSMAN R, STAFF I, TORTORA J, CHAMPAGNE A, MERANEY A, KESLER SS, WAGNER JR. Impact of active surveillance on pathology and nerve sparing status. *Can J Urol* 2014;21(3):7299-7304.

Introduction: *We assessed whether, in comparison to immediate surgery, a time delay in performing radical prostatectomy (RP) in patients electing to undergo a period of active surveillance (AS) of low grade prostate cancer, is associated with adverse pathologic features, biochemical recurrence and the ability to perform effective nerve sparing surgery.*

Materials and methods: *From our RP database of 2769 patients, we identified 41 men under AS who subsequently underwent RP. This study group was compared to control group A (164 patients who chose RP rather than AS), matched for prostate-specific antigen (PSA) and initial diagnostic biopsy characteristics. With time, PSA and biopsy characteristics in the AS study group changed, prompting these men to undergo RP. These changes were matched to create a separate control group B (123 patients most of whom did not meet AS criteria). The incidence of nerve sparing surgery, pathologic features, and biochemical recurrence were compared. Outcome variables were compared using Chi-square tests of proportions. Fisher's Exact test was used for recurrence rates due to the low expected frequencies in some cells.*

Results: *Compared with control group A, the AS patients experienced higher rates of Gleason score upgrading (33/41; 81.1% versus 76/164; 46.3%, $p < 0.001$), biochemical recurrence (5/41; 11.4% versus 2/164; 1.3%, $p = 0.012$) and lower rates of bilateral nerve sparing surgery (31/41; 75.6% versus 154/164; 93.9%, $p < 0.001$). Control group B and active surveillance group were comparable across all indices measured.*

Conclusions: *Delaying RP, through undergoing a period of AS, had a significant negative impact on the incidence of bilateral nerve sparing surgery and adverse pathologic features when compared to patients with similar parameters at the time of diagnosis. Close monitoring and surveillance biopsies did not improve pathologic outcomes compared to patients from whom a single diagnostic biopsy was obtained (and were not candidates for AS), and who subsequently underwent immediate surgery.*

Key Words: active surveillance, prostatectomy, outcome, robotic

Introduction

Prostate cancer is the most common cancer (excluding non-melanoma skin cancers) and the third leading cause of death from cancer in Canadian men.[1] Treatment options for localized prostate cancer include radical prostatectomy, external beam radiation, brachytherapy, particle beam therapy, cryotherapy and active surveillance (AS). While the advent of widespread prostate-specific antigen (PSA) screening in the 1990's has significantly reduced the rate of prostate cancer-related mortality, it has also increased the diagnosis of otherwise indolent prostate cancers.[2] The European Randomized Study of Screening for Prostate Cancer determined that, after 11 years of follow up, PSA-based screening reduced mortality from prostate cancer, but did not affect all-cause mortality.[3] Since all prostate cancer treatment options carry a risk of non-trivial complications, AS has been proposed as an alternative treatment approach in men with newly diagnosed, low risk cancers in an attempt to minimize superfluous treatment.[4-6] There is a paucity of data examining the reasons why patients go on to receive definitive treatment after a period of AS, and how their outcomes compare to men with similar cancers that received immediate intervention.

Accepted for publication April 2014

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In the current study, our primary objective was to compare outcomes in men with low grade prostate cancer initially selected for AS that subsequently underwent radical prostatectomy (RP), with patients who elected to immediately undergo RP. Specifically, we evaluated whether the time between performing RP following an initial period of AS was negatively associated with adverse pathologic features, biochemical recurrence and an inability to perform effective nerve sparing surgery.

Materials and methods

Institutional review board approval

The study was conducted with the approval of Hartford Hospital Institutional Review Board (IRB) as part of an ongoing outcomes study in men with prostate cancer and their treatment.

Study design

A retrospective review of a prospectively maintained, IRB approved prostate cancer database was performed. Patients undergoing robotic assisted laparoscopic radical prostatectomies (RALP) between March 1, 2006 and June 30, 2011 were eligible for inclusion in the study cohort.

