Oncologic outcomes following radical prostatectomy in the active surveillance era

Alyssa S. Louis, MD Cand.;[*] Robin Kalnin, MSc;[†] Manjula Maganti, MSc;[§] Melania Pintilie, MSc;[§] Andrew G. Matthew, PhD;[±] Antonio Finelli, MD, MSc, FRCSC;[¥] Alexandre R. Zlotta, MD, PhD, FRCSC;[¥] Neil Fleshner, MD, MPH, FRCSC;[¥] Girish Kulkarni, MD, Cand.; FRCSC;[¥] Robert Hamilton, MD, MPH, FRCSC;[¥] Michael Jewett, MD, FRCSC;[¥] Michael Robinette, MD, FRCSC;[¥] Shabbir M.H. Alibhai, MD ,MSc, FRCPC;[£] John Trachtenberg, MD, FACS, FRCSC[¥]

[*]Princess Margaret Cancer Centre, University Health Network, Toronto, ON; [†]Meridian Software, Toronto, ON; [§]Department of Biostatistics, University Health Network, Toronto, ON; [±]Department of Psychosocial Oncology and Palliative Care, University Health Network, Toronto, ON; [¥]Division of Urology, Department of Surgical Oncology, University Health Network, Toronto, ON; [£]Department of Medicine, University Health Network, Toronto, ON

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Abstract

Objective: In this study, we examine the oncologic outcomes of men with low, intermediate and high preoperative risk for prostate cancer treated with radical prostatectomy prior to and during the active surveillance era.

Methods: We analyzed records from patients who underwent radical prostatectomy at our Canadian tertiary care facility from 2000 to 2012. Patients were stratified by D'Amico preoperative risk category and by year of treatment. Biochemical recurrence-free survival was estimated using the Kaplan-Meier method.

Results: We included 2643 consecutive patients in our analysis. The proportion of men with low-risk disease undergoing radical prostatectomy decreased from 2007 onwards coincident with the implementation of an active surveillance strategy in our institution. Men with low-risk and high-risk disease showed significantly worse biochemical outcomes from 2007 to 2012 compared to 2000 to 2006 ($p < 0.05$), while men with intermediate-risk prostate cancer showed no significant differences ($p = 0.27$). Within the low-risk cohort, the later treatment group displayed significantly lower age, pre-treatment prostate specific antigen and tumour volume and significantly higher testosterone and body mass index.

Conclusions: The time period corresponding with the implementation of active surveillance at our institution corresponded with significant deterioration of biochemical outcomes in the low- and high-risk groups. This suggests that the men with most favourable disease deferred treatment, whereas men with worse preoperative disease characteristics were increasingly treated with radical prostatectomy in the past 6 years perhaps to their benefit.

Introduction

In the current paradigm of prostate cancer screening and early detection, prostate cancer is increasingly diagnosed when the tumour remains confined to the prostate gland.[1] Depending on the anticipated risk of systemic progression, men may be stratified into low-, intermediate- or high-risk categories based on prostate-specific antigen (PSA), Gleason score and clinical TNM stage as described by D'Amico and colleagues.[2,3] Historically, radical total-gland therapy (surgery or radiation) was the standard of care regardless of pre-treatment risk classification. However, the considerable morbidity and apparent insignificant survival benefit offered by radical therapy over observation led to the development and adoption of conservative management strategies, including active surveillance (AS) for men with low-risk disease.[4]

