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Treatment-Related Toxicity Using Prostate-Only Versus Prostate and Pelvic Lymph Node Intensity-Modulated Radiation Therapy: A National Population-Based Study

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PURPOSE There is a debate about the effectiveness and toxicity of pelvic lymph node (PLN) irradiation for the treatment of men with high-risk prostate cancer. This study compared the toxicity of intensity-modulated radiation therapy (IMRT) to the prostate and the pelvic lymph nodes (PPLN-IMRT) with prostate-only IMRT (PO-IMRT).

MATERIALS AND METHODS Patients with high-risk localized or locally advanced prostate cancer treated with IMRT in the English National Health Service between 2010 and 2013 were identified by using data from the Cancer Registry, the National Radiotherapy Dataset, and Hospital Episode Statistics, an administrative database of all hospital admissions. Follow-up was available up to December 31, 2015. Validated indicators were used to identify patients with severe toxicity according to the presence of both a procedure code and diagnostic code in patient Hospital Episode Statistics records. A competing risks regression analysis, with adjustment for patient and tumor characteristics, estimated subdistribution hazard ratios (sHRs) by comparing GI and genitourinary (GU) complications for PPLN-IMRT versus PO-IMRT.

RESULTS Three-year cumulative incidence in the PPLN-IMRT (n = 780) and PO-IMRT (n = 3,065) groups was 14% for both groups for GI toxicity, and 9% and 8% for GU toxicity, respectively. Patients receiving PPLN-IMRT and PO-IMRT had similar levels of severe GI (adjusted sHR, 1.00; 95% CI, 0.80 to 1.24; *P* = .97) and GU (adjusted sHR, 1.10; 95% CI, 0.83 to 1.46; *P* = .50) toxicity rates.

CONCLUSION Including PLNs in radiation fields for high-risk or locally advanced prostate cancer is not associated with increased GI or GU toxicity at 3 years. Additional follow-up is required to answer questions about its impact on late GU toxicity. Results from ongoing trials will provide insight into the anticancer effectiveness of PLN irradiation.

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INTRODUCTION

The combination of prostate radiotherapy (RT) with androgen deprivation therapy is well established as treatment for intermediate-risk, high-risk, and locally advanced prostate cancer.¹ One particular area of interest for RT is whether pelvic lymph nodes (PLNs) should be included in radiation fields for high-risk cases. In the United Kingdom, the National Institute for Health and Care Excellence currently recommends PLN irradiation only for patients with a high risk of nodal involvement, but there is no clear standard to follow.¹

All randomized controlled trials (RCTs) to date have shown no clinically important differences in cancer outcomes. However, several limitations have been highlighted, such as the inclusion of low-risk men and differences in duration of hormonal treatment.²⁻⁴ The recent update of the Radiation Therapy Oncology

Group RTOG-9413 trial demonstrates the benefit of PLN irradiation at 10 years but only when it is used alongside neoadjuvant hormone therapy, which represents an important but somewhat unusual interaction between field size and neoadjuvant or adjuvant hormone use.^{4,5} It is also important to note that those trials were conducted before the dose-escalation era by using conventional four-field or 3D-conformal techniques, which are becoming more and more outdated in prostate cancer. Results from three RCTs that used intensity-modulated radiation therapy (IMRT) and dose escalation are awaited to confirm the effectiveness of PLN irradiation in achieving cancer control.⁶⁻⁸

External beam RT to the prostate gland is associated with both GI and genitourinary (GU) complications. However, results are mixed regarding whether the addition of PLN irradiation, and consequently the inclusion of a larger volume of normal tissue in the

ASSOCIATED CONTENT

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treatment field, confers worse toxicity. Studies to date have been relatively small, and until recently, IMRT was not used.^{3,5,9-16} Because IMRT is now the accepted standard for primary prostate RT, historic data on the effectiveness and toxicity after 3D-conformal techniques have limited value.¹⁷ There is currently no comparative data on how PLN-IMRT affects toxicity.

PLN irradiation features in contemporary guidelines for selected high-risk prostate cancer cases. Thus, knowledge of treatment toxicity is particularly important, given the ongoing debate surrounding its optimal use.¹ For this study, we used linked national data sets to quantify how prostate and pelvic lymph node IMRT (PPLN-IMRT) alters the toxicity that patients' experience compared with those who receive prostate-only IMRT (PO-IMRT).

MATERIALS AND METHODS

Patient Population

This study used English Cancer Registry data,¹⁸ the National Radiotherapy Dataset (RTDS),¹⁹ and Hospital Episode Statistics (HES),²⁰ linked at the patient level to observe men who were diagnosed with prostate cancer and treated with radical RT between January 1, 2010, and December 31, 2013. The International Classification of Diseases 10th Edition²¹ code C61 was used to identify men with prostate cancer in the cancer registry data set.

In all, 10,569 men receiving IMRT for nonmetastatic prostate cancer were identified using the Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4 code X671²² in the RTDS. The cohort was stratified according to a modified D'Amico risk stratification algorithm developed previously by the National Prostate Cancer Audit to account for the absence of prostate-specific antigen information.¹⁷ Figure 1 shows exclusions, which resulted in a final cohort of 3,845 men with high-risk or locally advanced prostate cancer.

