Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study

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Summary

Background Studies of complications resulting from surgery or radiotherapy for prostate cancer have mainly focused on incontinence and erectile dysfunction. We aimed to assess other important complications associated with these treatments for prostate cancer.

Methods We did a population-based retrospective cohort study, in which we used administrative hospital data, physician billing codes, and cancer registry data for men who underwent either surgery or radiotherapy alone for prostate cancer between 2002 and 2009 in Ontario, Canada. We measured the 5-year cumulative incidence of five treatment-related complication endpoints: hospital admissions; urological, rectal, or anal procedures; open surgical procedures; and secondary malignancies.

Findings In the 32 465 patients included in the study, the 5-year cumulative incidence of admission to hospital for a treatment-related complication was 22·2% (95% CI 21·7–22·7), but was 2·4% (2·2–2·6) for patients whose length of stay was longer than 1 day. The 5-year cumulative incidence of needing a urological procedure was 32·0% (95% CI 31·4–32·5), that of a rectal or anal procedure was 13·7% (13·3–14·1), and that of an open surgical procedure was 0·9% (0·8–1·1). The 5-year cumulative incidence of a second primary malignancy was 3·0% (2·6–3·5). These risks were significantly higher than were those of 32 465 matched controls with no history of prostate cancer. Older age and comorbidity at the time of index treatment were important predictors for a complication in all outcome categories, but the type of treatment received was the strongest predictor for complications. Patients who were given radiotherapy had higher incidence of complications for hospital admissions, rectal or anal procedures, open surgical procedures, and secondary malignancies at 5 years than did those who underwent surgery (adjusted hazard ratios 2·08–10·8, p<0·0001). However, the number of urological procedures was lower in the radiotherapy than in the surgery group (adjusted hazard ratio 0·66, 95% CI 0·63–0·69; p<0·0001)

Interpretation Complications after prostate cancer treatment are frequent and dependent on age, comorbidity, and the type of treatment. Patients and physicians should be aware of these risks when choosing treatment for prostate cancer, and should balance them with the clinical effectiveness of each therapy.

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Introduction

Treatment options for men with clinically localised prostate cancer include radical prostatectomy (surgery) or radiotherapy. Which treatment offers the better chance of survival is not yet clear,[1] and the choice of treatment is affected by patient preference. Patients want to know the frequencies and severities of various complications associated with different treatments.

Two common and well-described side-effects of surgery or radiotherapy are urinary incontinence and erectile dysfunction,[2] and studies have traditionally focused on these adverse effects. However, other complications can ensue and compromise quality of life, some of which need admission to hospital or a surgical intervention, including post-treatment urinary or rectal bleeding, infection in the urinary or lower gastrointestinal tract, and recto-urethral fistulae. An increased prevalence of secondary malignancies in men who received radiotherapy has also been reported.[3] Other complications are treated on an outpatient basis and might necessitate minimally invasive urological procedures (eg, cystoscopy) or other endoscopic procedures (eg, colonoscopy). Accurate knowledge of the incidence of such complications would enhance patient-centred decision making.

We analysed a large cohort of 32 465 patients in Ontario, Canada, who underwent treatment for prostate cancer between 2002 and 2009. We assessed the incidence of treatment-related complications that are not related to urinary incontinence or erectile dysfunction, including secondary procedures, hospital admissions, and

secondary malignancies in patients who had undergone either surgery or radiotherapy.

Methods

Participants

We did a population-based, retrospective cohort study of all men aged 18 and older who underwent a radical prostatectomy or had radiotherapy for localised prostate cancer between Jan 1, 2002, and Dec 31, 2009, in Ontario. We excluded patients who underwent laparoscopic or robotic prostatectomy (since this procedure was not widely adopted in Ontario during the study period) and those who underwent both radiation treatment and radical prostatectomy.

All medical procedures in Ontario are reimbursed by a government-operated health insurance system (Ontario Health Insurance Plan [OHIP]). OHIP fee codes are listed for specific procedures with specific indications. We used OHIP fee code S651 (radical prostatectomy) to identify patients who underwent surgery; and fee codes X310, X311, X312, and X313 (planning codes for radiotherapy), and A343, A340, A341, and K013 (follow-up codes for radiotherapy) to identify patients who underwent radiation treatment. Codes X310 and X311 are for planning for conventional radiation simulators, X312 is for complex treatment planning involving CT scans, and X313 is for full 3D treatment planning, including the development of a dose volume histogram. We linked these OHIP codes to patients who were diagnosed with prostate cancer from the Ontario Cancer Registry to identify those who had surgery or radiotherapy for prostate cancer within 1 year of diagnosis. Radiation can be given as treatment with curative intent or as palliative therapy. To exclude people who received palliative radiotherapy, we excluded those who had developed metastatic disease or who died within 5 years of the date of initial treatment (n=839).

See Online for appendix

We also identified a control group with no history of prostate cancer from the general population of Ontario to compare the outcome measures of the patients who had surgery or radiotherapy with the incidence in the general population. We randomly identified men from the Registered Persons Database—a personal information bank for health insurance coverage in Ontario—and matched them with patients by age and year of treatment or inception on a 1:1 basis. These controls were accrued for the same study period. We excluded any patients with a diagnosis of prostate cancer at the time of inception and followed these people for the same outcome measures.

