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Clinical Investigation

National Population-Based Study Comparing Treatment-Related Toxicity in Men Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer

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Summary

Intensity modulated radiation therapy (IMRT) has been rapidly adopted despite a lack of evidence demonstrating superiority over 3D-conformal radiation therapy (3D-CRT). A national cohort study using real-world data was performed on 23,222 men comparing severe gastrointestinal (GI) and genitourinary (GU) toxicity between IMRT and 3D-CRT. Men who received radical radiation therapy using IMRT were less likely to experience severe GI toxicity and had similar GU toxicity compared with those who received 3D-CRT.

Purpose: To compare, in a national population-based study, severe genitourinary (GU) and gastrointestinal (GI) toxicity in patients with prostate cancer who were treated with radical intensity modulated radiation therapy (IMRT) or 3-dimensional conformal radiation therapy (3D-CRT).

Methods and Materials: Patients treated with IMRT (n = 6933) or 3D-CRT (n = 16,289) between January 1, 2010 and December 31, 2013 in the English National Health Service were identified using cancer registry data, the National Radiotherapy Dataset, and Hospital Episodes Statistics, the administrative database of care episodes in National Health Service hospitals. We developed a coding system that identifies severe toxicity (at least grade 3 according to the National Cancer Institute Common Terminology Criteria for Adverse Events scoring system) according to the presence of a procedure and a corresponding diagnostic code in patients' Hospital Episodes Statistics records after radiation therapy. A competing risks regression analysis was used to estimate hazard ratios (HRs), comparing the incidence of severe GI and GU complications after IMRT and 3D-CRT, adjusting for patient, disease, and treatment characteristics.

Results: The use of IMRT, as opposed to 3D-CRT, increased from 3.1% in 2010 to 64.7% in 2013. Patients who received IMRT were less likely than those receiving 3D-CRT to experience severe GI toxicity (4.9 vs 6.5 per 100 person-years; adjusted HR 0.66; 95% confidence interval 0.61-0.72) but had similar levels of GU toxicity (2.3 vs 2.4 per 100 person-years; adjusted HR 0.94; 95% confidence interval 0.84-1.06).

Conclusions: Prostate cancer patients who received radical radiation therapy using IMRT were less likely to experience severe GI toxicity, and they had similar GU toxicity compared with those who received 3D-CRT. These findings in an unselected "real-world" population support the use of IMRT, but further cost-effectiveness studies are urgently required.

Introduction

External beam radiation therapy (RT) is a well-established definitive treatment for localized and locally advanced prostate cancer. Dose-escalation to the tumor has been shown to improve biochemical progression-free survival; however, this can be at the cost of increased gastrointestinal (GI) and genitourinary (GU) side effects (1-4). Gastrointestinal toxicity can occur in the acute phase typically within 3 months, caused by a mucosal inflammatory response, and in the late phase, characterized by fibrotic changes resulting in chronic GI impairment (5). Similarly, GU side effects such as hematuria can occur soon after treatment, whereas bladder outflow obstruction and radiation cystitis may occur later (6).

Attempts to improve the therapeutic ratio, in particular a reduction in treatment-related side effects, has driven advances in modern RT technologies such as intensity modulated radiation therapy (IMRT) (4). The advantage of IMRT compared with 3-dimensional conformal radiation therapy (3D-CRT) is the potential to deliver high-dose radiation to the prostate (7, 8), while limiting the radiation dose to surrounding tissue, including the rectum and bladder, reducing acute and late toxicities (9-12).

Intensity modulated radiation therapy was taken up rapidly from the early 2000s in the United States and then in the United Kingdom (13) at considerable cost (14) in the absence of robust randomized controlled trial evidence demonstrating its superiority over 3D-CRT (15). A recent meta-analysis including 23 clinical studies with 9556 patients demonstrated that the use of IMRT greatly reduced acute and late GI toxicity (16). This also suggested that IMRT was linked to a small increase in acute GU toxicity and a small reduction in biochemical failure (ie, rise of prostate-specific antigen level of 2 ng/mL or more). However, the authors of this meta-analysis highlighted the heterogeneity of the results and that more high-quality studies were needed.

The rapid adoption of IMRT means that future randomized controlled trials assessing its effectiveness are no longer feasible. However, "real-world" data provide an opportunity to understand the true value of IMRT compared with 3D-CRT. We carried out a national population-based study including more than 23,000 men diagnosed with prostate cancer between 2010 and 2013 in the English National Health Service, who received either IMRT or 3D-CRT. We used a coding system that was specially developed to identify severe toxicity, comparable to at least grade 3 toxicity as measured by the National Cancer Institute Common Toxicity Criteria for Adverse Events scoring system (version 4.0) (17), in administrative hospital data.

