RESEARCH ARTICLE

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Long-term adverse effects after retropubic and robot-assisted radical prostatectomy. Nationwide, population-based study

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Background and Objectives: Surgery for prostate cancer is associated with adverse effects. We studied long-term risk of adverse effects after retropubic (RRP) and robot-assisted radical prostatectomy (RARP).

Methods: In the National Prostate Cancer Register of Sweden, men who had undergone radical prostatectomy (RP) between 2004 and 2014 were identified. Diagnoses and procedures indicating adverse postoperative effects were retrieved from the National Patient Register. Relative risk (RR) of adverse effects after RARP versus RRP was calculated in multivariable analyses adjusting for year of surgery, hospital surgical volume, T stage, Gleason grade, PSA level at diagnosis, patient age, comorbidity, and educational level.

Results: A total of 11 212 men underwent RRP and 8500 RARP. Risk of anastomotic stricture was lower after RARP than RRP, RR for diagnoses 0.51 (95%CI = 0.42-0.63) and RR for procedures 0.46 (95%CI = 0.38-0.55). Risk of inguinal hernia was similar after RARP and RRP but risk of incisional hernia was higher after RARP, RR for diagnoses 1.48 (95%CI = 1.01-2.16), and RR for procedures 1.52 (95%CI = 1.02-2.26).

Conclusions: The postoperative risk profile for RARP and RRP was quite similar. However, risk of anastomotic stricture was lower and risk of incisional hernia higher after RARP.

KEYWORDS
adverse effects, cancer of prostate, long-term, prostatectomy

1 | INTRODUCTION

Retropubic (RRP) and robot-assisted radical prostatectomy (RARP) have had similar oncological outcome in systematic reviews and meta-analyses[1,2] and no statistically significant difference in 90-day postoperative death was found in a recent study, RRP (0.20%) and RARP (0.13%).[3] To date, most studies have shown similar risk for urinary incontinence and erectile dysfunction after RRP and RARP[4,5] but recent systematic reviews on observational studies have suggested that urinary incontinence and erectile dysfunction are less frequent after RARP than RRP.[6-8] Compared to RRP, RARP is associated with shorter postoperative hospital stay,[9] less perioperative bleeding,[10] fewer postoperative infections,[11-13] and fewer thromboembolic events,[14] whereas the operating time is shorter and direct costs are lower for RRP.[15,16] Radical prostatectomy increases the risk of inguinal hernia but it is unclear if there is any difference in risk after RRP and RARP.[17,18] Furthermore, one

study from the Surveillance, Epidemiology, and End Results Program (SEER) database reported that minimally invasive radical prostatectomy was associated with more than threefold increased risk of incisional hernia repair compared to open radical prostatectomy.[19] A recent single center randomized clinical trial from Australia showed similar short-term results after RRP and RARP.[20] However, only outcomes at up to 12 weeks were reported in that study and there are currently little data on long-term adverse effects after RRP and RARP other than for urinary incontinence and erectile dysfunction.

The aim of this study was to analyze the risk of severe urinary incontinence, anastomotic stricture, inguinal hernia and, incisional hernia after RARP and RRP up to 10 years after surgery.

2 | MATERIALS AND METHODS

2.1 | Study population and data collection

The National Prostate Cancer Register (NPCR) of Sweden captures 98% of all prostate cancer cases reported to the Swedish Cancer Register to which registration is mandated by law.[21] NPCR registers comprehensive data on cancer characteristics, diagnostic work-up, and primary treatment.[22,23] We included men diagnosed with prostate cancer between 2004 and 2013 who underwent RRP or

RARP within 1 year. Men with stage N1 or M1 disease or serum levels of prostate specific antigen (PSA) above 50 ng/mL at diagnosis were excluded. In a modification of the National Comprehensive Cancer Network (NCCN) categorization, four risk categories were defined; low-risk: PSA < 10 ng/mL, T1-2 and Gleason grade group (GGG) 1; intermediate-risk: PSA < 20 ng/mL, T1-2, GGG 1-3 and at