We linked records from the OHIP physician claims database, the Canadian Institute for Health Information (CIHI) hospital Discharge Abstract Database, the Ontario Cancer Registry, and the Registered Persons Database. The CIHI compiles data from 22 databases and registries, including all hospital admission data.[4] The study protocol was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre (ON, Canada).

Outcomes

We used five different outcome measures for treatment-related complications: those necessitating hospital admission to manage a treatment-related problem; those that needed a minimally invasive urological procedure (eg, cystoscopy); those requiring a rectal or anal procedure (eg, endoscopy); those that needed an open surgical procedure related to the urinary tract, rectum, and anus; and the development of a secondary malignancy, for which we included cancers at all sites in our analysis.

For each patient, we identified the development of the first outcome for each of the five outcome measures using the CIHI Discharge Database (using the most responsible diagnosis code based on *International Classification of Diseases Tenth Revision* diagnostic codes for hospital admissions), OHIP fee codes for surgical and endoscopic procedures, the CIHI same day surgery database for percutaneous procedures, and the Ontario Cancer Registry for secondary cancer diagnoses. We did not measure repeat procedures or complications and analysed only time to first complication. The appendix lists the various complications that comprise these categories. All diagnostic and procedural codes that occurred after the date of treatment were reviewed by the first author (RKN), who was masked to the index treatment, and then narrowed to those that could be a treatment-associated complication. We removed only obvious codes that could not be related to treatment for further consideration, such as CNS, cardiac, respiratory, musculoskeletal, skin, and haematological system-related

	Radical prostatectomy (N=15 870)	Radiotherapy (N=16 595)	p value
Age distribution at time of treatment			
Mean age, years (SD; IQR)	61·5 (6·58; 57–66)	69·4 (7·42; 65–75)	<0·0001
Distribution by age group (years)			<0·0001
<60	6726 (42%)	2191 (13%)	..
60–70	7968 (50%)	6148 (37%)	..
>70	1176 (7%)	8256 (49%)	..
Comorbidity score (ADG)			<0·0001
Mean (SD)	4·95 (2·1)	5·30 (2·3)	
Median (IQR)	5 (3–6)	5 (4–7)	
Year of treatment			<0·0001
2002	1546 (10%)	1938 (12%)	..
2003	1524 (10%)	1980 (12%)	..
2004	1850 (12%)	2166 (13%)	..
2005	2160 (14%)	2128 (13%)	..
2006	2330 (15%)	2220 (13%)	..
2007	2479 (16%)	2474 (15%)	..
2008	2327 (15%)	2241 (14%)	..
2009	1654 (10%)	1448 (9%)	..

Data are n (%) unless otherwise indicated. ADG=aggregated disease group.

Table 1: **Baseline variables in the two treatment groups**

codes. Diagnostic codes and procedures related to urinary incontinence or erectile dysfunction were not considered. The selected codes were then reviewed by a panel of urologists, radiation oncologists, and a general medical internist, who were also masked to the index treatment, to derive a final list of codes by consensus. Each diagnostic, procedural, or secondary cancer code was applied to both the surgery and radiotherapy groups.

Statistical analysis

For all categories of complications, we used Kaplan-Meier survival analysis to estimate cumulative incidence. We considered patients to be at risk of complications from the date of their radical prostatectomy or radiotherapy until the development of the outcome, death, or the last date of follow-up. For secondary malignancies, we assumed a minimum lag time of 5 years from the date of radiation exposure to the development of a second primary cancer,[5] and we judged patients to be at risk of developing such a cancer from 5 years until 9 years (the maximum follow-up time of the study) after treatment. Dates of death and last follow-up were obtained from the Registered Persons Database. To further quantify the risk of second cancers due to treatment, we compared occurrence of second cancers from the treatment groups to cancer occurrences from the general population of Ontario[6] by calculating the standardised incidence ratio (SIR). We calculated the expected number of cancers in each treatment group and age group, based on the cancer incidence in the general population during the study period. We calculated the SIR as the number of observed cancers in each treatment group and age group divided by the number of expected cases in each group. The observed incidence of second cancers were calculated based on the person-years at risk after 5 years from the date of index treatment.[5]

To estimate the hazard ratios (HRs) for development of a complication in each category, we did Cox proportional hazard modelling, adjusted for age and comorbidity at the time of treatment, year of treatment, and the index treatment (radiotherapy *vs* surgery). For each outcome measure, we tested the proportional hazards assumption with the Schoenfeld residuals method. We calculated the Pearson correlation coefficients of Schoenfeld residuals of the treatment covariate and time, logarithm of time, and square root of time. The proportional hazards assumption was not met if we recorded significant associations ($p<0·05$) for all three correlation coefficients.

To measure comorbidity, we used the Johns Hopkins University ACG Case-Mix System.[7] We used the sum of aggregated disease groups (ADG), which form a high-level classification scheme for groups of diseases and disorders.[7] We used SAS version 9.2 for all statistical analyses.

Role of the funding source

The study sponsor had no role in any part of the study, including study design, data collection, data analysis, data interpretation, or writing of the report. RS and JS had access to the raw data. RKN had full access to all the data and the final responsibility to submit for publication.