AS strategies suggest that men with very low-risk disease features defer treatment until clinical evidence of progression is found, thus prolonging, sometimes indefinitely, the period without side effects of therapy until treatment is necessary without jeopardizing oncologic outcome. Multiple AS strategies have been proposed with varying inclusion criteria. In general, candidates include men with clinical stage T1c/T2a, PSA <10 ng/mL and prostate biopsy Gleason ≤6 in three or fewer cores with ≤50% involvement of any core and a life expectancy <10 to 15 years.[5-7] These men were often treated with radical prostatectomy (RP) or radiotherapy prior to widespread AS adoption and, if treated immediately, men with these disease features typically displayed excellent response to RP with 5-year biochemical recurrence-free survival rates ranging from 81% to 92%.[8,9] If AS protocols are followed correctly and the trigger for active treatment is clinical progression out of the very-low-risk category and founded on an oncologic basis rather than patient anxiety, the disease characteristics of the cohort of men being treated

with RP would theoretically worsen. Indeed recent reports suggest a reverse stage migration of men presenting for RP in the era of AS, with a significant decrease in the percentage of low-risk patients.[10,11] Here we sought to determine whether there was a significant change in the biochemical recurrence outcomes following RP that may be associated with the beginning of the AS era, and how this specifically affected each risk group over time.

Methods

After obtaining Institutional Review Board approval, we abstracted records from our institutional Prostate Centre Database of patients who were treated with RP at The University Health Network (Princess Margaret Cancer Centre –Toronto General Hospital) from January 2000 to June 2012. Inclusion criteria were a known RP date and known biochemical status post-RP, with at least one postoperative PSA record. Records were excluded if neoadjuvant or adjuvant treatment was documented without PSA failure or recurrence. We abstracted additional information including age at surgery, ethnicity, total testosterone, PSA history, biopsy history, clinical stage, pathologic stage, grade and tumour volume, margin status, adjuvant treatments, as well as salvage treatments following failure or recurrence.

Our primary outcome measure was PSA elevation following RP, evidenced by a persistently detectable PSA or PSA that was undetectable <0.05 ng/mL immediately post-RP and subsequently rose. We stratified patients into pre-treatment low-, intermediate- and high-risk groups (Table 1) based on the D'Amico classification system and determined the percentages of men in each risk group in each year from 2000 to 2012.[3] To define the time periods for comparison, we looked specifically at trends within the low-risk group and identified when a trend towards decreased number and proportion of low-risk men began.

Association between clinical variables and the two time periods was determined using the Chi-square test for categorical variables and Student's t-test for continuous variables. Recurrence-free estimates were obtained using the Kaplan-Meier method at each time period and compared using the Log-rank test in each group. To adjust for a shorter length of follow-up in the later time period, follow-up time was truncated at 5 years for the early time period. All statistical analyses were conducted using SAS (version 9.2, SAS Institute, Cary, NC).

Table 1. Preoperative risk stratification criteria

Low risk	Intermediate risk	High risk
Preoperative PSA <10 ng/mL and biopsy Gleason ≤6	10-20 ng/mL or biopsy Gleason =7 (without PSA >20 ng/mL or biopsy Gleason >7)	Preoperative PSA >20 ng/mL or biopsy Gleason >7

PSA: prostate-specific antigen.

Table 2. Demographic variables of study population

Age at time of surgery	**n=2643**
Mean	60.8±6.9
Median	61 (38-77)
Ethnicity	**n=1544**
Asian	4.4%
Black	8.8%
European	77.5%
Indian	2.1%
Other	7.2%
BMI	**n=2079**
Mean	27.6±3.8
Median	27.3 (16.7-48.5)
Testosterone	**n=1774**
Mean	15.2±5.8
Median	14.3 (1.3-50.8)
Preoperative PSA	**n=2472**
Mean	7.6±7.9
Median	5.81 (0.12-165.43)
Clinical stage	**n=2180**
T1	70.2%
T2	29.3%
T3	0.5%
Preoperative biopsy Gleason score	**n=2405**
Gleason ≤6	38.7%
Gleason =7	52.8%
Gleason ≥8	8.5%
Prostatectomy method	**n=2601**
Open	81.8%
Laparoscopic	5.7%
Robotic	12.4%
Preoperative risk	**n=2347**
Low	34.6%
Intermediate	54.0%
High	11.4%

BMI: body mass index; PSA: prostate-specific antigen. Means ± standard deviation. Means (minimum-maximum).