All RALP were performed via a transperitoneal approach by one of four surgeons using DaVinci, DaVinci S, DaVinci S HD, and DaVinci Si Surgical Systems (Intuitive Surgical, Sunnyvale, CA, USA) and a modified Vattikuti Institute technique.[7] Pelvic lymph node dissection was generally performed for intermediate and high risk patients according to D'Amico's risk classification.[8] The extent of pelvic lymph node dissection varied depending on accepted practice at the time of surgery and the clinical scenario.

Patient demographics, clinical staging and intraoperative details were prospectively collected and entered into the database. Patients who were selected for AS as the primary management option after diagnosis of prostate cancer and who subsequently received RALP as a secondary treatment comprised the study group. Patients were selectively offered AS if they met the USCF low risk diagnostic criteria: PSA < 10 ng/mL, biopsy Gleason sum ≤ 6 with no pattern 4 or 5, cancer involvement of < 33% of biopsy cores, < 50% cancer in any one core, and clinical stage T1/T2a tumor.[9]

Two control groups were utilized in the study. A control group A (164 patients) had baseline data from initial diagnostic biopsies that were comparable with patients entering AS. With time, PSA and biopsy characteristics in the AS study group changed (median delay in the study group between diagnosis and surgery was 20 months). These changes were matched to create a separate control group B (123 patients of which most did not meet AS selection criteria). The algorithm for the selection of patients in control groups A and B and the study (AS) group is shown in Figure 1.

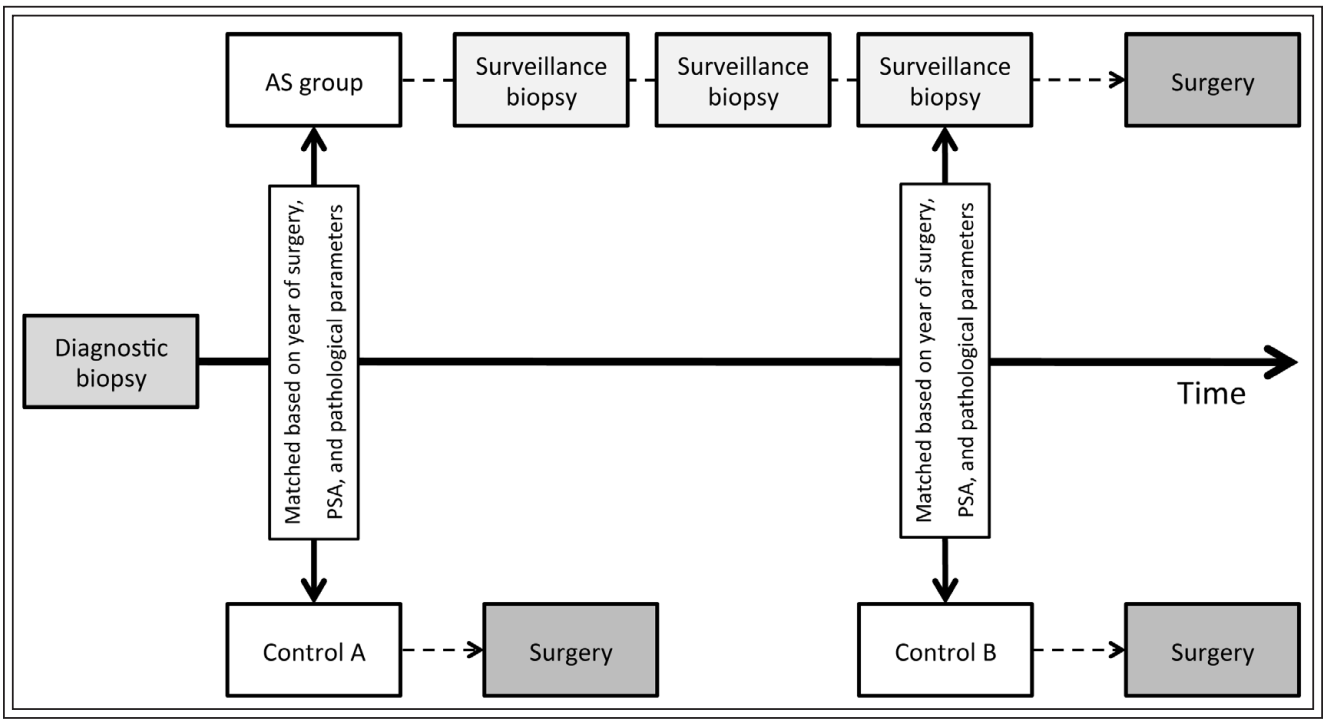

Figure 1. Algorithm for the selection of patients in the study active surveillance group and control groups A and B.