Results

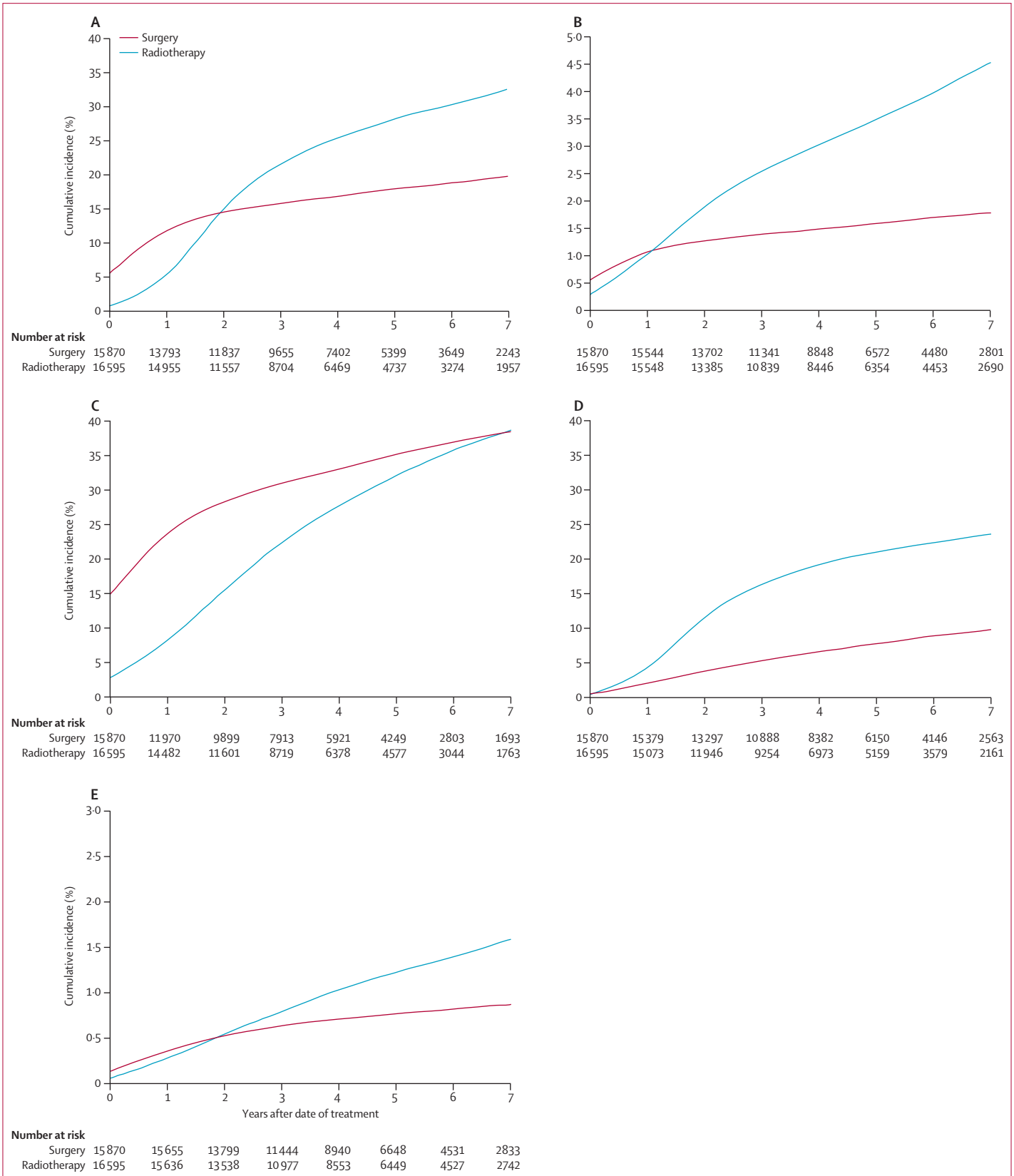
32 465 patients were treated for prostate cancer in Ontario between Jan 1, 2002, and Dec 31, 2009, and were eligible for inclusion in the study. Of these patients, 15 870 underwent radical prostatectomy and 16 595 had radiotherapy. Patients who had surgery were younger (median age 62 years) than those who received radiotherapy (median age 70 years). The surgical group also had a lower level of comorbidity (measured with the ADG comorbidity score) than the radiation group (table 1).

The 5-year cumulative incidence of hospital admission for a treatment-related complication was 22·2% (95% CI 21·7–22·7). The most common diagnosis was for urinary

	Minimally invasive urological procedure	Admission to hospital	Rectal or anal procedure	Secondary malignancy	Open surgical procedure
Age (years)	1·01 (1·009–1·014; p<0·0001)	1·007 (1·003–1·010; p<0·0001)	1·02 (1·01–1·02; p=0·011)	1·04 (1·03–1·05; p<0·0001)	1·00 (0·98–1·02; p=0·97)
Comorbidity ADG score	1·08 (1·07–1·09; p<0·0001)	1·08 (1·07–1·09; p<0·0001)	1·10 (1·08–1·11; p<0·0001)	1·04 (1·03–1·05; p<0·0001)	1·04 (0·98–1·09; p=0·19)
Treatment					
Surgery	1·00	1·00*	1·00	1·00	1·00*
Radiotherapy	0·66 (0·63–0·69; p<0·0001)	1 year: 0·86 (0·82–0·92; p<0·0001) 2 year: 1·62 (1·51–1·73; p<0·0001) 3 year: 3·05 (2·78–3·36, p<0·0001) 4 year: 5·74 (5·01–6·57; p<0·0001) 5 year: 10·8 (9·04–12·9; p<0·0001)	2·72 (2·40–3·08; p<0·0001)	2·08 (1·48–2·91; p<0·0001)	1 year: 1·15 (0·85–1·55; p=0·38) 2 year: 1·53 (1·16–2·02; p=0·002) 3 year: 2·05 (1·49–2·82; p<0·0001) 4 year: 2·75 (1·81–4·16; p<0·0001) 5 year: 3·68 (2·16–6·26; p<0·0001)

