ABSTRACT

Introduction

Randomised controlled trials (RCTs) have demonstrated comparable early oncological outcomes after hypofractionated (H-RT) and conventionally fractionated radiation therapy (C-RT) in the radical treatment of prostate cancer (PCa). The effect of hypofractionation on treatment-related (gastrointestinal) GI and (genitourinary) GU toxicity remains uncertain, especially in older men and those with locally advanced PCa.

Materials and Methods

Population-based study of all patients treated with radical C-RT (n=9,106) and H-RT (n= 3,027) in all radiotherapy centres in the English National Health Service between 2014 and 2016. We identified severe GI and GU toxicity using a validated coding-framework and compared C-RT and H-RT using a competing-risks proportional hazards regression analysis.

Results

The median age in our cohort was 72 years old and the majority of patients had locally advanced disease (65%). There was no difference in GI toxicity (C-RT: 5.0 events/100 person-years; H-RT: 5.2 events/100 person-years; adjusted sHR: 1.00, 95%CI: 0.89-1.13; p=0.95) or GU toxicity (C-RT: 2.3 events/100 person-years; H-RT: 2.3 events/100 person-years; adjusted sHR: 0.92, 95%CI: 0.77 -1.10; p=0.35) between patients who received C-RT and H-RT

Conclusions

This national cohort study has demonstrated the use of H-RT in the radical treatment of PCa does not increase rates of severe GI or GU toxicity. Our findings also support the use of H-RT in older men and those with locally advanced PCa.

INTRODUCTION

External beam radiotherapy (RT) is a well-established treatment for localised and locally advanced prostate cancer (PCa). A conventionally fractionated regimen (C-RT, 1.8 – 2 Gy per fraction) delivered over 7-8 weeks has been widely used as standard of care for primary treatment of PCa (1). However, the use of hypofractionated regimens (H-RT), which deliver >2Gy over 4 weeks, may offer a therapeutic and economic advantage by delivering an equivalent biologically effective dose in a shorter time (2).

Four recent non-inferiority randomised controlled trials (RCTs) have demonstrated the comparable efficacy of C-RT and H-RT without significant differences in 5-year biochemical or clinical failure-free survival in localised PCa (3-7). However, these RCTs and meta-analyses (2, 8) have reported conflicting data on the effect of hypofractionation on patient/physician-reported acute and late gastrointestinal (GI) and genitourinary (GU) toxicity.

"Real-world" data provide an opportunity to understand the true comparative toxicity between C-RT and H-RT. We carried out a contemporary national cohort study, including more than 12,000 patients from all English National Health Service (NHS) RT centres, who were diagnosed with PCa between 2014 and 2016 and received either C-RT or H-RT. We used a validated coding system that was specifically developed to identify severe GI and GU toxicity. The identified toxicity is comparable to grade 3 toxicity as measured by the National Cancer Institute Common Toxicity Criteria (CTCAE) for Adverse Events scoring system (version 4.0). In addition, this coding system also included patients with confirmed radiation proctitis (Grade 2 – CTCAE) (9), in administrative hospital data (10).

METHODS

Data sources and patient population

English cancer registry data (11) linked with prospective data from the National Prostate Cancer Audit (NPCA) and the National Radiotherapy Dataset (RTDS) (12) were used to identify men with a diagnosis of PCa (ICD-10 "C61") who received intensity-modulated radical RT between April 1, 2014 and March 31, 2016. The use of intensity-modulated radiotherapy (IMRT) was captured using the OPCS-4 code "X671" within RTDS. These men were then linked to the Hospital Episode Statistics (HES) database, an administrative database of all care episodes in the English NHS (13).