TABLE 1. **Criteria used to select control group patients**

Control group selection criteria	
Age (within ± 5 years)	
Year of surgery (within ± 3 years)	
Equivalent clinical Gleason score (sum)	
Equivalent clinical tumor stage	
Equivalent % prostate tumor volume positive for disease on biopsy (± 10%)	
Diagnostic PSA value within the same PSA category	1. <=2.549 2. >=2.550 and <=4.049 3. >=4.050 and >=6.049 4. <=6.050 and >=10.000 5. >=10.001

Criteria used to match patients in each control group included (i) age ± 5 years, (ii) year of surgery (± 3 years), (iii) equivalent Gleason score, (iv) equivalent tumor stage, (v) equivalent % prostate tumor volume found positive for disease on biopsy (± 10%), and (vi) diagnostic PSA value within the same PSA category, Table 1. For each group, the delay (i.e. time) between (i) surgery and the diagnostic biopsy and (ii) the last surveillance biopsy and subsequent surgery was expressed in months.

All unique patients fitting matching criteria (PSA Partin Table Category (0-2.5, 2.6-4.0, 5.1-6, 6.1-10, > 10), percent positive cores ± 10 %, clinical stage and Gleason score) were included. The two control groups were selected independently. The ability to perform nerve sparing surgery, Gleason upgrading on surgical pathology, surgical margins and biochemical recurrence were compared between the study group and each control group.

All outside biopsies were reviewed by in-house pathologists prior to a treatment decision being made (either active surveillance or definitive therapy). In the case of a discrepancy, a third party review determined the final reading. While we do not keep track of concordance rates, they are approximately 90%.

Surgical margin status was determined by pathologic evaluation of the specimen at a single institution. AJCC 2002 and AJCC 2011 staging guidelines were used consistently by the pathologists.[10] All specimens were whole-mounted and step-sectioned at 3 mm intervals with apex and base being additionally cross-sectioned. Positive surgical margin was defined as presence of cancer cells at inked resection margin in the final specimen. Intraoperative biopsy results or additional tissue excisions were not used to determine margin positivity.

Postoperative PSA values were routinely obtained at 1, 3, 6, 9, 12, 18 and 24 months and annually thereafter. PSA recurrence was defined as ≥ 0.2 ng/mL. Patients receiving adjuvant or salvage treatment were included in our analyses and were considered as having recurred at the time of PSA failure or receiving adjuvant treatment.

All statistical analyses were performed using SPSS v14.0 (SPSS, Inc., Chicago, IL, USA). Two separate analyses were conducted to compare each study group with its relevant control group. Chi-square tests of proportions for independent groups were used to compare the two groups on each of the outcome variables, while Fisher's Exact test was used for the recurrence rates due to the low expected frequencies in some cells. T-tests for independent groups were used in preliminary comparisons (to validate matching) for age, year of engagement, diagnostic PSA, Gleason score, and percent positive cores. We used a point/serial correlation test (distributed as Pearson correlation coefficients) to assess if the time intervals between each biopsy and surgery were associated with the occurrence of positive margins.

Results

A total of 294 male patients were included in the study. The AS study group consisted of 41 men with a median follow up time of 7 months (range: 0-37, IQR: 3-22). Two hundred and fifty-three men met our matching criteria with 221 men included only in one control group and 32 men included in both control groups. Control group A consisted of 164 men with a median follow up time of 11 months (range: 0-62, IQR: 4-24). Control group B consisted of 123 men and had a median follow up time of 10 months (range: 0-61, IQR: 3-22).