Data are HR (95% CI; p value). Multivariate Cox model also included year of index treatment, in addition to age, comorbidity, and type of treatment, but we recorded no significant associations with each of the five outcome measures for year of index treatment within the multivariate model. ADG=aggregated disease group. *Data did not meet proportional hazard assumption (ie, significant associations [p <0·05] recorded for all three correlation coefficients). Hazard ratios for 1-, 2-, 3-, 4-, and 5-year follow-up periods were calculated with a time-interaction factor from the Cox model.

Table 2: **Multivariate analysis with Cox proportional hazard modelling of factors that predict the development of complications**


A
Surgery
Radiotherapy
Cumulative incidence (%)
40
35
30
25
20
15
10
5
0
0 1 2 3 4 5 6 7
Number at risk
Surgery 15870 13793 11837 9655 7402 5399 3649 2243
Radiotherapy 16595 14955 11557 8704 6469 4737 3274 1957
B
5·0
4·5
4·0
3·5
3·0
2·5
2·0
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0·5
0
0 1 2 3 4 5 6 7
15870 15544 13702 11341 8848 6572 4480 2801
16595 15548 13385 10839 8446 6354 4453 2690
C
Cumulative incidence (%)
40
35
30
25
20
15
10
5
0
0 1 2 3 4 5 6 7
Number at risk
Surgery 15870 11970 9899 7913 5921 4249 2803 1693
Radiotherapy 16595 14482 11601 8719 6378 4577 3044 1763
D
40
35
30
25
20
15
10
5
0
0 1 2 3 4 5 6 7
15870 15379 13297 10888 8382 6150 4146 2563
16595 15073 11946 9254 6973 5159 3579 2161
E
Cumulative incidence (%)
3·0
2·5
2·0
1·5
1·0
0·5
0
0 1 2 3 4 5 6 7
Years after date of treatment
Number at risk
Surgery 15870 15655 13799 11444 8940 6648 4531 2833
Radiotherapy 16595 15636 13538 10977 8553 6449 4527 2742

obstruction, which accounted for 2487/6771 (36·7%) of all hospital admissions. The 5-year cumulative incidence for a minimally invasive urological procedure was 32·0% (95% CI 31·4–32·5), and the most common procedure was a diagnostic cystoscopy (5951/9974 [59·7%] of all urological procedures). The other three outcomes were less frequent—the 5-year cumulative incidence of a rectal or anal procedure was 13·7% (95% CI 13·3–14·1), for an open surgical procedure was 0·9% (0·8–1·1), and the cumulative risk (years 5–9) for secondary malignancy was 3·0% (2·6–3·5).

To assess the baseline incidence of these outcomes in the general population, we randomly identified 32 465 age-matched controls with no history of prostate cancer within the same inception period. The 5-year cumulative incidences were: hospital admission 5·0% (95% CI 4·8–5·3), urological procedure 13·0% (12·6–13·5), rectal or anal procedure 5·3% (5·0–5·5), and open surgical procedure 0·5% (0·4–0·7). After adjustment for age, comorbidity, and year of inception, in a comparison of all patients who had surgery or radiotherapy for prostate cancer versus the general population controls, the adjusted HRs were 17·9 (95% CI 14·8–21·7; p<0·0001) for hospital admission, 6·8 (6·2–7·4; p<0·0001) for a urological procedure, 2·2 (1·8–2·7, p<0·0001) for a rectal or anal procedure, and 6·0 (3·2–11·1, p<0·0001) for an open surgical procedure.

Table 2 shows the results of the multivariate analysis for patients who had surgery or radiotherapy. Age and comorbidity at the time of treatment were both positively associated with complications requiring hospital admissions, urological procedures, and rectal or anal procedures, and with secondary malignancies, but not with open surgical procedures (table 2). After adjustment for age, comorbidity, and year of treatment, patients who were treated with radiotherapy had fewer minimally invasive urological procedures than did those who had surgery, but had higher incidence of complications in the other four categories (table 2). The figure shows 5-year cumulative incidence for the first four outcomes by treatment.

Most of the hospital admission stays were for one night (5995/6771; 88·5%). A higher proportion of inpatients in the radiotherapy group than in the surgery group stayed for longer than one night (531/4022 [13·2%] for radiotherapy *vs* 245/2749 [8·9%] for surgery, p<0·0001). Most of the hospital admissions in the surgical group were for urinary obstruction, whereas in the radiotherapy group the highest number of hospital admissions was for radiation proctitis (table 3). When we restricted hospital admissions to stays that lasted for longer than one night, the 5-year cumulative incidence was 2·4% (95% CI 2·2–2·6) for all patients; the incidence for patients who had radiotherapy (3·3%, 95% CI 3·0–3·6) was again higher than in those who had surgery (1·5%, 1·3–1·7; p<0·0001) (figure B). The adjusted HR for hospital admission for longer than 1 day for patients who had radiotherapy compared with those who had surgery was 5·55 (95% CI 3·55–8·67, p<0·0001).