Methods and Materials

Data sources and patient population

English cancer registry data and the National Radiotherapy Dataset were used to identify men with a diagnosis of prostate cancer (International Classification of Diseases, 10th Revised Edition [ICD-10] "C61") who received radical RT between January 1, 2010 and December 31, 2013 (18). These men were linked to the Hospital Episode Statistics (HES) database, an administrative database of all care episodes in the National Health Service in England (19).

Control variables

Data items in HES records were used to determine age, the Royal College of Surgeons (RCS) Charlson comorbidity score expressed as the number of comorbidities (20), and socioeconomic deprivation status according to quintiles of the national ranking of the Index of Multiple Deprivation (21). Tumor characteristics, including TNM stage and Gleason score, were extracted from the cancer registry data to determine a modified D'Amico prostate cancer risk classification (a previously developed algorithm to group patients according to pretreatment prostate cancer risk in the absence of data on prostate-specific antigen levels) (13). The National Radiotherapy Dataset provided information on the RT treatment region (prostate only/prostate and regional), whether an IMRT technique was used (OPCS-4 code "X671") (22), and the total prescribed dose/fractions.

Inclusion and exclusion criteria

The records of 41,763 men with nonmetastatic prostate cancer who had received RT were studied. Patients were excluded if they had also received brachytherapy (n = 165), if they had an associated diagnosis of bladder cancer (ICD-10 "C67") (n = 1103) (23), or if they received RT after radical prostatectomy (n = 3341). Because this study used national data, variation existed in the fractionated regimes delivered. With reference to United Kingdom RT dose fractionation guidance and regimes used in randomized controlled trials (3, 24-27), we included patients who received 72 to 79 Gy in 35 to 40 fractions. The 3 further regimes that were most commonly used were also included (72 Gy/32 fractions; 69 Gy/37 fractions; 70 Gy/35 fractions). This resulted in the exclusion of a further 13,932 men. The final cohort included 23,222 men (Fig. 1).

Coding framework

We have previously developed and validated a method using linked administrative data to identify severe GU complications after radical prostatectomy (28). This methodologic approach was used to capture severe urinary complications after RT. With reference to earlier studies that used procedure codes to measure toxicity (11, 29, 30), a comprehensive list of OPCS-4 procedure codes (22) related to GU complications after RT was prespecified ("forward coding"). We also examined the most frequently occurring procedure codes in records of day-case and in-patient hospital episodes after RT and added these to the prespecified list if they were not already included but likely to be related to GU complications ("backward coding") (Appendix, Table E1; available online at www.redjournal.org).

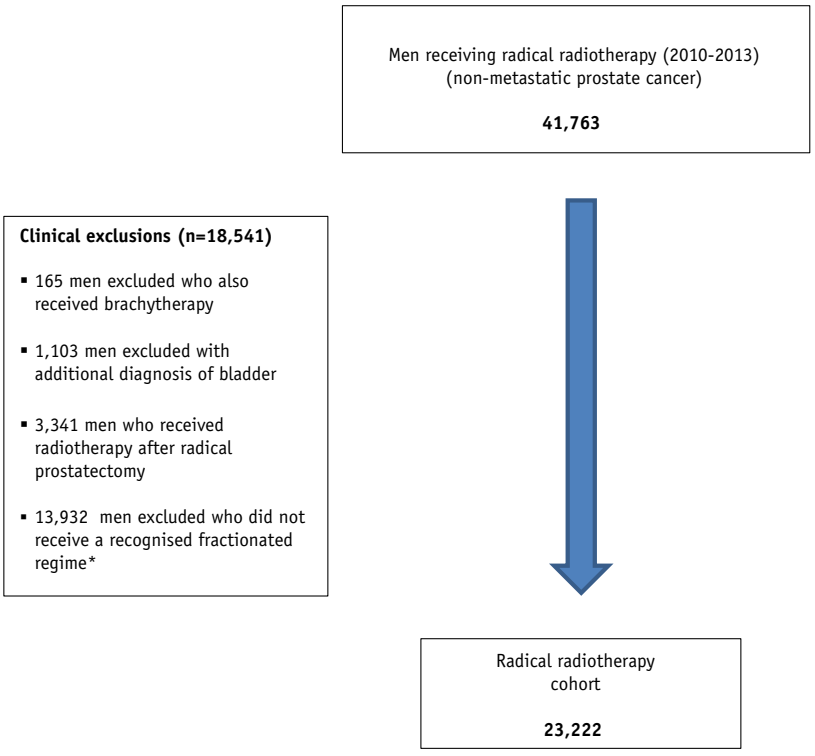
The forward and backward coding approach was repeated to identify ICD-10 diagnostic codes related to urinary complications. In addition to a "radiation-specific" code (N304, "irradiation cystitis"), we also captured other common side effects, including hematuria, GU strictures, and urinary incontinence (Appendix, Table E2; available online at www.redjournal.org). The GU toxicity outcome measure was defined as the occurrence of both a procedure and corresponding GU diagnostic code in a patient record after the first RT treatment session. This approach confined our analyses to what were likely to be more severe complications, comparable to at least grade 3 toxicity as measured by National Cancer Institute Common Toxicity Criteria for Adverse Events Scoring system (ie, requiring hospital admission or procedural intervention) (17).

