TITLE

Toxicity of pelvic lymph node irradiation with intensity modulated radiation therapy for high-risk and locally advanced prostate cancer: a national population-based study using patient-reported outcomes.

RUNNING TITLE

Functional outcomes of pelvic lymph node IMRT.

KEYWORDS

Prostate cancer; intensity-modulated radiotherapy; pelvic lymph nodes; patient-reported outcomes measures.

ABSTRACT

Purpose: Little is known about the toxicity of additional pelvic lymph node irradiation in men receiving intensity-modulated radiotherapy (IMRT) for prostate cancer. The aim of this study was to compare patient-reported outcomes following IMRT to the prostate only (PO-IMRT) versus the prostate and pelvic lymph nodes (PPLN-IMRT).

Methods and Materials: Patients diagnosed with high-risk or locally advanced prostate cancer in the English National Health Service between April 2014 and September 2016 treated with IMRT were mailed a questionnaire at least 18 months after diagnosis. Patient-reported urinary, sexual, bowel and hormonal functional domains on a scale from 0 to 100 with higher scores indicating better outcomes and generic health-related quality of

life were collected using the EPIC-26 and EQ-5D-5L. We used linear regression to compare PPLN-IMRT versus PO-IMRT with adjustment for patient, tumour and treatment characteristics.

Results: Of the 7017 men who received a questionnaire, 5468 (77.9%) responded with 4196 (76.7%) having received PO-IMRT and 1272 (23.3%) PPLN-IMRT. Adjusted differences in EPIC-26 domain scores were smaller than 1 (*p* always >0.2) except for sexual function with men who had PPNL-IMRT reporting a lower mean score (adjusted difference 2.3, 95% confidence interval 0.9 to 3.7; p=0.002), which did not represent a clinically relevant difference. There was no significant difference in HRQoL (*p*=0.5).

Conclusions: Additional pelvic lymph node irradiation does not lead to clinically meaningful increases in the toxicity of IMRT for prostate cancer according to patient-reported functional outcomes and HRQoL.

INTRODUCTION

In the UK, the National Institute for Health and Care Excellence currently recommends considering pelvic lymph node (PLN) irradiation for patients with a high risk of nodal involvement (Roach score ≥15%) (1). However, according to results of the National Prostate Cancer Audit (NPCA), only 18% of men undergoing radiotherapy between 2010 and 2013 with high-risk or locally advanced prostate cancer had PLN irradiation (2).

Recently published results from the STAMPEDE trial support the routine use of radiotherapy in men with non-metastatic prostate cancer who have positive PLNs, where conformal or intensity-modulated radiotherapy was used (3). The 10-year follow-up results of the NRG/RTOG 9413 trial indicate a benefit of PLN irradiation in terms of progression-free

survival when used alongside androgen deprivation therapy (ADT) (4, 5), but results of other randomised controlled trials were inconclusive (6, 7). The relevance of all these trials is somewhat limited, given that they were conducted in the pre-dose-escalation era when radiotherapy doses did not exceed 64 Gy and intensity-modulated radiotherapy (IMRT) was not used.

The use of PLN irradiation in clinical practice is limited, most likely because of concerns about its worse toxicity compared to prostate-only (PO) radiotherapy. However, we recently demonstrated that there is no evidence of an association between additional PLN irradiation and severe gastrointestinal (GI) and genitourinary (GU) toxicity within three years of IMRT. Our study included 3845 men diagnosed with prostate cancer between 2010 and 2013 in England and used clinical measures of toxicity derived from linked national cancer registry, radiotherapy and administrative hospital data (8, 9).

To date, studies have not used patient-reported outcome measures (PROMs) to compare patient groups who received IMRT with and without PLN irradiation. Studies using PROMs are needed because clinical measures based on clinical diagnostic and procedure data do not always fully capture the outcomes that are relevant to patients (10). We used data collated for the National Prostate Cancer Audit to compare patient-reported functional outcomes in patients, with high-risk or locally advanced prostate cancer, who had IMRT to either the prostate only or the prostate and pelvic lymph nodes (PPLN-IMRT).