TABLE 1 Domains of diagnoses and procedures and their respective codes

Diagnoses	Most common diagnoses	Diagnostic codes (ICD)
Urinary incontinence	Stress incontinence, other incontinence	N393, N394, R329
Anastomotic stricture	Bladder neck obstruction, urethral stricture	N320, N358, N359, N991, R339
Inguinal hernia	Inguinal hernia	K40
Incisional hernia	Incisional hernia	K430, K431, K432, K436, K439
Procedures	Most common procedures	Intervention codes (NOMESCO)
Urinary incontinence	Artificial urinary sphincter, paraurethral injection	KDK00, KDV21, KDV22
Inguinal hernia	Inguinal hernia repair	JAB
Incisional hernia	Incisional hernia repair	JAD
Anastomotic stricture	Bladder neck incision, urethrotomy	KCH42, KDH62, KDH70, KDV12, TKD00, TKC10, TKC20
Urethrocystoscopy	Cystoscopy, urethroscopy	UKC02, UKC05, UKD02, UKD05

TABLE 2 Baseline characteristics of prostate cancer cases in prostate cancer data base (PCBaSe) 3.0 treated with primary retropubic radical prostatectomy (RRP) or RARP in 2004-2014

	RRP (%)	RARP (%)
Men	11 212 (100)	8500 (100)
Follow-up (years)		
0-3	1875 (17)	3383 (40)
3-6	3575 (32)	3506 (41)
6-9	3620 (32)	1454 (17)
9-11	2142 (19)	157 (2)
Age at prostatectomy		
Median (IQR)	63 (59-67)	63 (58-67)
<65 years	7443 (66)	5724 (67)
65-69 years	3154 (28)	2181 (26)
70+ years	615 (5)	595 (7)
Marital status		
Married	8150 (73)	6035 (71)
Not married	3061 (27)	2462 (29)
Missing data	1 (0)	3 (0)
Educational level[a]		
Low	3359 (30)	1737 (20)
Middle	4768 (43)	3450 (41)
High	3042 (27)	3278 (39)
Missing data	43 (0)	35 (0)
Charlson comorbidity index		
CCI 0	9878 (88)	7642 (90)
CCI 1	787 (7)	469 (6)
CCI 2+	547 (5)	389 (5)
Risk category[b]		
Low risk	4622 (41)	3181 (37)
Intermediate risk	5185 (46)	4371 (51)
Localized high risk	1197 (11)	789 (9)
Locally advanced high risk	208 (2)	159 (2)

IQR, interquartile range; CCI, Charlson comorbidity index.
Primary treatment refers to procedures performed within 1 year after date of diagnosis.
Men with M1 and N1 tumors or serum PSA >50 ng/mL were excluded.
[a]Educational levels: low = compulsory school (<10 years), middle = upper secondary school (10-12 years), high = college or university (>12 years).
[b]Low-risk category: PSA < 10 ng/mL, T1-2 and Gleason grade group (GGG) 1; intermediate-risk: PSA <20 ng/mL, T1-2, GGG 1-3 and at least one of PSA ≥ 10 ng/mL or GGG 2-3; localized high-risk: PSA 20-50 ng/mL or GGG 4-5 and T1-2; locally advanced high-risk: PSA < 50 ng/mL and clinical T.

least one of PSA ≥ 10 ng/mL or GGG 2-3; localized high-risk: PSA 20-50 ng/mL or GGG 4-5 and T1-2; locally advanced high-risk: PSA < 50 ng/mL and T3.

