Does surgical delay for radical prostatectomy affect patient pathological outcome? A retrospective analysis from a Canadian cohort

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Abstract

Introduction: We sought to assess the impact of surgical wait time (SWT) to robot-assisted radical prostatectomy (RARP) on final pathological outcome.

Methods: A retrospective review of RARP patient records operated between 2006 and 2015 was conducted. SWT was defined as period from prostate biopsy to surgery. Primary outcome was the impact on postoperative Cancer of the Prostate Risk Assessment (CAPRA-S) score. Patients were stratified according to D'Amico risk categories. Univariate analysis (UVA) and multivariable (MVA) analysis with a generalized linear model was used to evaluate the effect of SWT and other predictive factors on pathological outcome in individual risk group and on the overall sample.

Results: A total of 835 patients were eligible for analysis. Mean SWT was significantly different between the three D'Amico groups, with mean SWT of 180.22 days (95% confidence interval [CI] 169.03; 191.41), 159.14 days (95% CI 152.38; 165.90), and 138.96 days (95% CI 124.60; 153.33) for low-, intermediate-, and high-risk groups, respectively ($p<0.001$). After stratification by D'Amico risk group, no significant association was observed between SWT and CAPRA-S score in the three risk categories on UVA and MVA. Predictors of higher CAPRA-S score in the multivariable model in the overall cohort were: older age ($p=0.014$), biopsy Gleason score ($p<0.001$), percentage of positive cores ($p<0.001$), and clinical stage ($p<0.001$).

Conclusions: In the present study evaluating SWT for RARP in a Canadian socialized system, increased delay for surgery does not appear to impact the pathological outcome. Further studies are required to evaluate the impact of wait time on biochemical recurrence-free survival, cancer-specific survival, and overall survival.

Introduction

Prolonged surgical wait time (SWT) have an impact on the overall quality of life and patient anxiety. Extending the wait time beyond a given threshold can also have a negative impact on the patient's clinical outcomes. Indeed, it has been established for non-urological cancer types that prolonged wait time has negative impact on oncological outcomes.[1-4]

With SWT on the rise in Canada,[5] it is important to question its impact on prostate cancer pathological outcomes, particularly for men awaiting robot-assisted radical prostatectomy (RARP) due to limited access to such technology.[6,7] In the era predating robotic surgery in Canada, a systematic review of the literature by Saad et al in 2006 reported that the median wait time for prostatectomy varied from 42 days (consultation to operation) to 83 days (consultation to hospital admission).[8] Furthermore, their review demonstrated that Canada, unlike other comparable industrialized countries, seemed to have a steadily increasing wait time.[8] Concerns that prolonged wait time may negatively influence patients' oncological outcomes arise. Furthermore, very few studies have reported a trend toward increased risk of biochemical recurrence (BCR)-associated with surgical delays for prostate cancer.[9-11] Therefore, the true impact of surgical delay remains controversial and the acceptable wait time is currently unknown. As such, we sought to address the impact of SWT to RARP on pathological outcomes for patients in two major academic centres in Canada.

Methods

Patient characteristics

After ethical review board approval, a prospectively collected robotic radical prostatectomy database from two major centres in Montreal (Hôpital du Sacré Cœur de Montréal and Hôpital Saint Luc) was queried to identify all patients who underwent RARP between 2006 and 2015. All cases were performed by one of two fellowship trained, experienced robotic surgeons (AEH, KCZ) using the previously reported technique.[12-14] A total of 835 patients had complete demographic, clinical, and pathologic data.

SWT evaluation

Time to surgery was calculated based on the difference between the date of diagnostic transrectal ultrasound (TRUS) biopsy and the date of surgery. Time from biopsy to robotic surgery consultation (date of RARP booking request) and from booking to actual surgery were also calculated for the overall cohort and in each D'Amico risk group.[15] Adverse pathological outcome was measured by the Cancer of the Prostate Risk Assessment (CAPRA-S) score, which has been well-documented to correlate with BCR, and cancer specific survival (CSS).[16-22] CAPRA-S score includes initial PSA, pathological Gleason, extracapsular extension (ECE), surgical margins (SM) status, seminal vesicle invasion (SVI), and lymph node (LN) status if lymph node dissection was done. Patients, who did not have LN dissection were considered LN-negative to calculate CAPRA-S score.

Statistical analysis

In order to test the association between predictive variables and CAPRA-S score, univariate analysis (UVA) and multivariable analysis (MVA) were done using a generalized linear model. SWT was considered a continuous variable. All statistical tests were two-sided with a level of significance set at $p<0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.3.3; http://www.r-project.org/).

Results

Baseline characteristics are displayed in Table 1.

