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, 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, 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. 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
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).

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.1 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 minimially 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
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, 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 by calculating the standardised incidence ratio (SIR). We calculated the SIR as the number of observed cancers in each treatment group and age group divided by the number of expected cancers in each treatment group and age 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.

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. We used the sum of aggregated disease groups (ADG), which form a high-level classification scheme for groups of diseases and disorders. 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
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, 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 (5955/6771; 88·5%). A higher proportion of inpatients in the radiotherapy group compared with the general population based on age-adjusted Ontario cancer statistics4 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 (2·3–4·7), whereas for those aged 65–90 years, there were 28 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 statistics4 within our same study period to calculate the SIRs. In the radiotherapy 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 50 cancers observed (2·3–4·7), whereas for those aged 65–90 years, there were 71·7 cancers expected versus 50 cancers observed (2·3–4·7), whereas for those aged 65–90 years, there were 71·7 cancers expected versus 50 cancers observed (2·3–4·7). 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 50 cancers observed (2·3–4·7). 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...
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 32465 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 fewer participants. Potosky and colleagues 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 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 for the complication at the hospital at which the radiotherapy was delivered. The absolute incidence of hospital admissions and gastrointestinal procedures for radiation-related toxicity 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 strictures that cause urinary obstruction, most of which can be treated with minimally invasive treatments, including catheterisation, bladder neck dilatation, or incision. Series from centres of excellence report an incidence of bladder neck stricture of 2-5%.

Our study shows a much higher incidence of urethral dilatations 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.

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.
are higher than reported in previously published single-centre studies and multicentre trials.²⁰⁻⁰ 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.³⁻⁰ Large cohort studies have shown consistently high occurrence of secondary cancers, especially those of the bladder, rectum, and lungs.³⁻⁰ 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 infer the specific procedure code. This might be important. Nevertheless, the procedures that were included in the study are all accepted complications related to surgery or radiotherapy. Sewell and colleagues 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

RK and YL conceived the study and were responsible for the study design and the development of the data analysis. RK, 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. RK, 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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