Patient and disease characteristics

Data items in HES records were used to determine age, comorbidities and socioeconomic deprivation status. The Royal College of Surgeons (RCS) Charlson score was used to identify any comorbidities a year prior to their PCa diagnosis (14). Socioeconomic deprivation status was determined for patients from the English 2012 Index of Multiple Deprivation (IMD) based on their area of residence and divided according quintiles of national distribution (15). Patient demographics, the use of androgen deprivation therapy and tumour characteristics including TNM-stage and Gleason score were extracted from the linked NPCA-cancer registry data to determine a modified D'Amico prostate cancer risk-classification using an algorithm developed by the NPCA (16). RTDS provided information on the RT treatment region (prostate only/prostate and pelvic lymph nodes) and the total dose/fractions received.

Inclusion and exclusion criteria

The records of 12,133 men with non-metastatic prostate cancer who received radical RT at all RT centres in the English NHS (n=52) were studied. Patients were only included if they received a known conventional or hypofractionated regimen, as variation exists in the regimens delivered across RT centres in the United Kingdom (UK). With reference to the UK RT dose fractionation guidance and regimens used in RCTs (1, 3-7) we defined C-RT as patients receiving 72 to 79 Gy in 35-40 fractions; 72 Gy/32 fractions; 69 Gy/37 fractions and 70Gy/35 fractions. The median dose delivered in C-RT group was 74 Gy/37 fractions. H-RT was defined as patients receiving 50-60 Gy in 16-20 fractions (median 60 Gy/20 fractions).

Patient were excluded if they had an associated diagnosis of bladder cancer (ICD-10 “C67”) (n= 290) or if there was any missing clinical data (n= 291). The final cohort included 12,133 men (Figure 1).

Coding framework

We used previously validated performance indicators to capture severe GI or GU toxicity following radical RT (10). The coding framework was based on procedures which are coded using the UK Office for Population Census and Surveys classification, 4th revision (17), and the diagnostic codes determined using the International classification of Diseases, 10th revision (ICD-10) (18). Men were classified as having experienced a complication if both a procedure and corresponding diagnosis code were present in a patient record following the start of RT. This approach confined our analyses to severe complications (i.e. requiring hospital admission or procedural intervention)(9).

The baseline GI and GU function of the included patients was estimated based on the presence of a GI or GU procedure code in the HES record up to one year before the start of RT.

Primary outcome measure

Time from the date of the first RT treatment to the first GI or GU complication requiring an intervention were the study primary outcomes. Patients were considered as not having experienced GI or GU toxicity if the relevant procedure and diagnosis codes were not present from the start of RT until the end of follow-up (December 31, 2017).

Endpoints

The 3-year cumulative incidence of both GI and GU complications were calculated using a competing risks method where death was the competing event (19). We also calculated incidence rates using total events per 100 person-years, where person-years was calculated as the sum of the time from radiotherapy until occurrence of an event (GI or GU complication), death or the end of follow-up, whichever occurred first.

Statistical analysis

A competing risks regression analysis, according to Fine and Gray (1999) via maximum likelihood, was used to estimate subdistribution hazard ratios (sHR) comparing the risk of GI or GU complications between C-RT and H-RT groups. When men reached the end of follow-up this was treated as a censoring event. The regression analysis was adjusted for patient, tumour and treatment characteristics.

Results are reported as sHRs with 95% confidence intervals (95%CI). A p-value smaller than 0.05 was considered statistically significant. P-values were based on the Wald test or the likelihood ratio test, as appropriate.

RESULTS

Patient population

Table 1 presents the characteristics of the study population. Out of the 12,133 men included, 9,106 (75.1%) received C-RT and 3,027 (24.9%) received H-RT. The median age (interquartile range) of all included men was 72 (67 - 76) years. The use of H-RT increased over the study period – 394 out of 1,849 men (21.3%) in 2014 compared to 969 out of 2,439 men (39.7%) in 2016.

In the H-RT group men were older (8.4% versus 5.4%, >80 years), fewer men had locally advanced disease (58.0% versus 66.9%), and fewer men received RT to prostate and pelvic lymph nodes (10.8% versus 15.6%). Baseline GI and GU toxicity were also similar in both groups.