Results

Our extraction algorithm yielded 2851 individual records, 153 of which were excluded due to adjuvant therapy, 51 were excluded due to unknown recurrence status, and 4 were excluded due to absence of prostate carcinoma in the pathology specimen, resulting in a total of 2643 records included for analysis. We tallied our demographic and clinical variables (Table 2). The mean preoperative PSA was 7.6 ± 7.9 ng/mL (median: 5.81, range: 0.12-165.43, n = 2472). Most men presented for RP with Gleason 7 disease with clinical stage T1c and intermediate preoperative risk (Table 2). In addition, most men underwent an open

approach with bilateral nerve-sparing RP, negative pathologic margins, negative seminal vesicles, no extra-prostatic extension, Gleason 7 disease and pathologic stage pT2. The 5-year recurrence-free estimates for the low-, intermediate- and high-risk groups overall were 79.0%, 59.2% and 34.3%, respectively.

When stratified by preoperative risk and analyzed by year of surgery, a break point was noted in 2007; the proportion of low-risk men receiving RP began to decrease (Fig. 1). This period coincided with the introduction, marked increase in publications, and general academic enthusiasm and adoption of active surveillance, as well as the emerging understanding of the true quality of life detriments of radical prostatectomy.[4] We therefore grouped the data based on year of surgery from 2000 to 2006 (n = 1190) and 2007 to 2012 (n = 1453). In the low-risk group, the later treatment cohort demonstrated significantly lower age at RP, pre-RP PSA and tumour volume, and significantly higher body mass index (BMI) and testosterone. In the intermediate group, the later cohort demonstrated significantly lower tumour volume and significantly higher BMI. Within the high-risk group, there were no significant differences by period (Table 3). We found similar distributions for specimen Gleason score, pathologic stage and surgical margin status between the two periods in all risk groups, except for the Gleason score of the intermediate-risk men which reached significance (Table 4).

When follow-up time was truncated to 5 years, mean follow-up was 1.6 ± 1.5 years in the earlier cohort, compared to 1.7 ± 1.4 years in the later cohort. Overall, the 5-year biochemical recurrence-free estimate for the entire cohort was 64.6 ± 1.3%, with a mean time to recurrence of 7.6 years (standard error 0.5 years) and 11.2% of men received salvage treatment. When analyzed by risk group and stratified by time period of treatment (Fig. 2), the 3-year recurrence-free estimate was significantly lower in the low-risk group after 2007 (89.6% and 80.3%, $p < 0.05$), and worse outcomes after 2007 at the threshold for significance was observed in the high-risk group (43.8% and 33.5%, $p = 0.049$), while the intermediate-risk group displayed no significant differences (74.1% and 70.6% $p = 0.27$).