2.2 | Adverse effects, comorbidity, socioeconomic factors, and hospital surgical volume

The Prostate Cancer data Base Sweden (PCBaSe) 3.0 has previously been described in detail.[24] In brief, by record linkage using the unique Swedish personal identity number, information on men in NPCR was obtained from other national healthcare registers and demographic databases. Data from both in-patient and out-patient care in the National Patient Register were used to determine date of surgery, diagnoses after surgery according to international classification of diseases (ICD) 9 or 10 and interventions according to NOMESCO classification of surgical procedures as measures of adverse effects after surgery. Charlson Comorbidity Index (CCI) was calculated based on discharge diagnoses in the National Patient Register and diagnoses in the Swedish Cancer Register up to 10 years before diagnosis, as described previously.[25,26] Data on socioeconomic factors including marital status and educational level were retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA by its Swedish acronym).[20] The educational levels were low = compulsory school (<9 years), intermediate = upper secondary school (10-12 years), and high = college or university (>12 years).

Hospital surgical volume was calculated as the number of radical prostatectomies (RPs) performed at each hospital the calendar year before date of surgery and defined as low, <50 RPs/year, intermediate, 50-100 RPs/year and high >100 RPs/year.

2.3 | Classification of diagnostic and intervention codes

Discharge diagnoses that indicated complications after surgery were classified into following domains; urinary incontinence, anastomotic stricture, inguinal, and incisional hernia. Surgical procedures indicating adverse effects were; procedures for urinary incontinence, repair of inguinal hernia, repair of incisional hernia, procedures for anastomotic stricture, and urethrocystoscopy. The capture of erectile dysfunction in the National Patient Register is low and therefore no analyses were conducted for erectile dysfunction.

A complete list of analyzed diagnostic and intervention codes is presented in Table 1.

2.4 | Statistical methods

Risk of adverse effects after RARP compared with RRP was calculated in multivariable analysis with Poisson regression adjusting for year of prostatectomy, hospital surgical volume, clinical T-stage, PSA at diagnosis, Gleason grade group, patient age at prostatectomy, comorbidity, and educational level.[27] The number of events was analyzed since multiple events likely indicate a more severe adverse effect. However, to avoid including the same occurrence of an adverse event multiple times in a short time period, a 2 month interval after an adverse event was defined, within which a second identical event was ignored. This time period was also excluded from the time at risk in all analyses.

All statistical tests were two-sided and all analyses were performed using R 3.1.1 (R foundation for foundation for statistical computing, Vienna, Austria) software.

The Research Ethics Review Board at Umeå University Hospital approved the study.

3 | RESULTS

In total, 19 712 men underwent radical prostatectomy (RP) as primary treatment for prostate cancer out of whom 11 212 underwent RRP and 8500 RARP. Age, marital status, and CCI were quite similar for men who underwent RRP and RARP but men who underwent RARP had a higher educational level (Table 2). Approximately 95% (10 597/ 11 212) and 93% (7905/8500) of men who underwent RRP and RARP respectively, were younger than 70 years at date of surgery. More men who underwent RRP had a low-risk cancer compared to RARP, likely due to the fact that RRP was the most common procedure in the early study period when low-risk prostate cancer was an indication for RP. Accordingly, longer follow-up was available for RRP (Table 3). All above mentioned differences between the RRP and RARP cohorts were statistically significant (P ≤ 0.01).

Table 4 shows the number of events and relative risk (RR) of adverse effects after RARP versus RRP. Risk of urinary incontinence was similar between the surgical techniques both in assessment of

TABLE 3 Number of men who received primary retropubic radical prostatectomy (RRP) or RARP in 2004-2014 and maximum follow-up time

Year of RP	Full study period	2004-2005	2006-2008	2009-2011	2012-2014
Primary treatment	n (%)	n (%)	n (%)	n (%)	n (%)
RRP	11 212 (57)	2355 (93)	3694 (71)	3497 (50)	1666 (34)
RARP	8500 (43)	165 (7)	1518 (29)	3518 (50)	3299 (66)
Maximum follow-up	11 years	11 years	9 years	6 years	3 years
Men	19 712 (100)	2520 (100)	5212 (100)	7015 (100)	4965 (100)

Primary treatment refers to procedures performed within 1 year after date of diagnosis.
A total of 898/19 712 (5%) men died or emigrated before December 31, 2014.