SWT was significantly different among the three D'Amico risk groups, with mean SWT of 180.22 days (95% confidence interval [CI] 169.03; 191.41), 159.14 days (95% CI 152.38;165.90), and 138.96 days (95% CI 124.60; 153.33) for low-, intermediate-, and high-risk groups, respectively ($p<0.001$). To control for this bias, a subgroup analysis was carried out on three groups: low-, intermediate-, and high-risk. Wait time from biopsy to booking, as well as from booking to surgery in the overall cohort and for each D'Amico risk group are presented in Table 2.

Upon analyzing the entire study cohort with MVA, advanced age ($p=0.014$), higher biopsy Gleason score ($p<0.001$), advanced clinical stage (<0.001) and higher percentage of positive cores (<0.001), were predictors of pathological post-surgical CAPRA-S score; however, SWT did not affect CAPRA-S score ($p=0.196$) (Table 3).

Table 1. Baseline characteristics of the overall cohort

	Low-risk	Intermediate-risk	High-risk
Mean age, years (95% CI)	58.62 (57.78, 59.46)	61.18 (60.65, 61.72)	63.71 (62.49, 64.93)
Mean PSA, ng/ml (95% CI)	5.09 (4.85, 5.33)	6.47 (6.20, 6.74)	11.14 (9.14, 13.13)
Mean biopsy Gleason score	6	6.93	7.93
Gleason score, n (%)	240 (100)		
6		30 (6.07)	4 (4.04)
3 + 4		364 (73.68)	10 (10.10)
4 + 3		100 (20.24)	7 (7.07)
8–10			78 (78.78)
Clinical stage, n (%)			
cT1b			1 (1.01)
cT1c	205 (85.41)	356 (72.06)	45 (45.45)
cT2a	35 (14.58)	110 (22.26)	24 (24.24)
cT2b		28 (5.66)	14 (14.14)
cT2c			10 (10.10)
cT3			5 (5.05)
Mean TRUS prostate volume (95% CI)	31.58 (30.99, 32.18)	31.60 (31.11, 32.08)	31.74 (30.69, 32.78)
Mean BMI (95% CI)	38.93 (36.91, 40.96)	39.83 (38.32, 41.34)	41.45 (37.74, 45.16)

BMI: body mass index; CI: confidence interval; PSA: prostate-specific antigen; TRUS: transrectal ultrasound.

Table 2. SWT divided into time from biopsy to booking and booking to surgery among D'Amico risk groups

	Mean days between prostate biopsy to surgical booking	Mean days between surgical booking to surgery	p
Overall SWT (95% CI)	87.10 (81.39, 92.82)	76.59 (72.72, 80.47)	**0.002**
High-risk (95% CI)	81.44 (65.52, 97.35)	55.21 (44.12, 66.30)	**0.008**
Intermediate-risk (95% CI)	82.79 (76.57, 89.00)	76.76 (72.02, 81.49)	0.120
Low-risk (95% CI)	97.22 (84.17, 110.27)	86.38 (78.52, 94.24)	0.161
p	0.063	**<0.001**	

CI: confidence interval; SWT: surgical wait time.

Table 3. Multivariate analysis of the impact of different covariates on CAPRA-S score for overall cohort (SWT considered continuous variable)

	OR	CI lower	CI upper	p
SWT	1.001	0.999	1.003	0.196
Biopsy Gleason score	3.400	2.747	4.207	**<0.001**
Positive cores percentage	1.014	1.006	1.021	**<0.001**
Clinical stage	2.987	1.888	4.726	**<0.001**
Age	1.027	1.005	1.050	**0.014**
BMI	1.015	0.989	1.042	0.268
TRUS prostate volume	0.998	0.990	1.007	0.694

BMI: body mass index; CI: confidence interval; OR: odds ratio; SWT: surgical wait time; TRUS: transrectal ultrasound.

On subgroup analysis, there was no association between SWT and CAPRA-S on UVA and MVA for low-, intermediate-, and high-risk groups.

Discussion

This study provides unique insight on prolonged SWT caused by limited resources and operative time associated with public healthcare in Canada, as well as its impact on pathological outcomes. SWT for RARP is long and seems to be longer than previously reported for open radical prostatectomy (ORP) in 2006 by Saad et al;[8] however, further increase in SWT appear to have no impact on pathological outcomes, as represented by CAPRA-S score in the present study.