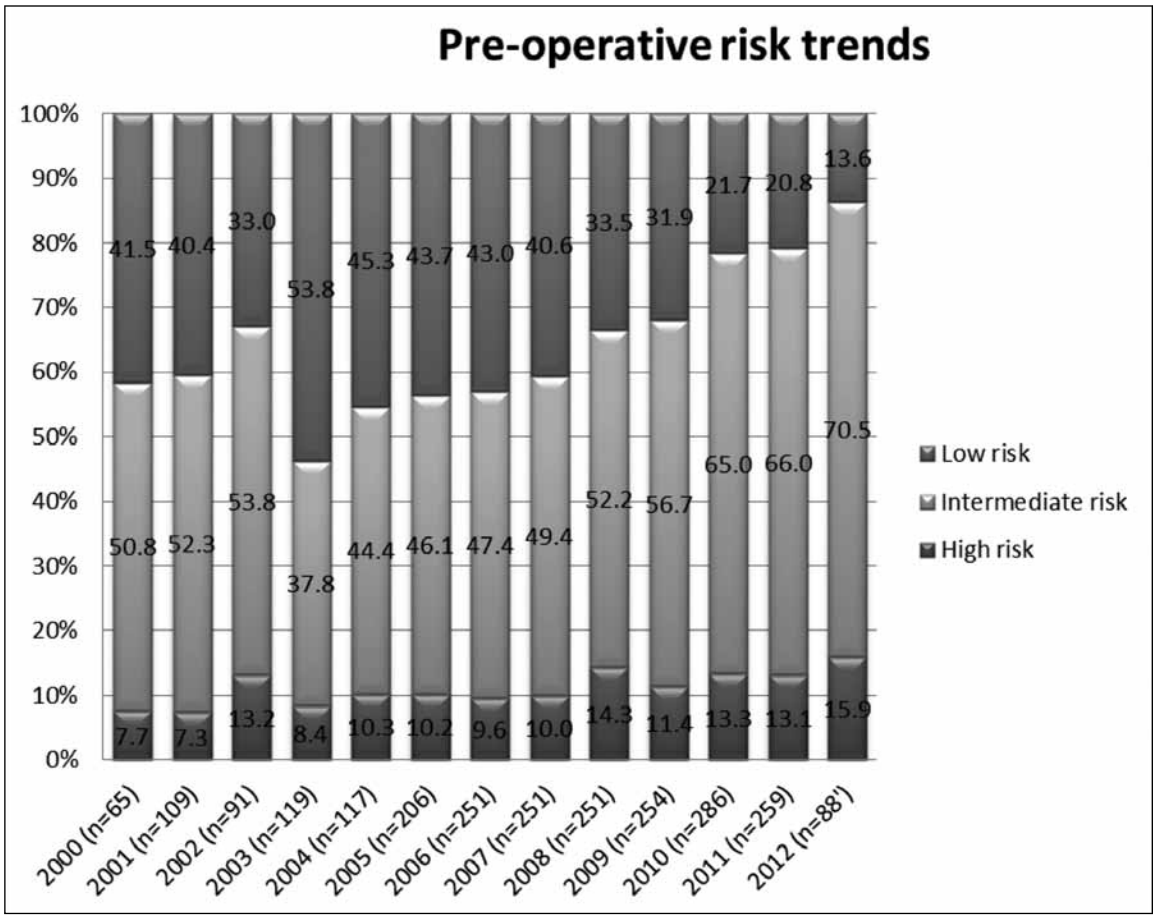

Fig. 1. Normalized risk for each year. ':indicates that the radical prostatectomy record for the year is incomplete.