Open surgical procedures were the least frequent of all adverse outcomes. The most extensive procedure, which required a cystectomy and urinary diversion, occurred only in the radiotherapy group (0·2 per 1000 person-years). No associated bladder cancer diagnosis occurred with these cystectomy procedures.

The risk of developing a second malignancy between 5 and 9 years post-treatment was 113 per 100 000 person-years in the surgery group and 309 per 100 000 person-years in the radiotherapy group. The cumulative incidence in years 5–9 was 4·5% (95% CI 3·8–5·5) in the radiotherapy group and 1·8% (1·3–2·4) in the surgery group. The most common site of secondary malignancy was the gastrointestinal tract (87 per 100 000 person-years in the radiotherapy group and 28 per 100 000 person-years in the surgery group; p<0·0001) (table 3). Increased cancer risks for the radiotherapy group compared with the surgery group were also reported for lung, haematological, and genitourinary sites (p<0·0001 for each comparison). To establish whether treatment was associated with the development of secondary cancers, we compared the occurrence of secondary cancer with cancer incidence in the general population based on age-adjusted Ontario cancer statistics[6] within our same study period to calculate the SIRs. In the radiotherapy group, between the ages of 40 and 65 years, there were 8·9 cancers expected versus 31 cancers observed (SIR 3·5, 95% CI 2·3–4·7), whereas for those aged 65–90 years, there were 135·1 cancers expected versus 110 cancers observed (0·8, 0·7–1·0). The SIR for all patients in the radiotherapy group compared with the general population was 2·0 (95% CI 1·7–2·3). In the surgery group, between the ages of 40 and 65 years, there were 27 cancers expected versus 36 observed (SIR 1·3, 95% CI 0·9–1·8), whereas for those aged 65–90 years, there were 71·7 cancers expected versus 29 cancers observed (0·4, 0·3–0·6). The SIR for all patients in the surgery group compared with the general population was 0·8 (95% CI 0·6–1·0).

Of the 16 595 patients who had radiotherapy, 12 539 (75·6%) had a contemporary form of the treatment (full 3D treatment planning, including the development of a dose volume histogram). Restriction of our comparison to patients who had contemporary

Figure: **Kaplan-Meier cumulative incidence of four outcome measures**
(A) Hospital admissions: 5-year cumulative incidence for surgery group 17·5% (95% CI 16·9–18·1) and for radiotherapy group 27·1% (26·4%–27·9). (B) Hospital admissions for patients with a length of stay >1 day: 5-year cumulative incidence for surgery group 1·5% (95% CI 1·3–1·7) and for radiotherapy group 3·3% (3·0–3·6). (C) Minimally invasive urological procedures: 5-year cumulative incidence for surgery group 34·2% (95% CI 33·4–35·0) and for radiotherapy group 30·0% (29·2–30·8). (D) Rectal or anal procedures: 5-year cumulative incidence for surgery group 7·0% (95% CI 6·4–7·6) and for radiotherapy group 18·4% (17·3–19·4). (E) Open surgical procedures: 5-year cumulative incidence for surgery group 0·8% (95% CI 0·6–0·9) and for radiotherapy group 1·1% (1·0–1·4). Surgery=radical prostatectomy. Radiotherapy=radical radiation.