MATERIAL AND METHODS

Patient population

This study used NPCA data derived from English Cancer Registry data (11), the National Radiotherapy Dataset (RTDS) (12) and Hospital Episode Statistics (HES) (13) to identify men who were diagnosed with prostate cancer between 1st April 2014 and 30th September 2016 and treated with radical radiotherapy. The International Classification of Diseases 10th Edition code 'C61' and cancer stage information from the cancer registry data was used to identify men with prostate cancer and the Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4 code 'X671'in the RTDS was used to identify men who had received IMRT (14). 22,866 men with non-metastatic prostate cancer who received IMRT could be identified in this way **(Figure 1)**.

Prostate cancer risk was based on TNM stage, Gleason score, and PSA level according to a modified D'Amico risk stratification algorithm developed previously by the NPCA (8, 15). Men were excluded if they had intermediate-risk disease (n = 7353), low-risk disease (n = 254) or if prostate cancer risk was unknown (n = 458).

The RTDS provided information on radiotherapy doses and number of attendances to classify each radiotherapy regimen. Men were excluded if they underwent a hypofractionated radiotherapy regimen (n = 4430), if they did not have a recognised radiotherapy regimen (n = 733), or if the radiotherapy treatment region could not be established (n = 53). Finally, men were excluded if they had moved or died (n = 71), or had received radiotherapy less than six months before completing the survey (n = 28). As a result, 7017 men were eligible for inclusion in the study.

Patient survey

Patient questionnaires were mailed out to men eligible for inclusion at least 18 months after diagnosis. Two reminders were sent out to non-responders 4 and 8 weeks after the initial mailing (**Supplementary Material A**). Median time from diagnosis to radiotherapy was 5.4 months (interquartile range [IQR]: 4.5 to 6.9) and 5.7 months (IQR: 4.7 to 7.8), and median time from radiotherapy to survey completion was 16.2 months (IQR: 13.8 to 22.1) and 15.1 months (IQR: 13.0 to 19.1) for the PO-IMRT and PPLN-IMRT groups, respectively.

The questionnaire included the Expanded Prostate Cancer Index Composite 26-item version (EPIC-26), a validated instrument to measure functional outcomes in men with prostate cancer in the following five domains: urinary incontinence, urinary irritation/obstruction and sexual, bowel, and hormonal function (16). Each domain contains between 4-7 items. Scores were summarised for each domain on a scale of 0 to 100 with higher scores representing better function. The questionnaire also includes the EuroQol (EQ-5D-5L) which describes generic health-related quality of life (HRQoL) based on five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with a score expressed on a scale with 0 representing ’death’ and 1 representing ’perfect health (17). Minimal clinically important differences (MCID), which are thresholds for clinically relevant differences, have been previously estimated for each EPIC-26 domain (urinary incontinence: 6 – 9 point change; urinary irritation/obstruction: 5 – 7 point change; sexual function: 10 – 12 point change; bowel function: 4 – 6 point change; and hormonal function: 4 – 6 point change) (18) and for the EQ-5D-5L (MCID threshold: 0.08) (19).

Study outcome

Primary outcomes were the five EPIC-26 domain scores and the EQ-5D-5L score according to treatment region (PO-IMRT versus PPLN-IMRT). Missing response data to individual questions were handled according to the specific guidelines for EPIC-26. An EPIC-26 domain score was still calculated if at least 80% of the items that comprise a domain summary score were available (20).

Explanatory variables

The RTDS was used to determine the radiotherapy treatment region (PO and PPLN). Given that PPLN-IMRT is usually divided into a PPLN dose and a PO boost dose, it was only possible to ascertain the total PPLN dose and not the isolated dose delivered to the PLNs. HES records were used to determine age, ethnicity, socioeconomic deprivation according to the Index of Multiple Deprivation (21), and the number of comorbid conditions according to the RCS Charlson Score (22). T-stage, N-stage, M-stage, Gleason score and PSA were identified from the cancer registry data. Information on ADT use and number of comorbid conditions was available from the patient survey. Comorbidity data from the patient surveys was used for the primary analysis and the RCS Charlson score from HES was only used for the comparison between survey responders and non-responders.