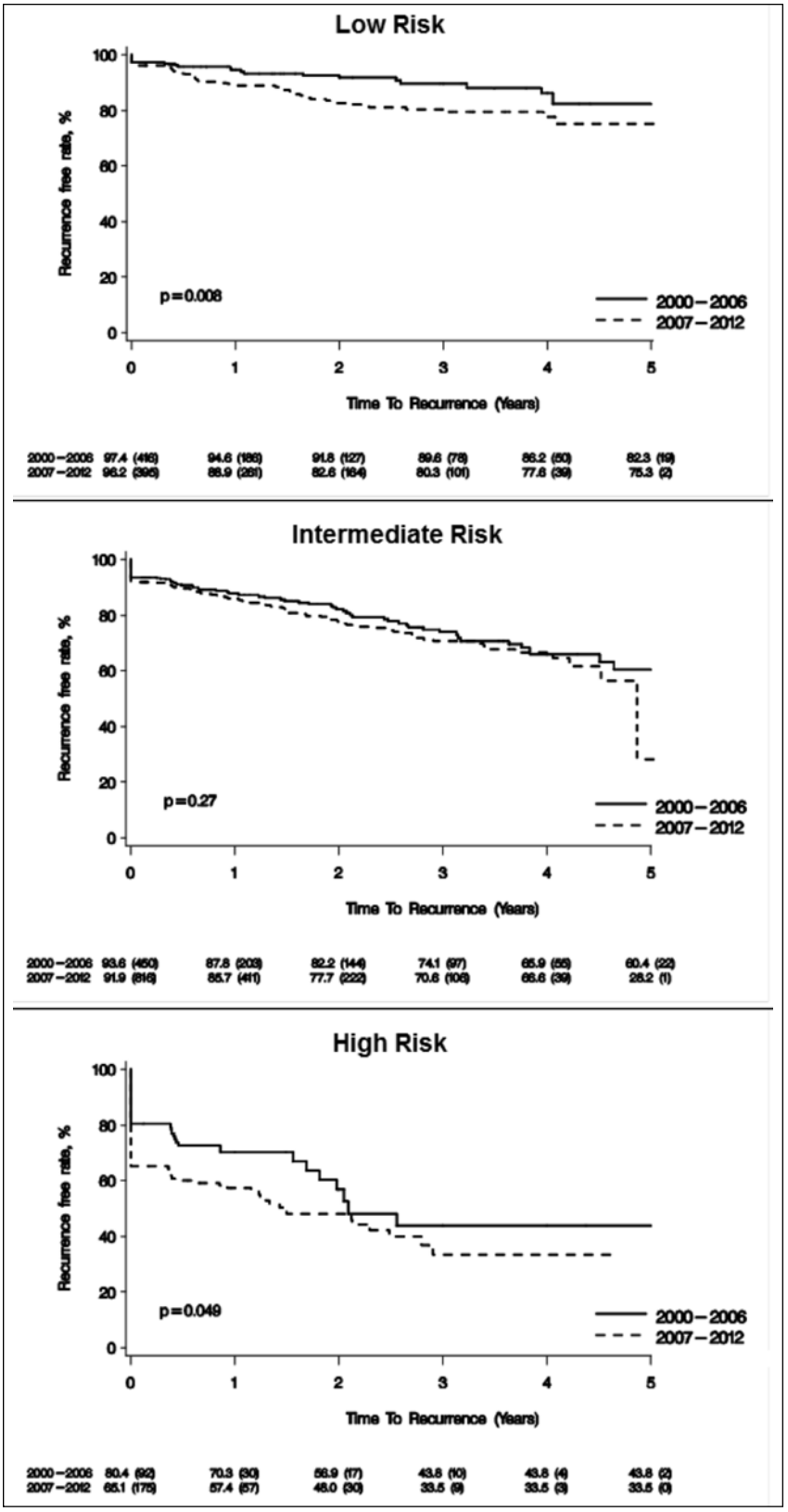

Fig. 2. Kaplan Meier survival curves for low-, intermediate- and high-risk patients. Below axes is percentage biochemical recurrence-free survival, number of men followed is in brackets. Significance threshold $p < 0.05$.

Discussion

Our results revealed a decrease in the proportion and frequency of men with low-risk disease presenting for RP after 2007. We interpret this result to be an outcome of the adoption of AS at our institution at that time. With AS a subset of men with favourable risk disease deferred treatment until a trigger, such as detection of a more extensive tumour on biopsy or clinical progression, occurred. This may have caused a decrease in the percentage of the low-risk cohort and an increase in the percentage of intermediate-risk patients. A similar trend was reported from a single European tertiary care centre by Budaus and colleagues.[10] However, the extent of increase in the intermediate-risk cohort would depend on whether the trigger for treatment is oncologic progression, which is frequently not the case.[12]