TABLE 2. **Clinical indices of patients**

	Gleason upgrading (n; %)	pT3 (n; %)	Bilateral nerve sparing (n; %)	Positive margins (n; %)	Biochemical recurrence (n; %)
Control group A* (n = 164)	76; 46.3	21; 12.8	154; 93.9	32; 19.5	2; 1.3
Active surveillance group (n = 41)	33; 81.1	10; 24.4	31; 75.6	13; 31.7	5; 11.4
P value	0.001	NS	0.001	NS	0.012
Control group B† (n = 123)	43; 35.0	25; 20.2	104; 84.2	34; 27.6	7; 5.7
Active surveillance group (n = 41)	13; 31.7	10; 24.4	31; 75.6	13; 31.7	5; 11.4
P value	NS	NS	NS	NS	NS

In the AS study group, 33/41 (81.1 %) of patients had Gleason upgrading based on surgical pathology, compared with 76/164 (46.3 %) of control group A (p = 0 .001; Table 2). In the AS group, 31/41 (75.6 %) of patients had bilateral nerve sparing surgery compared to 154/164 (93.9 %) of men in control group A (p = 0 .001). Following RALP, 5/41 (11.4 %) of patients in the AS group had evidence of biochemical recurrence compared with 2/164 (1.3 %) of men in control group A (p = 0.025). Although there was a trend for higher rates of pT3 disease and positive margins in the active surveillance group compared to control group A, this was not statistically significant.

When the AS group was compared to control group B, there were no statistically significant differences between Gleason upgrading, pT3 disease, bilateral nerve sparing surgery, positive margins or biochemical recurrence, Table 2.

The time from diagnostic biopsy to surgery in the AS group was significantly greater compared to each control group. In contrast, there was no significant difference in the time period from when the biopsy was taken before immediate surgery to when surgery actually occurred between the AS group and the control groups, Table 3.

A point/serial correlation test (distributed as Pearson correlation coefficients) showed that the time interval between biopsy is not associated with the chance of positive margins on biopsy, Table 4.

Discussion

In a retrospective study of 645 Canadian men who underwent RP, a delay in surgery greater than 3 months was associated with an increase in biochemical recurrence and metastasis, although these results lost statistical significance after adjusting for grade, stage and serum PSA at diagnosis.[11] While a number of subsequent studies have suggested a survival benefit from initial treatment when compared to AS, some of these studies included men from before the era of PSA testing.[12-14]

TABLE 3. **Time intervals between biopsy and surgery in the two control groups, and the active surveillance group**

	Time from first diagnostic biopsy to surgery (months)					Time from last biopsy to surgery (months)				
	IQR	Median	Max	Min	P	IQR	Median	Max	Min	P
Active surveillance group	14.2-31.6	20.0	124	4.4	-	2.9-8.4	4.6	43	0.7	-
Before surgery control (B)	2.8-5.0	4.0	15	0	$p < 0.05$	2.8-5.0	4.0	17	0	NS
Diagnostic control (A)	3.3-5.8	4.5	17.6	0	$p < 0.05$	3.3-5.8	4.5	13	0	NS

IQR = interquartile range

TABLE 4. **The time interval between biopsy and surgery is not associated with the chance of positive margins on biopsy**

	Pearson correlation coefficients	
	Time from first diagnostic biopsy to surgery	**Time from last biopsy before surgery**
Before surgery control B	0.002	-0.065
Diagnostic biopsy control A	0.067	-0.028

Subsequent studies have provided conflicting information regarding the impact of surgical delay in men with clinically localized prostate cancer, and there is currently no consensus of opinion regarding the most appropriate strategy. The Randomized Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) showed that over a 15 year period initial surgery was associated with a reduction in the rate of death from prostate cancer.[15] However, The Swedish section of the European Randomized Study for Screening for Prostate Cancer (ERSPC) reported no statistically significant difference between postoperative Gleason score > 6, capsular penetration, positive margins, RP tumor volume, or biochemical progression among men undergoing immediate and delayed RP, although all data were in favor of immediate RP.[16] A retrospective study from UCSF examined 33 men who initially chose AS and went on to RP.[17] There was no association between surgical delay and adverse pathological features for men with low risk disease. In common with our study, pre-surgery Gleason grade was higher in the delayed RP group since most of the patients elected for surgical intervention as a result of higher-grade disease being detected on subsequent biopsy. Though the statistical significances vary between our two studies, both show increased upgrading, pT3 staging, and positive margins in the AS + RP groups compared to the immediate RP groups. A number of other studies have shown no significant association between surgical delays and the risk of biochemical progression.[18-23] However, the majority of patients in these studies had surgical delays of a few months rather than the longer time periods seen in men in this study initially choosing AS.