Gastrointestinal and genitourinary toxicity

Patients experienced 5.1 GI events/100 person years of follow-up in the C-RT group compared to 5.3 in the H-RT group (unadjusted HR: 1.02 (0.91 – 1.15)). With respect to GU events, patients who received C-RT experienced 2.3 GU events/100 person years of follow-up compared to 2.3 in the H-RT group (unadjusted HR: 1.00 (0.84 – 1.19)) (Table 2). Median (interquartile range) follow-up was 2.6 (2.3 – 3.0) years for all men in the study; 2.7 (2.3 – 3.0) years for C-RT group and 2.4 (2.1 – 2.9) years for H-RT group.

The cumulative incidence of GI toxicity was higher in the H-RT group up to approximately 1 year (4.3% compared to 3.2%) however at 3 years they were similar

(13.4% in C-RT group, 13.7% H-RT group) (Figure 2). GU toxicity remained similar in both groups throughout the follow-up period (Figure 3).

Following adjustment and using a competing-risks approach we found that there was no statistically significant difference in GI toxicity (sHR: 1.00; 95% CI: 0.89 – 1.13, p= 0.95) or GU toxicity (sHR: 0.92; 95% CI: 0.77 – 1.10, p=0.35) between both groups (Table 2) (Supplementary material).

DISCUSSION

Summary

In this national population-based study of more than 12,000 men with PCa we found no overall difference in severe GI and GU toxicity between patients who received C-RT and H-RT. There was a trend towards increased GI toxicity in the H-RT group up to 1 year after treatment although this was not seen at the end of follow-up at 3 years.

Our study also included men who are older and more often have locally advanced disease compared to existing RCTs. All men in the study received recognised conventionally fractionated and hypofractionated radical RT regimens which were delivered using contemporary IMRT, and furthermore toxicity was captured using a validated outcome measure.

Comparison with other studies

There is increasing evidence supporting the use of H-RT for men with PCa. Four large RCTs demonstrated similar 5-year effectiveness data after H-RT for biochemical and clinical failure-free survival in localised PCa (3-6, 20). However, there have been differences with regard to treatment-related toxicity outcomes. The PROFIT trial randomised 1,206 men with intermediate-risk disease and found significantly lower late GI toxicity rates (grade ≥2, RTOG score) in the hypofractionated (60 Gy/20 fractions) arm compared to the conventional arm (78 Gy/39 fractions). These results were in contrast to the RTOG 0415 study which included 1,092 men all with low-risk disease and reported an increase in both late GI and GU ≥2 toxicity (NCI CTCAE scoring system) in the hypofractionated group (70

Gy/28 fractions) compared to conventional group (73.8Gy/41 fractions). Both of these studies did not find a difference in acute ≥3 GI and GU toxicity.

The CHHiP trial included 3,216 men with predominantly intermediate-risk disease and compared a conventional regimen (74 Gy/37 fractions) with two hypofractionated schedules (60 Gy/20 fractions and 57 Gy/19 fractions). Similar to our study, CHHiP reported significantly more acute GI toxicity (≥ grade 2, RTOG score) in both hypofractionated groups (38%) compared to the conventional group (25%), however by 18 weeks this difference was no longer present. In our study increased GI toxicity persisted in the H-RT group up to 1 year. This may be due to our study having a higher proportion of men with high-risk localised/locally advanced disease (65%) compared to CHHiP (12%) as well as some men receiving RT to pelvic nodes in our study which was an exclusion criterion in CHHiP. However, in line with our findings, CHHiP reported no difference in long-term GI toxicity and also no difference between groups in terms of acute/long-term GU toxicity.