Similar to previously reported studies on surgical delay, our SWT was defined as the interval of time between biopsy date and surgical intervention.[10,23-26] Furthermore, the overall SWT was divided into time from biopsy to booking of surgery (overall mean of 87.1 days) and time from booking to surgery (overall mean of 76.6 days). To the best of our knowledge, this is the first unique reporting of SWT categorization. Both time intervals observed are long compared to most other U.S. and European centres, which reflects not only the delay in operating room scheduling and access to surgical time, but in the other steps of patient management as well. More specifically, in our universal Canadian system, particularly in the province of Quebec, the typical time from biopsy to pathology report finalization is 3–4 weeks. For high-risk patients, the turnaround time to schedule a nuclear medicine bone scan and computed tomography (CT) scan is approximately 30 days, and additional delay is added to do the interpretation of the imaging studies, followed by the interval of time during which the exam transcription will be sent to the urologist. This is based on our clinical experience. Also of note, the majority of men treated by RARP were initially worked up by a community urologist and then referred for RARP surgery. As such, the pre-booking wait time was consistent among all three groups, as this period is out of the operating surgeon's influence. With regards to the time from surgery booking to the procedure, we observed a significant difference between the subgroups (Table 2). Men with higher-risk disease had RARP done quicker, suggesting the influence of the surgeon/scheduling team who are consciously expediting surgery. As expected, SWT was longer for lower D'Amico risk groups.

It is important to highlight that many of the previously published studies on SWT were based on low-risk prostate cancer patients who were on active surveillance (AS).[11,26-29] Understandably, this is one of a few ways to ethically study SWT with prolonged delays. Otherwise, in most other global centres, men who are not eligible for AS are operated with minimal delay, considering greater access to surgical resources. Due to the prolonged SWT in Canada, particularly in a country with only 25 Da Vinci robot systems for a population of 36.2 million,[30] we had the unique opportunity to evaluate the effect of delay for patients with intermediate- and high-risk disease.

Several studies have previously observed negative associations between prolonged SWT and adverse outcomes[24,25,27,29,31,32] or have demonstrated positive association only on UVA that became negative on MVA after adjustment.[33,34] The majority of such reports were conducted on low-risk patients.[10,31,35-38] Despite relatively long SWT in our cohort, there was no observed effect on CAPRA-S scores in the low-risk group, suggesting that surgery can be performed safely within six months of biopsy. This seems intuitive to a low-risk group where AS may be a treatment option.

In the intermediate-risk subgroup of Holmstrom et al, upgrading of Gleason score was higher for patients who had deferred prostatectomy (median wait time was 3.5 months for primary and 19.2 months for deferred group). No difference in overall mortality was observed at eight years follow-up.[28] Furthermore, Abern et al demonstrated that delay over nine months (biopsy to surgery) was associated with greater positive surgical margin (PSM) (p=0.005) for the intermediate-risk group on multivariate analysis.[10] PSMs were, 47%, 50%, 50%, and 76%, for delays <3 months, 3–6 months, 6–9 months and >9 months, respectively. Similarly, Berg et al determined a cutoff of 60 days for adverse pathological outcomes for patients with Gleason 7 and prostate-specific antigen (PSA) >20 (p=0.032).[23] The above mentioned studies showed positive association between wait time and pathological features used separately. Our study showed negative association of SWT with overall adverse pathological features represented by CAPRA-S score. To the best of our knowledge, this represents the first study to use the CAPRA-S as an outcome measure.

For high-risk prostate cancer, only a couple have identified association between SWT and oncological outcomes[9,23] — albeit few studies were conducted. No association was found in our subgroup analysis for high-risk patients.

In contrast with other studies on adverse pathological outcomes, where several pathological features were consid-

ered endpoints,[23,27,28] we used a unique primary objective endpoint, namely the CAPRA-S score, which combines all relevant pathological features and has proved to be a strong postoperative predictor of prostate cancer oncological outcomes.[39-41] Also, the universal healthcare context with limited access to resources make this study unique, allowing the inclusion of a good number of intermediate- and high risk patients.

Limitations of our study include its retrospective nature, which is subject to biases inherent to retrospective studies. The main outcome was the pathological features represented by a validated composed score, CAPRA-S score (which is a well-recognized surrogate for BCR), cancer-specific survival, and overall survival. Additionally, we must take into account the effect of local policies in two respective hospitals and urologists applying individualized wait times for every case. We tried to compensate for this selection bias by stratifying our patients with the D'Amico risk groups and adjusting in MVA.

Conclusion

In the present study, we evaluated SWT for Canadian men in a publicly funded, universal healthcare system and evaluated variation between D'Amico risk categories and impact on CAPRA-S post-surgical scores. Based on our findings, it appears that SWT does not affect pathological outcome. While surgeon case selection appears to influence SWT, other factors also require closer evaluation to improve timing to definitive prostate cancer treatment. Further studies are warranted to assess the impact of SWT on BCR-free survival, cancer-specific survival, and overall survival.

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This paper has been peer-reviewed.

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