Study Outcome

We used previously validated performance indicators to identify men who experienced any urinary or bowel-related toxicity after RT that was severe enough to require a diagnostic or therapeutic procedure.²³ GI or GU toxicity was defined as the presence of both a diagnostic code, according to the International Classification of Diseases 10th Edition,²¹ and a procedure code, according to the Office of Population Censuses and Surveys Classification of Surgical Interventions and Procedures Version 4,²² in a patient's HES record that were related to complications after RT. This is comparable to at least grade 3 toxicity, according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE).²⁴ GU toxicity included a procedure of the lower urinary tract alongside a diagnosis of either hematuria, cystitis, GU obstruction, retention, stricture, or incontinence. GI toxicity included an endoscopic procedure or an anal or peri-anal operation alongside a relevant diagnosis for

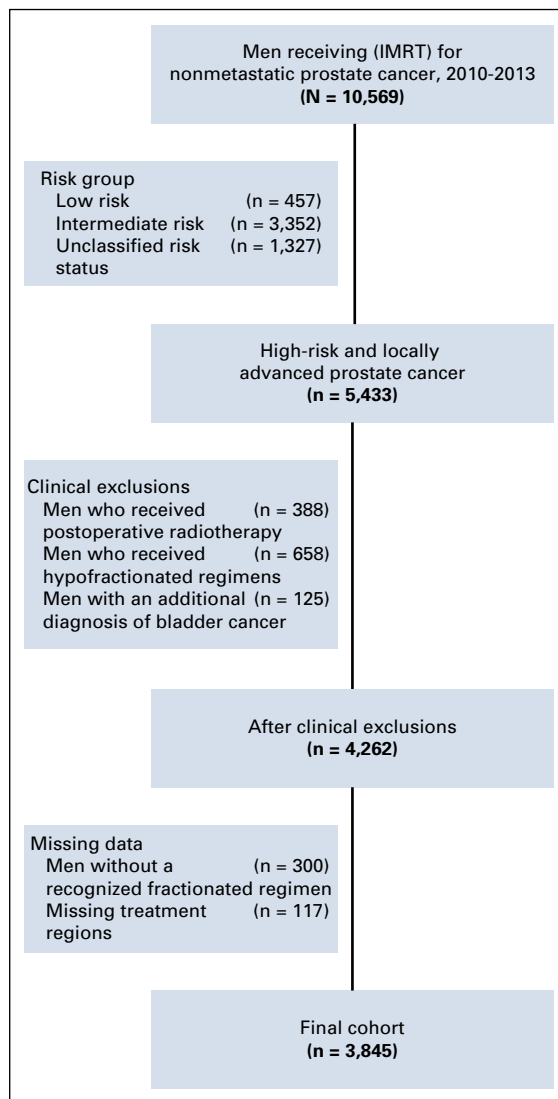


FIG 1. Flowchart of patients included in study. IMRT, intensity-modulated radiation therapy.

gastroenteritis, colitis, proctitis, lower GI fistula, stenosis, ulcer, or hemorrhage. The primary outcomes were the proportion of men experiencing a GI or GU complication from the date of their initial RT. Patients were observed until December 31, 2015. Baseline GI and GU function was estimated on the basis of the presence of a GI or GU procedure code in the HES record up to 1 year before the start of RT.²³

Explanatory and Control Variables

The RTDS was used to provide information on the RT field (PO and PPLN). Given that PPLN-RT 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. Data items in the HES records were used to determine age, comorbidities, and socioeconomic deprivation status. The Royal College of Surgeons Charlson score was used to identify any comorbid conditions coded

in the HES records within 1 year of diagnosis.²⁵ Socioeconomic deprivation status was determined for patients from the English 2012 Index of Multiple Deprivation on the basis of their area of residence and divided according to quintiles of the national distribution.²⁶ T stage, N stage, M stage, and Gleason score were identified from the Cancer Registry data to enable disease staging.

Statistical Analysis

We compared patient and tumor characteristics at baseline using χ^2 tests. The 3-year cumulative incidences of both GI and GU complications were calculated by using a competing risks method in which death was the competing event.²⁷ We also calculated incidence rates using total events per 100 person-years, which took account of death as the competing event.

A competing risks regression analysis, according to Fine and Gray²⁸ via maximum likelihood, was used to estimate subdistribution hazard ratios (sHRs) with 95% CIs comparing the risk of GI or GU complications between PO-IMRT and PPLN-IMRT groups. Men were censored at the end of follow-up, and the regression analysis was adjusted for patient and tumor characteristics. Missing values for deprivation status ($n = 31$), T stage ($n = 188$), N stage ($n = 723$), and Gleason score ($n = 104$) were imputed using multiple imputation by chained equations. In all, 50 data sets were created, and Rubin's rules were used to combine the sHRs. Wald tests were used to calculate P values with significance set at $P < .05$.