We observed a concurrent increase in the frequency and percentage of men with intermediate- and high-risk disease. To our knowledge, there have been no large cohort systematic reports of time trends in treatment choice over the time period we studied. Our database is limited to RP and thus referral patterns for other treatments were not available for analysis. However, we may speculate that the increase in high-risk referrals stemmed from the general increase in interest in surgery for prostate cancer especially in the robotic era, which began at our institution September 2008. Another possibility is increased interest in surgery as nerve-sparing techniques, general morbidity and side effects reduced over time. Additionally, high-risk patients may have been increasingly referred for surgery due to the improvement of salvage treatments and novel multimodal management strategies. Several recent reports of favourable RP outcomes for high-risk patients for high-risk cases exist in the literature, supporting surgery.[13-15] Another possibility is that with the loss of the low-risk candidates to AS, surgeons maintained steady operating room time by adding higher risk cases, similar to the supply sensitivity of surgery use described by Birkmeyer and colleagues.[16] We excluded the possibility of a detection bias, as postoperative PSA follow-up practices were consistent over the time period we studied. The overall number of RPs per-

Table 3. T-tests for values in each time group

	Low (n=811)			Intermediate (n=1268)			High (n=268)		
	2000-2006 (n=416)	2007-2012 (n=395)	*p* value	2000-2006 (n=450)	2007-2012 (n=818)	*p* value	2000-2006 (n=92)	2007-2012 (n=176)	*p* value
Age at RP	60.0±6.7	58.8±6.7	0.007*	61.6±6.7	61.3±7.0	0.50	62.4±6.8	62.8±5.9	0.63
Pre-RP PSA (ng/mL)	5.2±2.2	4.9±2.3	0.0162*	7.5±4.2	7.1±3.8	0.10	18.2±17.0	16.7±18.8	0.53
Tumour volume†	8.1±10.2	6.4±6.7	0.0109*	11.7±11.0	9.2±10.1	0.0001*	19.2±19.7	19.0±21.8	0.95
BMI (kg/m^2)	26.7±3.3	27.7±3.6	0.0004*	27.2±4.4	28.0±3.7	0.006*	27.4±3.7	28.4±3.9	0.08
Testosterone	14.9±5.3	16.0±5.5	0.0333*	15.4±6.8	14.8±5.7	0.35	14.1±4.3	15.1±6.1	0.22

*$p < 0.05$. †Percentage of specimen involved by tumour. Means ± standard deviation.
RP: radical prostatectomy; BMI: body mass index.

formed at our institution increased over time, driven mostly by an increase in intermediate-risk men. The growth of the intermediate-risk cohort may also have occurred as a result of patient preference for surgery over radiotherapy, which was previously preferred.[17] In addition, the later treatment group was significantly younger, which may influence treatment preference.[18,19]

We considered alternate explanations for the shift in the risk profile of men presenting for RP independent of treatment decision and referral pattern, and while they cannot be precluded we consider them less likely. Within the time period we examined, the Gleason scoring system changed resulting in tumours with primary pattern of Gleason 3 and less than 5% Gleason 4 to be classified as Gleason 7, whereas it was formerly classified as Gleason 6.[20] Theoretically, this alone would cause the risk profile to shift towards intermediate risk, as men would be upgraded from Gleason 6 disease without any change in tumour biology. However, the consensus for this change occurred in 2005, whereas the shift we reported was after 2007. Another possibility is that the preoperative risk classifications changed, independent of tumour biology over time as described by Albertsen and colleagues who demonstrated that the slides classified prior to 2002 were upgraded when re-reviewed from 2002 to 2004.[21] However, this would result in artefactual improved outcomes, rather than the worse outcomes we reported.

The upward migration in the risk profile over time was matched by a deterioration of biochemical outcomes for the low- and high-risk groups. Surprisingly, the mean preoperative PSA of the low-risk group was significantly lower in the 2007-2012 time period, despite the smaller number of men and the absence of the very low-risk cancers that would be expected to have a lowering effect on the mean PSA. A possible explanation is the tendency for younger men to have smaller prostates, and the later treatment group had significantly younger men, although we were not able to compare prostate mass between the two groups. Another possibility is that the concept of a normal PSA has changed over time, and men with lower PSAs are now being sent for biopsy, however we cannot confirm this with our database.