For GI toxicity after RT, we also determined a list of procedure and diagnostic codes based on previous studies (Appendix, Tables E3 and E4; available online at www.redjournal.org) (11, 29, 30). The ICD-10 diagnostic codes included "radiation-specific" codes (K520 "gastroenteritis and colitis due to radiation"; K627 "radiation proctitis") as well as those likely to be a GI complication of radiation, such as rectal bleeding and fistulae formation (Appendix, Table E4; available online at www.redjournal.org). Just as for GU toxicity, we defined the GI toxicity outcome measure, also capturing grade 3 or higher toxicity, as the occurrence of both a procedure and corresponding GI diagnosis code to be present in a patient record. This was important because it excluded men who underwent procedures such as a "colonoscopy" for other reasons not related to post-RT GI toxicity.

Time from date of the first RT treatment to the first GU or GI complication requiring an intervention were the study primary outcomes. For both outcomes, if more than one procedure code matched to a corresponding diagnosis code in the patient record, then the code in the first procedural field was used because it was most likely to represent the most relevant procedure. Patients were considered as not having experienced GU or GI toxicity if there were no day-case or in-patient hospital episodes from the first date of RT until the end of follow-up (December 31, 2015).

Statistical analysis

Differences between patient, disease, and treatment characteristics were assessed using the χ^2 test. The 5-year cumulative incidence of complications was estimated using a competing-risks approach (31). To be consistent with existing literature (32), for each outcome measure we



Included fractionated regimes:

Regimen (Dose (Gy)/Fractions)	No. of patients
72-79/35-40	21,046
72/32	1439
70/35	443
69/37	294

Fig. 1. Flow chart of men included in study.

calculated the number of events per 100 person-years of follow-up. This metric provided a single figure for the rate of GU and GI complications in both groups.

A competing-risks regression analysis was used to compare time to complication between IMRT and 3D-CRT groups, with complication as the event of interest and death as the competing event. We adjusted for year of RT, age, RCS Charlson comorbidity score, socioeconomic deprivation status, prostate cancer risk group, and RT treatment region.

Results are reported as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). A P value $<.05$ was considered statistically significant. P values were based on the Wald test or the likelihood ratio test, as appropriate.

Before the regression analysis, missing values for prostate cancer risk group (n = 5753), RT treatment region (n = 3793), and socioeconomic deprivation status (n = 61) were imputed using multiple imputation by chained equations. We created 50 datasets and used Ruben's rules to combine the estimated HRs across the datasets (33). The distribution of patients in categories did not change significantly after multiple imputation.

Results

Patient population

Among the patients who received radical RT (n = 23,222), the use of IMRT increased from 3.1% in 2010 to 64.7% in 2013 (Table 1). Approximately 60% of men included were between 65 and 74 years old, approximately 1 in 5 men had at least 1 recorded comorbidity, and nearly 60% of patients were staged with locally advanced disease. The median dose per fraction and total dose received were the same in both groups (2 Gy per fraction and 74 Gy, respectively). Men in the 3D-CRT group were more likely to be older and have an RCS Charlson score ≥ 1 but were less likely to have locally advanced disease and receive radiation to the prostate and nodes compared with the IMRT group (Table 1). Median (interquartile range) follow-up was 3.6 (1.9) years for all men in the study; 2.7 (1.0) years for the IMRT group and 4.1 (1.6) years for the 3D-CRT group.