It is not uncommon to delay RP to avoid the inherent risks and complications associated with surgical treatment. Our data suggests that this delay may result in a diminished ability to perform nerve sparing surgery, which is known to be associated with the risk of decreased postoperative potency and timely recovery of full continence.[24,25] To our knowledge, there are no published studies that have systematically examined the impact of delayed RP on the ability to effectively perform bilateral nerve sparing surgery. In a previous study, Lavery et al compared 352 men (who met the criteria for AS but chose immediate surgery), with 1084 patients who were ineligible for AS and underwent RP.[26] Both groups had similar rates of preoperative incontinence. In common with our current study, bilateral nerve sparing was successfully performed on 96% and 86% of patients in the AS cohort and non-AS candidates, respectively. In a multivariable regression model, Lavery et al also determined that younger age and candidacy for AS were independently correlated with recovery of continence, but that candidacy for AS was not an independent predictor of recovery of categorical potency.

How may the urologist interpret these findings and put them into clinical practice? First, we would like to stress that we are not suggesting that urologists should use this data to support immediate surgery for low risk patients. Given the current level of evidence-based medicine available concerning survival advantage and morbidity for RP in low risk patients, we continue to advocate AS for our patients meeting the UCSF surveillance criteria. However, if patients with low grade prostate cancer remain on AS for a significant period of time, they may at some point transition outside the AS selection criteria, due to elevated PSA or upgrading/increasing tumor on surveillance biopsy. If a patient subsequently undergoes RP, he may be less likely to receive effective bilateral nerve sparing surgery or recover continence compared to if he had opted out of AS and elected for immediate surgery. Alternatively, some patients have more aggressive cancers diagnosed that are simply not picked up due to sampling bias. Our standard clinical practice is to obtain an immediate second set of biopsies for patients considering AS and, as such, we believe that the incidence of this occurring is low. Over time, these more aggressive cancers are finally diagnosed, and the patients are committed to receiving more aggressive surgery that may benefit them from the standpoint of cancer recurrence in the future. These patients may in fact do better than those who choose immediate surgery.

In common with previous studies, our study may be limited by the follow up time.[17] Prostate cancer tends to be indolent and BCR may not be captured within our follow up period of 12 months, possibly limiting the interpretation and long term applicability of our findings. As a tertiary care center, the majority of our patients receive follow up care with their local urologists, and we are exploring other avenues for data capture such as on-line surveys and automated follow up calls to expand our database. Future studies capturing data over longer follow up periods would undoubtedly allow the evaluation of more direct metrics such as disease-specific survival, metastasis-free survival and overall survival.

Conclusions

In men with low risk prostate cancer, disease management with AS and an inherent delay in performing RP, negatively impacted the incidence of performing effective bilateral nerve sparing surgery. There was an association between delayed RP and adverse pathologic features as well as biochemical recurrence when comparing our cohort to a group of men with similar parameters at the time of diagnosis that chose immediate treatment with RP. Since a high proportion of patients went on to receive surgery due to upgrading on surveillance biopsies, this phenomenon was not unexpected.

We initially hypothesized that close monitoring and multiple surveillance biopsies during regular follow up visits would translate into improved pathologic outcomes, compared to patients who underwent a single biopsy procedure, did not meet the criteria for AS, and immediately underwent surgery. However, our data show that this hypothesis is incorrect, with our patient cohort exhibiting similar outcomes when compared to men with similar parameters just prior to surgery who were not an on AS protocol. □

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