	Radiotherapy group (N=16 595)		Radical prostatectomy (surgery) group (N=15 870)	
	Frequency distribution	Risk in person-years*	Frequency distribution	Risk in person-years*
Minimally invasive urological procedures				
Cystoscopy	2848 (61·8%)	48·0/1000	3103 (57·8%)	66·3/1000
Catheterisation	723 (15·7%)	12·2/1000	1184 (22·1%)	25·3/1000
Urethral dilation or incision	300 (6·5%)	5·1/1000	1014 (18·9%)	21·7/1000
Calculi or clot removal	61 (1·3%)	1·0/1000	67 (1·2%)	1·4/1000
Transurethral resection of prostate†	20 (0·4%)	0·3/1000	..	..
Prostate biopsy†	654 (14·2%)	11·0/1000	..	..
Admission to hospital				
Genitourinary or gastrointestinal fistula	12 (0·3%)	0·2/1000	30 (1·1%)	0·5/1000
Genitourinary bleeding	575 (14·3%)	11·1/1000	165 (6·0%)	2·8/1000
Gastrointestinal bleeding	553 (13·7%)	10·0/1000	0	0
Renal insufficiency	139 (3·5%)	2·7/1000	45 (1·6%)	0·8/1000
Infection	433 (10·8%)	8·3/1000	370 (13·5%)	6·2/1000
Urinary obstruction	487 (12·1%)	9·4/1000	2000 (72·8%)	33·5/1000
Radiation proctitis	1663 (41·3%)	31·7/1000	0	0
Radiation cystitis	160 (4·0%)	3·1/1000	0	0
Bladder stone	0	0	139 (5·1%)	2·3/1000
Rectal or anal procedure				
Excision of haemorrhoids	214 (7·3%)	3·7/1000	130 (11·5%)	1·9/1000
Cauterisation of fissures	761 (26·0%)	13·3/1000	72 (6·4%)	1·1/1000
Lower gastrointestinal endoscopy	1954 (66·7%)	34·1/1000	927 (82·1%)	15·5/1000
Secondary malignancy				
Breast	2 (1·3%)	4/100 000	1 (1·7%)	2/100 000
CNS	6 (3·8%)	12/100 000	0	0
Otolaryngology	11 (6·9%)	21/100 000	3 (5·0%)	6/100 000
Eye	1 (0·6%)	2/100 000	0	0
Gastrointestinal	45 (28·3%)	87/100 000	15 (25·0%)	28/100 000
Genitourinary	17 (10·7%)	33/100 000	12 (20·0%)	23/100 000
Haematological	24 (15·1%)	46/100 000	12 (20·0%)	23/100 000
Lung	40 (25·2%)	78/100 000	6 (10·0%)	12/100 000
Skin	12 (7·5%)	23/100 000	10 (16·7%)	17/100 000
Soft tissue	1 (0·6%)	2/100 000	1 (1·7%)	2/100 000
Open surgical procedure				
Ureteric re-implant	10 (7·8%)	0·1/1000	0	0
Cystotomy	23 (18·0%)	0·3/1000	124 (76·0%)	1·7/1000
Open bladder neck repair	35 (27·3%)	0·5/1000	0	0
Genitourinary or gastrointestinal fistula repair	46 (35·9%)	0·6/1000	39 (24·0%)	0·5/1000
Cystectomy and conduit	13 (10·2%)	0·2/1000	0	0
Open lymphocele drainage	1 (0·8%)	0·01/1000	0	0

*Person-year based on Kaplan-Meier survival analysis of participants at risk during the study period. †Prostate biopsy and transurethral resection of prostate recorded only for patients who had radiotherapy.

Table 3: **Specific breakdown of procedures and diagnoses used to define complication categories**

radiotherapy versus surgery did not change our results in the adjusted HRs (data not shown).

Discussion

The findings from our study of a cohort of 32 465 men who had surgery or radiotherapy for prostate cancer show high incidence of treatment-related complications requiring admission to hospital, urological procedures, rectal or anal procedures, open surgical procedures, and development of secondary malignancies, ranging from 1% to 30%. Increasing age and comorbidity were associated with higher incidence of complications, but the type of treatment was the most important determinant. Patients who had primary radiotherapy had higher incidence of hospital admission, rectal or anal procedures, open surgical procedures, and secondary malignancies, whereas those treated with surgery were more likely to have urological procedures.

To our knowledge, this study is the first to comprehensively assess incidence of specific treatment-related complications after radical prostatectomy or radiotherapy, beyond the well-studied effects of urinary incontinence and erectile dysfunction (panel). Previous studies assessed a narrower range of complications, were not population based, and included far fewer participants. Potosky and colleagues[2] measured quality of life in 1187 patients who had surgery or radiotherapy and reported higher incidence of urinary problems in the surgery group and higher incidence of bowel problems in the radiotherapy group. In a prospective study of 3533 patients given surgery or radiotherapy, Resnick and colleagues[8] showed similar patterns in urinary, sexual, and bowel function, but they did not report on specific complications or their associated treatments.

The main strength of our study is the population basis for the analysis for which there is a publicly funded health-care system with one payer system (OHIP). All cancer treatments and ensuing complications could be identified comprehensively within the study period based on the OHIP registry. Patients who move within the province and who are treated for a complication at a different centre from their original place of treatment are still identifiable. Within Ontario, only nine of 157 hospitals provided radiation treatments, but patients were treated for complications in all provincial hospitals; only 23% of patients were treated for the complication at the hospital at which the radiotherapy was delivered.

In general, the occurrence of complications in both the surgery and radiation groups was unexpectedly high. Our comparison of the outcome measures with age-matched controls from the general population with no history of prostate cancer further strengthens our findings given their low incidence and the associated high HRs associated with treatment (up to 17·9), which suggest that these complications are mainly attributable to prostate cancer treatment. A high number of complications needed a urological procedure, the most common of which in both treatment groups was diagnostic cystoscopy. Although the process of undergoing diagnostic cystoscopy might not be a complication itself, the fact that a patient needed to have this invasive test is an indication of troublesome and abnormal urinary symptoms that prompted this procedure. Nevertheless, these incidences have not previously been described. We included prostate biopsy within the urological procedure outcome for patients who had radiotherapy because prostate biopsy is not an expected or a routine procedure after radiotherapy. Moreover, bladder neck stricture after surgery was common. Patients who undergo surgery can develop such strictures that cause urinary obstruction, most of which can be treated with minimally invasive treatments, including catheterisation, bladder neck dilatation, or incision.[9] Series from centres of excellence report an incidence of bladder neck stricture of 2·5%.[10,11] Our study shows a much higher incidence of urethral dilations or incisions—7·5%—which is probably a more accurate estimate because our study is population based and unselected.