Table 1 Patient, disease, and treatment characteristics of men receiving radical radiation therapy

Characteristic	3D-CRT (n = 16,289)	IMRT (n = 6933)	*P*
Year of radiation therapy			<.01
2010	4248 (26.1)	216 (3.1)	
2011	5159 (31.7)	624 (9.0)	
2012	4678 (28.7)	1605 (23.1)	
2013	2204 (13.5)	4488 (64.7)	
Age (y)			<.01
<60	1069 (6.5)	532 (7.7)	
60-64	2409 (14.8)	1096 (15.8)	
65-74	9311 (57.2)	3879 (56.0)	
>75	3500 (21.5)	1426 (20.6)	
RCS Charlson comorbidity score			<.01
0	12,407 (76.2)	5463 (78.8)	
≥1	3882 (23.8)	1470 (21.2)	
Socioeconomic deprivation status (national quintiles)			.19
1 (least deprived)	3683 (22.6)	1649 (24.0)	
2	4063 (25.0)	1735 (25.2)	
3	3552 (21.8)	1471 (21.4)	
4	2707 (16.6)	1112 (16.2)	
5 (most deprived)	2270 (14.0)	919 (13.4)	
Missing	14	47	
Prostate cancer risk group			<.01
Locally advanced	6433 (56.4)	3603 (59.4)	
Intermediate risk localized	4433 (38.9)	2211 (36.4)	
Low risk localized	534 (4.7)	384 (5.3)	
Missing	4889	864	
Radiation therapy treatment region			<.01
Prostate	11,782 (72.3)	5786 (86.4)	
Prostate and regional	950 (5.8)	911 (13.6)	
Missing	3557	236	

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; RCS = Royal College of Surgeons.
Values are number (percentage).

Timing and frequency of occurrence of toxicity

The most frequent intervention for GI toxicity was a "diagnostic fiber optic sigmoidoscopy" (3607 of 9300 procedures, 38.8%), and the commonest associated GI diagnosis was "radiation proctitis" (5962 of 8701 diagnoses, 68.5%). For GU toxicity, an "unspecified endoscopic examination of the bladder" (1470 of 3625 procedures, 40.6%) was the most frequent intervention, and "hematuria" was the most common associated GU diagnosis (1265 of 4061 diagnoses, 31.1%) (Appendix, Tables E1-E4; available online at www.redjournal.org).

Patients experienced 4.9 GI events per 100 person years of follow-up in the IMRT group, compared with 6.5 in the 3D-CRT group (Table 2). Patients who received IMRT experienced 2.3 GU events per 100 person years of follow-up, compared with 2.4 in the 3D-CRT group (Table 2).

Cumulative incidence curves showed GI toxicity was low in the first 9 months (approximately 2%) and similar in the IMRT and 3D-CRT groups (Fig. 2). However, beyond 9 months after RT, patients in the 3D-CRT group more frequently had complications than the IMRT group. Conversely, GU toxicity steadily increased in both IMRT and 3D-CRT groups after radical RT (Fig. 2).

Outcome measures

Adjusting for patient, disease, and treatment characteristics and using a competing-risks approach, we found that men treated with IMRT were less likely to experience GI toxicity (HR 0.66; 95% CI 0.61-0.72; $P<.01$) than those who received 3D-CRT. There was no significant difference in GU toxicity between the groups (HR 0.94; 95% CI 0.84-1.06; $P=.31$) (Table 2) (Appendix, Table E5; competing-risks regression analysis with all variables, available online at www.redjournal.org).

Discussion

Summary

Using outcome measures that were systematically developed, we demonstrated a significantly lower incidence of

Table 2 Adjusted outcomes for gastrointestinal (GI) and genitourinary (GU) toxicity after radical radiation therapy

	GI toxicity				GU toxicity			
Therapy	5-y cumulative incidence (%) (95% CI)	Rate (total events/100 person years)	HR* (CI)	*P*	5-y cumulative incidence (%) (95% CI)	Rate (total events/100 person-years)	HR* (CI)	*P*
3D-CRT	24.5 (23.8-25.3)	6.5	1.00	-	11.1 (9.2-13.3)	2.4	1.00	-
IMRT	17.0 (15.6-18.5)	4.9	0.66 (0.61-0.72)	<.01	10.7 (10.1-11.3)	2.3	0.94 (0.84-1.06)	.31

Abbreviations: CI = confidence interval; HR = hazard ratio. Other abbreviations as in Table 1.