Among the limitations to our results is that all patients were treated at a single Canadian academic centre, and may not be applicable to other settings. Our approach of examining the effect of AS on RP outcomes would have been bolstered if accurate recording methods of AS had been in place from the outset of this strategy. However, documentation of surveillance as AS occurred after the gradual adoption of this strategy, and thus any attempt to associate these figures with RP outcomes would have produced an artefactual result. Furthermore, even with the concept of

Table 4. Results of Chi Square analysis for disease characteristics of time cohorts

	Low % (n)			Intermediate % (n)			High %(n)		
	2000-2006	2007-2012	*p* value	2000-2006	2007-2012	*p* value	2000-2006	2007-2012	*p* value
Pathologic specimen Gleason score			0.43			0.0158*			0.10
Gleason ≤6	57.5 (237)	58.3 (228)		9.7 (43)	14.4 (117)		5.6 (5)	1.1 (2)	
Gleason 7	41.5 (171)	41.4 (162)		84.9 (376)	82.3 (668)		54.4 (49)	59.2 (103)	
Gleason ≥8	1.0 (4)	0.3 (1)		5.4 (24)	3.3 (27)		40.0 (36)	39.7 (69)	
Pathologic stage			0.96			0.54			0.43
pT2	85.1 (338)	85.2 (333)		62.6 (263)	62.6 (503)		36.5 (31)	28.9 (50)	
pT3	13.4 (53)	13.5 (53)		35.2 (148)	34.2 (275)		55.3 (47)	60.1 (104)	
pT4	1.5 (6)	1.3 (5)		2.2 (9)	3.2 (26)		8.2 (7)	11.0 (19)	
Margins			0.85			0.92			0.82
Negative	85.2 (350)	84.7 (332)		80.9 (363)	81.0 (655)		67.8 (61)	69.1 (121)	
Positive	14.8 (61)	15.3 (60)		19.1 (86)	19.0 (153)		32.2 (29)	30.9 (54)	

*$p < 0.05$.

surveillance adopted, the exact practice remains, even to date, to be standardized. Also, we exclusively examined outcomes following RP, which are not necessarily applicable to other therapies. Finally, our risk stratification was limited to Gleason score and preoperative PSA and did not include clinical stage, PSA density, PSA velocity, number of positive biopsy cores or percentage of cores occupied with carcinoma due to incomplete data capture and desire to include a large, representative cohort. However, those factors have been used by investigators to estimate risk.[22]

We anticipate that the outcomes of men in the low-risk cohort will continue to deteriorate as men with favourable disease continue to be referred for AS. We also predict that enthusiasm for prostate cancer screening will wane, reflecting scepticism of the benefits of therapy, especially in low-risk younger men thus delaying diagnosis. Moreover, patients are exploring organ-sparing techniques, such as focal therapy, and this leaves only the worst of the low-risk disease category for AS. Conversely, a recent large well-conducted trial suggested that in spite of the expected decreased disease-specific survival of men with high- and intermediate-risk disease compared with the low-risk cohort, only these men derived a survival benefit from RP perhaps inadvertently justifying these groups' appropriateness for surgery.[23]

Conclusion

In the AS era, the number of men presenting for RP with low-risk disease has decreased. There was a concurrent deterioration of biochemical outcomes that may reflect a change in the disease characteristics of low-risk men. This era also saw a concurrent increase in the number of men undergoing RP in the intermediate- and high-risk groups, with a trend for a decrease in outcome of the high-risk group, but associated with related evidence that this may be the group that derives the survival benefit from prostatectomy. Further investigation with additional risk indicators is warranted.

Competing interests: None declared.

This paper has been peer-reviewed.

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Correspondence: Dr. John Trachtenberg, University Health Network, Princess Margaret Hospital, Suite 3 208, 620 University Ave., Toronto, ON M5G 2M9; fax: 416-598-9997; john.trachtenberg@uhn.ca