TABLE 4 Number of events and relative risk (RR) with 95% confidence intervals (CI) of adverse effects of RARP compared to retropubic radical prostatectomy (RRP) in 2004-2014

Follow-up	Full period			0-3 years			3-6 years		
	RRP (n = 11169)	RARP (n = 8465)	RR (95%CI)	RRP (n = 11169)	RARP (n = 8465)	RR (95%CI)	RRP (n = 9299)	RARP (n = 5095)	RR (95%CI)
Diagnoses									
Urinary incontinence	1794	1112	1.16 (0.94-1.43)	946	788	1.19 (0.93-1.53)	677	294	1.10 (0.80-1.51)
Anastomotic stricture	2157	555	0.51 (0.42-0.63)	1622	416	0.43 (0.35-0.53)	441	125	0.98 (0.60-1.60)
Inguinal hernia	2313	1162	0.96 (0.84-1.09)	1407	851	0.87 (0.74-1.02)	762	282	1.10 (0.88-1.38)
Incisional hernia	191	232	1.48 (1.01-2.16)	118	205	1.65 (1.08-2.53)	61	27	1.06 (0.54-2.07)
Procedures									
Urinary incontinence	385	171	0.95 (0.74-1.23)	196	125	1.09 (0.79-1.49)	175	46	0.77 (0.49-1.23)
Anastomotic stricture	1951	469	0.46 (0.38-0.55)	1502	357	0.37 (0.31-0.45)	388	103	1.05 (0.63-1.74)
Repair of inguinal hernia	1335	643	0.93 (0.82-1.06)	835	485	0.86 (0.74-1.01)	475	155	1.07 (0.85-1.35)
Repair of incisional hernia	107	123	1.52 (1.02-2.26)	73	110	1.65 (1.07-2.55)	33	13	1.01 (0.46-2.23)
Urethrocystoscopy	4131	1781	0.85 (0.75-0.96)	2439	1286	0.79 (0.70-0.91)	1348	440	0.90 (0.72-1.13)

LUTS, Lower urinary tract symptoms.

Poisson regression models adjusting for year of prostatectomy, age at prostatectomy, hospital prostatectomy volume*, education, comorbidity, clinical T-stage, PSA at diagnosis and Gleason grade group (GGG).

RR >1 indicates a higher risk after RARP compared to RRP, while RR <1 indicates a lower risk.

*Radical prostatectomy (RP) volume was calculated as the number of RPs performed during the previous year

diagnostic and intervention codes. Relative risk of anastomotic stricture was lower after RARP compared to RRP, RR for diagnoses 0.51 (95%CI = 0.42-0.63) and RR for procedures 0.46 (95%CI = 0.38-0.55). However, at 3 years after surgery no statistically significant difference was observed between the surgical approaches. Similarly, risk of urethrocystoscopy was lower after RARP up to 3 years postoperatively but no difference in the risk was observed between the surgical approaches at 3 years and thereafter. The relative risk of anastomotic stricture decreased over time. Between 2004 and 2008 was the RR of procedures after RARP versus RRP 0.68 (95%CI = 0.50-0.93) but between 2009 and 2014 the RR was 0.38 (95%CI = 0.30-0.47).

Risk of inguinal hernia was similar after RRP and RARP but risk of incisional hernia was higher after RARP, RR for diagnosis of incisional hernia 1.48 (95%CI = 1.01-2.16) and RR for procedures 1.52 (1.02-2.26). As for anastomotic stricture, there was a trend toward decreased relative risk of incisional hernia over time. Between 2004 and 2008 risk of incisional hernia was higher after RARP 0-3 years after surgery but no difference between the surgical techniques was observed after longer follow-up or at any time between 2009 and 2014.

In order to analyze the impact of hospital surgical volume on outcome, analyses were performed not adjusting for hospital surgical volume. In these analyses, risk of urinary incontinence was higher after RARP, RR 1.28 (95%CI = 1.07-1.53) but the risk of procedures for urinary incontinence were similar, RR 0.96 (95%CI = 0.77-1.19). Furthermore, the risk of procedure for inguinal hernia was lower after RARP, RR 0.86 (95%CI = 0.77-0.96) but risk of other adverse effects and procedures were quite similar.