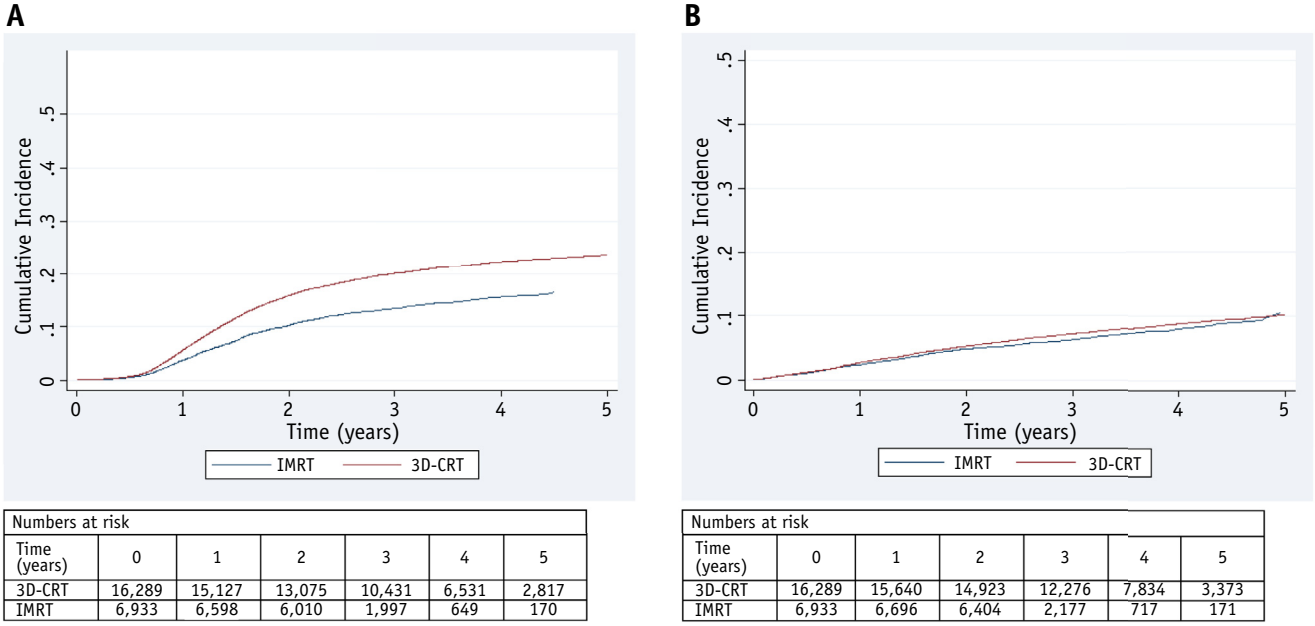
* Adjusted for year of radiation therapy treatment, age, RCS Charlson comorbidity score, socioeconomic deprivation status, prostate cancer risk group, and radiation therapy treatment region.

severe GI toxicity and a similar incidence of severe GU toxicity in men who received IMRT compared with those who received 3D-CRT. This is the largest study comparing treatment-related complications in patients receiving IMRT or 3D-CRT. It used "real-world" data from a national population-based cohort without excluding patients according to age or socioeconomic status.

We have used outcome measures specifically designed to capture urinary complications severe enough to require an intervention and comparable to at least grade 3 toxicity (National Cancer Institute Common Toxicity Criteria for Adverse Events scoring system). This is in contrast to all other studies using existing routine data (11, 34, 35) that used discrete diagnosis, procedure, and claims codes without explicitly developing these codes as toxicity outcomes measures for a specific level of severity. A further strength of our study was the availability of data on radiation doses and fractions received by patients within the National Radiotherapy Dataset, which was not present in previous studies (8, 11, 30). This ensured that only recognized fractionated regimes were included and that patients in both IMRT and 3D-CRT groups received comparable radiation doses, which are often confounders in population-based studies.