The relative risk of experiencing a complication was not constant in the follow-up period. For complications requiring a urological procedure, admission to hospital, or a major surgical procedure, patients who had radical prostatectomy experienced higher incidence of these complications in the first year, but at 3 years post-treatment, patients who had radiotherapy experienced significantly higher incidence. This situation is perhaps to be expected because radiation-induced side-effects, especially radiation cystitis and proctitis, can occur many years after treatment.[12–14]

About a quarter of the hospital admissions were for radiation proctitis. Proctitis is usually treated on an outpatient basis. Most of the hospital admissions in both groups had a length of stay of 1 day. Some patients were probably admitted electively to have a procedure done rather than being admitted as an emergency per se. Indeed, the incidence of hospital stays longer than 1 day was 3·3% for the radiation group and 1·5% for the surgery group. For other hospital admissions common to both treatments, hospital coders would not distinguish patients with different primary treatments at the time of admission. Thus, the relative comparison of the hospital admissions between surgery and radiation is not systematically biased.

The absolute incidence of hospital admissions and gastrointestinal procedures for radiation-related toxicity

Panel: Research in context

Systematic review

We did a systematic review to establish the prevalence of complications after surgery or radiation for the treatment of prostate cancer. We searched PubMed with the terms "prostate cancer", "radical prostatectomy", and "radiation". For each of these terms, we then did separate searches with the terms "complications", "secondary cancer", "hospital admission", or "procedures". We excluded studies that measured the occurrence of urinary incontinence or erectile dysfunction. We also searched the reference lists from the retrieved papers. We included only studies published after 1987, which is viewed as the prostate-specific antigen-screened era for prostate cancer. We found no population-based studies that have assessed the incidence of urological procedures, admission to hospital, rectal or anal procedures, or open surgical procedures. We identified several studies that assessed secondary cancer occurrence after radiation treatment, but not after surgery.

Interpretation

To the best of our knowledge, this study is the first to establish incidence of complications beyond urinary incontinence and erectile dysfunction after radical prostatectomy and radiotherapy for prostate cancer. Our study indicates that complications including hospital admission, urological procedures, rectal or anal procedures, open surgical procedures, and secondary malignancies are significant. The most important determinant is the choice of primary treatment, with radiation being associated with higher incidence of all complications except for urological procedures. Clinicians should discuss these complications, in addition to the well-known adverse effects of incontinence and erectile dysfunction, with their patients when talking about treatment options for clinically localised prostate cancer.

are higher than reported in previously published single-centre studies and multicentre trials.[15,16] Our complication incidence might be more representative of community practice because our study included all hospitals in Ontario. Additionally, a few patients who had open surgical procedures in the radiotherapy group underwent a cystectomy and urinary diversion (which was not associated with bladder cancer). No patients in the surgery group needed this intervention.

The magnitude and clinical significance of second cancers attributable to pelvic radiation remains controversial.[3,5,17,18] Large cohort studies have shown consistently high occurrence of secondary cancers, especially those of the bladder, rectum, and lungs.[5,17,18] To our knowledge, our study has shown one of the highest incidences of secondary malignancy development after radiotherapy, compared with surgery, which is especially shown by the high SIR for the radiotherapy group and a neutral SIR for the surgery group in comparison with the general population.

Our study has some limitations. We could not establish the specific type of radiotherapy used for treatment. Within our study, external-beam conformal radiation (2D and 3D), intensity-modulated radiation therapy, image-guided radiation therapy, brachytherapy, and stereotactic-body radiation therapy were used. In future studies, analysis of data by specific radiation treatments will be important. Nevertheless, we were able to restrict our analysis to patients who received contemporary methods of radiation treatments and we noted similar results. We did not have information about whether patients received androgen-deprivation therapy within our cohort, and the provincial databases did not have information about prescription drugs for all participants. Other complications related to androgen deprivation, such as cardiovascular events, will need to be assessed in future studies.

Moreover, we did not have information about tumour stage or grade. Complications could vary between patients with differences in these factors. A further limitation is that for some secondary procedures we could not unequivocally attribute the procedure to the cancer treatment. Because of the nature of population-based databases, the procedure might have been done for another reason. As such, the incidences of treatments and secondary cancers could have been overestimated. Medical chart reviews will be necessary to resolve these issues. Nevertheless, the procedures that were included in the study are all accepted complications related to surgery or radiotherapy. Sewell and colleagues[19] analysed the accuracy of administrative diagnostic codes based on physicians' claims in 406 men with prostate cancer treated with radiotherapy and reported excellent specificity after medical chart validation for complications, describing similar complications assessed in our study such as urethral stricture, fistulae, and radiation proctitis. We also ensured that each specific procedural code was included in both groups. Finally, since this study is the first of its type to comprehensively report occurrence of these complications, the patient-oriented decision-making process could lead to imbalance. Future studies will be needed to assess how these complications are weighed up from a patient perspective, to better assess their importance. In conclusion, these are important complications of treatment for prostate cancer that should be considered in addition to urinary incontinence and erectile dysfunction.

Contributors

RKN and YL conceived the study and were responsible for the study design and the development of the data analysis. RKN, PC, SH, LHK, MC, GSK, YL, and RTK were responsible for data assembly, data collection, and analysis of the primary endpoints. RS and JS had access to the raw data and were responsible for the data analysis. RKN, PC, SH, LHK, GSK, RTK, and SAN were responsible for data interpretation. RKN wrote the first draft. The report was edited by all authors, who have approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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that three similar drugs are available to for first-line treatment of this niche group of patients, while the question of how to treat patients after disease progression and how to overcome resistance remains unclear and without approved drugs.