The Dutch HYPRO trial included men with predominantly high-risk disease and demonstrated acute ≥2 GI toxicity (RTOG score) was higher with hypofractionation (C-RT 31%, H-RT 42%; P 0.0015) although this difference disappeared after 3 months. The incidence of late GI ≥2 toxicity was similar in both groups. The incidence of acute GU ≥2 toxicity was also similar in both group but in contrast to our study, the cumulative incidence of late GU ≥2 toxicity was higher in the H-RT arm.

Most existing retrospective studies have demonstrated similar GI and GU toxicity with hypofractionation but were predominantly performed at a single institution and report on a low numbers of patients (21, 22).

Strengths and limitations

The current study has a number of strengths. First, to our knowledge, this is the largest comparative study assessing toxicity following C-RT and H-RT and also exclusively includes patients treated with IMRT. In contrast, some of the major RCTs have included patients that received 3D-conformal RT (3, 6).

Second, our findings are reflective of "real-world" practice as we included all men diagnosed with PCa and treated at any NHS RT centres in the study period. Patients who underwent RT in the private sector were not included but these men represent less than 10% of the national case load (23).

Third, we report on an unselected population with appropriate variation in age and PCa risk distribution, increasing the generalisability of our results. The large RCTs (3-7) predominantly reported on intermediate-risk disease with some reporting on exclusively low-risk (6) and intermediate-risk disease (3). In contrast, our study included 7,844 men with locally advanced disease, many of whom would have received higher doses to the seminal vesicles which could increase toxicity rates. Our population was also older (median age = 72 years) than cohorts used in the larger RCTs and therefore more reflective of patients encountered in routine clinical practice. Our findings also confirm the safety of H-RT in older patients and those with more advanced disease.

Fourth, through linkage with RTDS, we extracted detailed information regarding RT doses and patient attendances. As a result we only included men who received recognised conventional and hypofractionated regimens.

Finally, the indicators we utilised have been specifically developed and validated to capture RT-related toxicity severe enough to require admission or an intervention which allowed us to measure GI and GU toxicity at a specific severity level. The supplementary use of diagnostic codes improved the validity of the indicator and allowed better identification of RT-related toxicity which we have previously used to compare different RT delivery techniques (10). Also using observational data to capture adverse events provides a more accurate reflection of the frequency of toxicity compared to super-selected RCT populations which often result in under-estimation (24). Of note, RCTs are increasingly advocating linkage to routine health records to more accurately capture treatment-related adverse events (25).

There are some limitations to this study. We adjusted the comparison of incidence of toxicity in the C-RT and H-RT groups for differences in a number of patient, disease and treatment characteristics. However, we could not control for additional therapeutic differences including the use of image-guided radiotherapy (IGRT). Retrospective studies have demonstrated IGRT can reduce late GU and GI toxicity (26-28). However, it is likely most men received IGRT in this cohort as a snapshot UK survey showed two-thirds of centres were using IGRT in March 2014, with this number likely to have increased over time (29). Furthermore, one would not expect there to be a significant difference in the use of IGRT across the H-RT and C-RT groups in the IMRT era. Although we report no difference in toxicity at 3 years, this may be too early to rule of later toxicity. However, one would expect some divergence in curves at 3 years if a difference were to exist later. Also, although we used a validated indicator to capture severe toxicity, we were unable to use our coding system to identify those who experienced less severe toxicity, which can still have an impact on quality of life. Finally, we did not have information about baseline bowel and urinary function of included patients but used and adjusted for the presence of a prior GI or GU procedure in the year before RT treatment, which acted as a surrogate for baseline function.

Clinical implications

The key benefits of hypofractionation are a shorter duration of treatment which increases patient convenience as well as a reduction in the use of RT resources which improves cost-effectiveness. However, avoidance of excessive toxicity is essential for hypofractionated regimens to be adopted into standard practice. Although large RCTs have demonstrated similar effectiveness with regard to early cancer control, there has been some uncertainty about treatment-related toxicity.