Approximately, 58% (4952/8500) of the RARPs were performed at high-volume hospitals but only 10% (1101/11 212) of RRPs, whereas 18% (1546/8500) of RARPs and 63% (7095/11 212) of RRPs were performed at low-volume hospitals.

A subgroup analysis was performed comparing the results stratified into high-, intermediate-, and low-volume hospitals (data not shown). No statistically significant difference in risk of adverse effects was observed and the confidence intervals were wide, likely due to the uneven distribution of patients between high- and low-volume hospitals in the RRP and RARP cohorts.

4 | DISCUSSION

In this population-based study, risk of long-term adverse effects was quite similar after RRP and RARP. There was a somewhat lower risk of anastomotic stricture but a higher risk of incisional hernia after RARP.

The nationwide, population-based cohort design and the extensive, and almost complete follow-up are the main strengths of the current study. Virtually, all radical prostatectomies performed in Sweden between 2004 and 2014 were included and the diagnoses in the in-patient Register are 85-95% accurate.[22,28] Thus, most serious adverse effects after surgery that require in-patient care were captured. By use of data from other nationwide registers, we were able to adjust for the most important confounders including hospital

surgical volume, comorbidity, educational level, and marital status. The main limitation of this study is the use of administrative data as end-point. Although the National Patient Register captures almost all in-patient episodes the capture of out-patient care is lower, approximately 80% between 1997 and 2007.[28] Furthermore, some common and anticipated adverse effects were poorly captured. For example, urinary incontinence not leading to a surgical procedure or other medical intervention was poorly captured. In our study, 1113/19 712 (6%) of the cases had some urinary incontinence. Questionnaire data from NPCR show that after RP approximately 33% of men have mild, 13% moderate, and 10% severe urinary incontinence.[29] Accordingly, in a recent report from a similar cohort in Sweden, 21% of men reported that they had some urinary incontinence.[5] However, the most severe adverse effects were captured and the results mirror clinically relevant end-points for adverse effects other than erectile dysfunction and mild urinary incontinence.

Little is known about long-term risk of anastomotic stricture after radical prostatectomy. Earlier studies have reported that risk of urethral stricture and urinary retention is higher after RRP as compared with RARP and that most urethral strictures occurred within 1 year after surgery.[30,31] Similarly, in the current study risk of anastomotic stricture was lower after RARP up to 3 years after surgery but similar between the surgical approaches thereafter. Speculatively, this could be due to the fact that anastomotic strictures usually occur quite soon after surgery and can be treated effectively.

In a questionnaire study of 1787 men who had undergone RRP or RARP, there was a lower risk of inguinal hernia after RARP compared to RRP.[18] However, no statistically significant difference in the risk of inguinal hernia was found between the surgical approaches in the current study although there was a tendency toward lower risk after RARP, particularly during the first 3 years after surgery. Furthermore, our results agree with the results from a study based on the SEER Medical dataset where Carlsson et al reported that minimally invasive radical prostatectomy was associated with a more than threefold higher risk of incisional hernia than RRP.[19]

The risk of anastomotic stricture was lower after RARP than RRP and that became more prominent over time. In contrast, RRP had a lower risk of incisional hernia but only when assessing RRPs performed between 2004 and 2009. In fact, the difference in risk of incisional hernia was only statistically significant between 2004 and 2009 up to 3 years after surgery. This might suggest that the outcome has become more favorable after RARP in recent years.

The results in this study are based on data from all hospitals in Sweden where prostate cancer was treated in a contemporary period and are likely to be more generalizable than results from tertiary referral centers.[32,33]

5 | CONCLUSION

Risk of adverse effects after RARP and RRP was quite similar up to 10 years after surgery. After RARP, the risk of anastomotic stricture was lower and risk of incisional hernia was higher.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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