We identified GI and GU procedure codes in HES records of hospital admissions within one year before the start of radiotherapy as a proxy for baseline GI and GU function. The procedure codes were based on a previously developed coding framework, developed using administrative hospital records, to identify GI and GU toxicity of radiotherapy for prostate cancer (23). PROMs were not collected at the time of diagnosis as part of the NPCA

patient survey, but we adjusted for GI and GU procedures recorded within one year before radiotherapy instead.

The questionnaire in the second year of the study included three questions asking patients to recall urinary, bowel and sexual function at the time of diagnosis on a five-point scale ranging from “no problem” to “large problem” so that an assessment of function at the time of diagnosis could be made. 59%, 59% and 57% of the included men had available recall results for baseline urinary, bowel and sexual function.

Statistical analysis

Multivariable linear regression was used to compare outcomes (EPIC-26 domain and EQ-5D-5L scores) between the PO-IMRT and PPLN-IMRT groups. The comparison was adjusted for patient characteristics (treatment year, age, ethnicity, socioeconomic deprivation status [national quintiles], number of comorbidities [0, 1 or ≥2], pre-treatment GI and GU procedures, ADT use, and time between RT and completion of survey (6-12, 12-18 and >18 months). A random intercept was modelled for each hospital to represent clustering of outcomes within hospitals. Missing values for adjustment variables (ethnicity) and outcomes were imputed using multiple imputation by chained equations so that we could include all survey responders. 25 data sets were created and Rubin’s rules were used to combine the estimates. All analyses were performed using Stata version 14.

RESULTS

Survey response

Of the 7017 men eligible for inclusion in the study, 5468 (77.6%) responded. Responders tended to be older, more frequently of a white ethnic background, from less socially deprived areas and have fewer comorbidities, than non-responders. There were no differences in response rates between PO-IMRT and PPLN-IMRT groups (**Supplementary Material B**).

Patient population

Of the 5468 responders, 1272 (23.3%) received PLN irradiation (**Table 1**). There were only small differences in patient characteristics between the PO-IMRT and PPLN-IMRT groups. The median dose per fraction and total dose to the prostate were the same in both groups (2 Gy per fraction and 74 Gy, respectively). Men receiving PPLN-IMRT were more likely to have received ADT (83.4%) than men receiving PO-IMRT (78.6%). There were only little differences between the PO-IMRT and PPLN-IMRT groups in the frequency of men who had received GU procedures (21.0% and 22.5%, respectively) or GI procedures (5.4 and 4.8%, respectively) within one year before the start of radiotherapy.

There were no relevant differences between the PO-IMRT and the PPLN-IMRT groups in their recall of bowel and sexual function at the time of diagnosis. Of those who had PO-IMRT, 2.0% and 21.2% rated their bowel and sexual function as a “large problem”, respectively, with corresponding percentages for those who had PPLN-IMRT being 1.8% and 19.5%, respectively. However, more men who had PPLN-IMRT rated their urinary function at the time of diagnosis a “large problem” (16.1%) than men who had PO-IMRT (12.9%).

Outcome measures

Mean EPIC-26 scores were between 85.5 and 86.8 for urinary and bowel function domains. Scores were lower for hormonal function (PPLN-IMRT: 65.3; PO-IMRT: 70.3) and very low for sexual function (PPLN-IMRT: 13.0; PO-IMRT: 14.1) (**Table 2**).

The PPLN-IMRT group had a lower mean EPIC-26 sexual function score than the PO-IMRT group but the difference was small (adjusted difference 2.3, 95% confidence interval 0.9 to 3.7), and did not meet the recognised threshold for a clinically relevant difference (**Table 2**). Differences in the other EPIC-26 domain scores between the treatment groups (urinary incontinence, urinary irritation/obstruction, bowel function and hormonal function) were small (always < 1) and not statistically significant. EQ-5D-5L scores were not statistically different between groups either (both 0.84), where a clinically meaningful difference corresponds to a difference of at least 0.08 (19).

DISCUSSION

There were no clinically relevant differences in function or generic HRQoL between men who were treated with either PO-IMRT or PPLN-IMRT, according to outcomes they reported themselves at least 18 months after being diagnosed with high-risk or locally advanced prostate cancer. This is the first study to use PROMs to compare PO and PPLN irradiation using modern dose-escalation techniques showing that additional irradiation of the PLNs does not increase long-term toxicity.