Comparison with other studies

The previous largest comparative study of IMRT and 3D-CRT using existing routine data reported on approximately 13,000 men who received treatment between 2002 and 2006 (11), on the basis of Surveillance, Epidemiology, and End Results—Medicare-linked data. Similar to our study findings, men who received IMRT were less likely to have GI toxicity, and there was no difference between the groups in GU toxicity. This study found a higher incidence of GI toxicity after 3D-CRT than after IMRT when considering GI diagnoses in both groups, but this was not the case when considering GI procedures. This discrepancy is to be expected given the use of toxicity based on diagnosis codes and procedure codes in



Numbers at risk						
Time (years)	0	1	2	3	4	5
3D-CRT	16,289	15,127	13,075	10,431	6,531	2,817
IMRT	6,933	6,598	6,010	1,997	649	170

Numbers at risk						
Time (years)	0	1	2	3	4	5
3D-CRT	16,289	15,640	14,923	12,276	7,834	3,373
IMRT	6,933	6,696	6,404	2,177	717	171

Fig. 2. Cumulative incidence curves for gastrointestinal toxicity (A) and genitourinary toxicity (B) after radical radiation therapy according to type of radiation therapy (intensity modulated radiation therapy [IMRT] vs 3-dimensional conformal radiation therapy [3D-CRT]).

isolation. In contrast, our study required the presence of a diagnosis and procedure code to ensure we captured complications comparable to grade 3 toxicity or higher.

Our findings are similar to those reported in a recent meta-analysis (16), which found that IMRT had a lower incidence of acute and late GI toxicity. This meta-analysis also found a very small increase in acute GU toxicity after IMRT, which was not observed in our study. It is important to note that in most of the studies included in the meta-analysis, patients in the IMRT group received a higher total radiation dose than those in the 3D-CRT group. A strength of our study is that both groups received comparable radiation doses.

We adjusted the comparison of the incidence of complications in men who received IMRT or 3D-CRT for differences in patient, disease, and treatment characteristics. However, we were not able to control for baseline GI and GU symptoms that could have an impact on post-RT toxicity. Furthermore, we could not control for additional therapeutic differences, including the use of image-guided radiation therapy, the use of specific bladder or bowel preparation protocols, RT field size, or the use of hormonal treatment. For example, the use of image-guided radiation therapy reduces GI and GU toxicity (36) and is more likely to have been used in IMRT patients. If this is the case, our study may have overestimated the relative benefit of IMRT. Information on the use of hormonal therapy was also not available, although results from previous studies demonstrate that hormonal therapy was not associated with the incidence of GI or GU toxicity (16, 37). Despite the absence of information on RT field size, we were able to account for whether men received treatment to the prostate alone or to the whole pelvis. At the time of this study the last follow-up date within our database was the December 31, 2015; therefore, we were not able to report on longer-term GI and GU toxicity—future studies will aim to address longer-term RT-related toxicity.

Because the use of IMRT compared with 3D-CRT increased during our study period, the median length of follow-up was higher in the latter. Although we adjusted for year of treatment in the regression model, we also performed a sensitivity analysis only including men who received RT in 2012 and 2013, all of whom had at least 2-years of follow-up. The results of this sensitivity analysis fully supported the findings from the primary analysis.

Clinical implications

Our findings are in line with the notion that IMRT allows the delivery of higher doses while reducing exposure to the rectum and in turn reducing GI toxicity. Furthermore, this reduction occurred despite a higher proportion of patients in the IMRT group receiving additional pelvic RT compared with the 3D-CRT group. The benefits of IMRT, however, do not seem to lead to a reduction in GU toxicity. A potential explanation for this is that the benefits of IMRT may be countered by the high variability in patients' bladder capacity and filling volumes. These findings are supported by other dosimetric studies, which have shown that rectal sparing is better with IMRT than with 3D-CRT but that the differences for bladder sparing may not be as significant (8, 38).

Given the substantial increased costs associated with delivering IMRT (39), further studies are required to evaluate the cost-effectiveness of IMRT in light of its improved toxicity profile with respect to severe GI toxicity. This is of particular relevance in low- and middle-income countries where there is an urgent need for expansion in access to RT (40). The lack of robust comparative clinical data has meant that the benefit from IMRT in a cost-effectiveness model remains uncertain, particularly the estimation of the incidence of toxicity after treatment (41). The morbidity outcomes from our study provide further means to strengthen economic models using existing administrative data.

Conclusion

In this national population-based study of patients with nonmetastatic prostate cancer, we have shown that men who received radical RT using IMRT were less likely to experience severe GI toxicity and that they had similar severe GU toxicity compared with those who received 3D-CRT. Our study used a transparent coding system that was specifically developed to identify only severe complications. This coding system can be used to provide a performance indicator for service evaluation and quality assessment. Furthermore, it can be used for comparative effectiveness research using existing administrative data to capture GU and GI toxicity after pelvic-based RT of other tumors, such as cervical cancer.

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