Our study, based on a large unselected "real-world" population has shown no difference in long-term GI and GU toxicity between C-RT and H-RT. Also given we captured severe toxicity (requiring hospital admission or an intervention which incurs a high cost) this further strengthens the cost-effectiveness of H-RT. Our findings support the growing evidence base for the use of H-RT in all men with non-metastatic PCa which has recently been advocated by both UK and international guidelines(30, 31).

Conclusions

This national population-based study has demonstrated that the use of H-RT in the radical management of PCa does not increase rates of severe GI or GU toxicity. Our findings strengthen recent guidelines supporting the use of H-RT in the management of non-metastatic PCa, especially in elderly men and those with locally advanced disease who were under-represented in the recent RCTs.

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Table 1: Patient, Disease and Treatment Characteristics of Men receiving Radical Radiotherapy (RT) (n=12,133)

	C-RT		H-RT		All men		
	n	**%**	**n**	**%**	**n**	**%**	**p-value**
No. of patients	9,106	75.1	3,027	24.9	12,133	100	
Treatment year							
2014	1,455	16	394	13	1,849	15.2	
2015	6,181	67.9	1,664	55	7,845	64.7	
2016	1,470	16.1	969	32	2,439	20.1	<0.001
Age (years)							
≤60	3,678	40.4	985	32.5	4,663	38.4	
61-70	2,621	28.8	840	27.8	3,461	28.5	
71-80	2,314	25.4	947	31.3	3,261	26.9	
>80	493	5.4	255	8.4	748	6.2	<0.001
Comorbidities							
0	6,950	76.3	2,220	73.3	9,170	75.6	
1	1,558	17.1	592	19.6	2,150	17.7	
≥2	598	6.6	215	7.1	813	6.7	0.003
Socioeconomic deprivation							
1	2,070	22.7	719	23.8	2,789	23	
2	2,206	24.2	626	20.7	2,832	23.3	
3	2,018	22.2	620	20.5	2,638	21.7	
4	1,532	16.8	573	18.9	2,105	17.3	
5	1,280	14.1	489	16.2	1,769	14.6	<0.001
Androgen deprivation							
No	1,669	18.3	758	25	2,427	20	
Yes	7,437	81.7	2,269	75	9,706	80	<0.001
Urinary procedure 1 year prior to RT							
No	7,283	80	2,299	75.9	9,582	79	
Yes	1,823	20	728	24.1	2,551	21	<0.001
Bowel procedure 1 year prior to RT							
No	8,638	94.9	2,881	95.2	11,519	94.9	
Yes	468	5.1	146	4.8	614	5.1	0.492
Cancer risk profile							
Locally advanced/High-risk	6,089	66.9	1,755	58	7,844	64.7	
Intermediate risk	2,923	32.1	1,193	39.4	4,116	33.9	
Low risk	94	1	79	2.6	173	1.4	<0.001
RT treatment region							
Prostate only	7,681	84.4	2,701	89.2	10,382	85.6	
Prostate & Pelvic LNs	1,425	15.6	326	10.8	1,751	14.4	<0.001

Table 2: Adjusted outcomes for GU and GI toxicity following radical radiotherapy: Conventionally fractionated (C-RT) vs hypofractionated regimen (H-RT).

	GI Toxicity				**GU Toxicity**			
	Rate (total events/100 person years)	3-year cumulative incidence (%)	sHR* (CI)	*p-value*	Rate (total events/100 person years)	3-year cumulative incidence (%)	sHR* (CI)	*p-value*
Conventionally fractionated Regimen (C-RT)	5.1	13.4	1.00	-	2.3	6.5	1.00	-
Hypofractionated Regimen (H-RT)	5.3	13.7	1.00 (0.89-1.13)	0.95	2.3	6.5	0.92 (0.77-1.10)	0.35

*sHR: subdistribution hazard ratios. Adjusted for year of RT, age, RCS Charlson comorbidity score, Socioeconomic deprivation, Prostate cancer risk group, previous GU/GI procedure 1 year prior to RT, RT treatment region.