Comparison with other studies

Three relatively small studies have previously used PROMs to assess the toxicity of additional PLN irradiation. Two of these studies used 3D-conformal radiotherapy and did not find clinically relevant differences in HRQoL between 12 and 24 months after the end of radiotherapy. The first was a randomised controlled trial of 444 patients published in 2007, and the second was a cohort study of 120 patients published in 2011 (7, 24). The third study was a cohort study of 120 patients, and published in 2014, which used IMRT to treat the PLNs and 3D-conformal radiotherapy to treat the prostate (25). This study found that urinary and bowel function were worse for the PPLN group at three months after radiotherapy but function was comparable at 12 months, representing a difference in acute toxicity which resolved over time.

Results from studies using clinician-reported outcome measures are in line with the studies using PROMs. One small cohort study of 277 patients, using IMRT to treat the prostate and a four-field technique for the PLNs, showed that there were no longer-term differences between those who did and did not have PLN irradiation (26). Similarly, a study that we carried out recently, using linked national datasets, to compare 3065 men who had PO-IMRT and 780 who had PPLN-IMRT found no evidence of differences in GI or GU toxicity 3 years after diagnosis (2).

Strengths and Limitations

The strengths of the current study include the relatively large number of patients (n=5468), the high response rate to the survey (78%), and the use of validated instruments to collect PROMs at a specified time after diagnosis. It is the largest study to date comparing functional outcomes and generic HRQoL in patients who had PO-IMRT and those who had

PPLN-IMRT. A further strength is that we used recent national datasets which ensures that our results are fully representative of modern-day clinical practice.

The main limitation of the study was the lack of baseline PROMs (EPIC-26 and EQ-5D-5L scores) at the time of diagnosis but the regression analyses were still adjusted for important patient characteristics and prior GI and GU procedures. Therefore the impact of including baseline PROMs in the models is likely to be small given that they will only be supplying additional adjustment over and above what is already captured. We also included three questions in the patient survey asking patients to recall their baseline urinary, bowel and sexual function. Our results show that more men who had PPLN-IMRT rated their urinary function at the time of diagnosis as a "large problem" compared to men who had PO-IMRT. If there was residual confounding present due to this difference in baseline urinary function we would expect the observed results to indicate worse urinary function after PPLN-IMRT compared to PO-IMRT. Given that this is not the case, residual confounding is likely to be small and further supports the interpretation of our findings that additional PLN irradiation does not increase long-term toxicity compared to PO-IMRT. In addition, for 57% of the study cohort where recalled baseline function results were available, a sensitivity analysis was performed adjusting for these additional variables and results were the same as the overall study results.

Although the response rate was high for a national patient survey, we need to consider the potential impact of selective non-response. It is important to note that the response rates did not vary between the PO-IMRT and PPLN-IMRT groups. Also, the differences we report are adjusted for patient characteristics which have been shown to be associated with survey response (age and comorbidity), which further reduces the impact of selective non-response on our results.

Clinical implications

The life expectancy of men with prostate cancer is increasing and as a result men are living longer with their disease as well as with their treatment-related side effects (27, 28). PROMs are therefore providing essential information for the evaluation of the benefits and harms of radical prostate cancer treatment (29, 30).

We did not find evidence that PPLN-IMRT is associated with clinically relevant differences in longer-term functional outcomes or HRQoL. This suggests that PPLN-IMRT should be considered in patients with high-risk or locally advanced prostate cancer, especially given emerging evidence that relapse patterns are often nodal-centric (31). In addition, with the advent of molecular imaging, men can be more appropriately assessed with respect to lymph node involvement. This will improve decision making with regards to the inclusion of pelvic lymph nodes within the radiation field as part of primary treatment or when used in the salvage setting.

CONCLUSION

There are no clinically relevant differences in functional outcomes or HRQoL in men with high-risk or locally advanced prostate cancer who undergo PO-IMRT or PPLN-IMRT.

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Figure 1. Flowchart of patient selection