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Complications from treatment of localised prostate cancer


Antonia Reeve/Science Photo Library

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Men with localised prostate cancer face treatments that have similar outcomes but varying toxicities. In terms of disease-free survival, the scarcity of randomised controlled trials hinders a high-level, evidence-based recommendation for the preferred use of either surgery or radiotherapy in localised disease. During patients' decision-making process, concerns about morbidity from radiotherapy are mainly concentrated on temporary bladder or bowel symptoms, and the risk of radiation proctitis, cystitis, and erectile dysfunction. Radiotherapy could also carry the risk of second malignancies. The main risks considered in relation to prostatectomy (surgery) are perioperative morbidity and mortality, incontinence, and erectile dysfunction.

In *The Lancet Oncology*, Robert Nam and colleagues[1] report comparative results for complications from both treatments from a population-based study. The study is a unique retrospective investigation using fee codes from the Ontario Health Insurance Plan. The codes were linked to the Ontario Cancer Registry and the hospital Discharge Abstract Database. As a clinically relevant selection bias, patients given radiotherapy were older and had a higher level of comorbidity than those who underwent surgery, since nearly half of the irradiated patients were older than 70 years of age, compared with only 7% of prostatectomy patients. Increased age and comorbidity level were important predictors for all outcomes.

Nam and colleagues' study[1] is the first population-based high-volume assessment of treatment-related complications necessitating a short or long-term hospital admission, or a minimally invasive or open surgical intervention for bladder and rectal disorders. Data for incontinence and erectile dysfunction were excluded from the study. The authors report that patients who were given radiotherapy had higher incidence of complications for hospital admissions, rectal or anal procedures, open surgical procedures, and second malignancies at 5 years than did those who underwent surgery ($p<0·0001$). However, there were fewer urological procedures in the radiotherapy than in the surgery group ($p<0·0001$). For the normal tissues affected by either radiotherapy or surgical procedures, the range of morbidities represents the different scopes of toxicities of the two treatment approaches, and the rate of interventions is high. The procedure itself was not always associated with the expected amount of morbidity, which could thus result in an overestimation of a clinically relevant toxicity. Nevertheless, relevant

data about possible treatment-related interventions could guide physicians in supporting their patients' decision-making process.

The risk of second malignancies caused by the mutagenic potential of ionising radiation is well recognised. Two different approaches could be taken to quantify the risk. A patient cohort from one institution could be followed and compared with an appropriate non-irradiated cohort. The largest published cohort study includes 1310 patients.[2] A bladder or rectal cancer within the therapeutic dose volume was observed in 1·2% or 0·53% of patients, with an out-of-treatment-field second malignancy rate of 6·6%. The excess risk was established with data from the Surveillance Epidemiology and End Results (SEER) programme of the US National Cancer Institute. After skin cancers were excluded, no excess risk was recorded. The advantage of a prospective dataset from patients who were treated and observed according to a standardised protocol is outweighed by an insufficient number of patients to detect a small increase in risk of secondary malignancies. Alternative approaches involve retrospective studies based on data from tumour registries. In the past two decades, key publications have relied on the SEER data. Brenner and colleagues[3] reported a significant excess risk for rectal cancer, whereas two other groups (Neugut and colleagues[4] and Kendal and coworkers[5]) were unable to detect any difference. In the largest record set from 297 069 men, Moon and colleagues[6] reported a significant second malignancy rate, irrespective of whether these occurred in the area exposed to radiation or outside. Bhojani and colleagues[7] first used a Canadian population-based database and reported a significant excess risk for lung (5·2%), bladder (3·9%), and rectal cancer (2·4%) after 5 years. After 10 years, only the lung cancer risk remained significantly raised. Nam and colleagues'[1] findings confirm these data with a cumulative risk of a second malignancy at 5–9 years of 4·5% in the radiotherapy group versus 1·8% in the surgery group. The most common site of second malignancies was the gastrointestinal tract, but the relative excess risk was highest for lung cancer.

Ionising radiation is widely understood to potentially increase the risk of secondary malignancies. This risk should be viewed as clinically relevant and therefore quantifiable in a risk-balanced patient cohort comparison. Could we obtain these data through a population-based approach? Age and comorbidity clearly affect the treatment decision-making process, resulting in an inherent risk of an imbalanced distribution of comorbidities. Older age, smoking, and nutritional factors are undoubtedly associated with an increased cancer incidence. Thus, the advantage of a huge patient cohort from a population-based study will be negated by the presence of unbalanced confounders. Nam and colleagues' population-based study is based on fee codes and hospital discard data, which were linked to the Ontario Cancer Registry. All medical procedures are reimbursed by a single health insurance system. This approach is promising for the linkage of a cancer registry with more detailed individual clinical data. However, existing billing systems, aimed to define and group medical services, were not able to present these detailed data. We should emphasise that linkage of modern IT database systems is a valuable process to find the bridge between huge patient cohorts and reliable prognostic and predictive clinical data. Nevertheless, data from recent population-based studies should be interpreted carefully in view of the known selection bias to prevent invalid comparisons from being made.

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