RESULTS

Patient Population

Of the 3,845 included men with high-risk or locally advanced prostate cancer who received IMRT between 2010 and 2013, 20% ($n = 780$) received PLN irradiation (Table 1). The median age was 70 years (range, 44 to 88 years), and 21% had at least one comorbidity. The presence of specific comorbidities associated with anticoagulation use (myocardial infarction, peripheral vascular disease, and cerebrovascular disease) did not vary between PO-IMRT and PPLN-IMRT groups. In total, 75% had T3/T4 disease, 13% had N1 disease, and 61% had a Gleason score of 8 or greater. 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 be aged 70 years or younger, to be more socioeconomically deprived, and to have more advanced disease (T3/T4 disease, N1 disease and a Gleason score of 8 or greater) than men receiving PO-IMRT. Baseline measures of GI and GU procedures up to 1 year before RT were similar between study groups. Follow-up time was defined as the time to the end of follow-up for men who were still alive and free from GI or GU toxicity. Median follow-up

was 2.7 years for all men, 2.7 years for the PPLN-IMRT group, and 2.6 years for the PO-IMRT group.

Outcome Measures

Although GI complications were rare in the first 9 months, cumulative incidence curves show that both GI and GU toxicity were similar between the study groups throughout the study period (Figs 2 and 3). The 3-year cumulative incidence of GI complications was 14% (95% CI, 11% to 17%) in men who had PPLN-IMRT and 14% (95% CI, 13% to 15%) in men who had PO-IMRT. Men experienced 4.9 (95% CI, 4.0 to 5.9) GI complications per 100 person-years in the PPLN-IMRT group compared with 5.1 (95% CI, 4.6 to 5.6) in the PO-IMRT group. The 3-year cumulative incidence of GU toxicity was also comparable with 9% (95% CI, 7% to 11%) in the PPLN-IMRT group and 8% (95% CI, 7% to 9%) in the PO-IMRT group. Men experienced 3.2 (95% CI, 2.5 to 4.0) GU complications per 100 person-years in the PPLN-IMRT group compared with 2.7 (95% CI, 2.4 to 3.1) in the PO-IMRT group (Table 2).

An adjusted competing risk regression analysis showed that the incidence of GI toxicity in men receiving PPLN-IMRT was similar to that in patients receiving PO-IMRT (sHR, 1.00; 95% CI, 0.80 to 1.24; $P = .97$). GU toxicity was also similar between the two groups (sHR, 1.10; 95% CI, 0.83 to 1.46; $P = .50$; Table 2). There was no significant difference in toxicity rates according to age, treatment year, T stage, N stage, or Gleason score (Data Supplement).

Men with at least one comorbidity were more likely to experience GU toxicity than men with no comorbidities (sHR, 1.39; 95% CI, 1.07 to 1.79; $P = .01$), but there was no statistically significant effect of comorbidity on the GI toxicity rate (sHR, 1.18; 95% CI, 0.97 to 1.45; $P = .11$). In addition, men in the highest quintile of socioeconomic deprivation (most deprived) had lower GI toxicity compared with men in the lowest quintile (least deprived) (sHR, 0.68; 95% CI, 0.49 to 0.96; $P = .01$) but no such effect was observed for GU toxicity (Data Supplement).

DISCUSSION

The results indicate that the risk of severe GI or GU toxicity does not vary between patients receiving PPLN-IMRT and those receiving PO-IMRT. Within 3 years of IMRT, 14% of patients experienced severe grade 3 GI toxicity, and 8% experienced severe grade 3 GU toxicity (CTCAE), irrespective of whether the PLNs were included in the radiation field.

Previous studies in this area are limited, and their results are conflicting. Two RCTs have compared the toxicity of PO-RT with PPLN-RT and they had different results. The RTOG-9413 RCT, which included 1,323 patients and published its results at various time points (2006, 2007, and 2018), showed that PPLN irradiation compared with PO irradiation was associated with an increase in acute grade 2 GI and GU toxicity (47% vs 20% and 31% vs 22%,

TABLE 1. Patient, Tumor, and Treatment Characteristics for Those With High-Risk or Locally Advanced Prostate Cancer Receiving IMRT

Characteristic	All Patients (N = 3,845)		PO-IMRT (n = 3,065)		PPLN-IMRT (n = 780)		P
	No.	%	No.	%	No.	%	
Age group, years							< .01
< 65	299	7.8	204	6.7	95	12.2	
65-70	602	15.7	445	14.5	157	20.1	
70-75	2,091	54.4	1,693	55.2	398	51.0	
> 75	853	22.2	723	23.6	130	16.7	
No. of comorbidities (RCS Charlson score)							.93
0	3,032	78.9	2,416	78.8	616	79.0	
≥ 1	813	21.1	649	21.2	164	21.0	
Deprivation status (national quintiles)							.01
1 (least deprived)	932	24.4	712	23.5	220	28.2	
2	962	25.2	778	25.6	184	23.6	
3	822	21.6	674	22.2	148	19.0	
4	604	15.8	467	15.4	137	17.6	
5 (most deprived)	494	13.0	404	13.3	90	11.6	
Missing	31		30		1		
T stage							< .01
1	250	6.8	214	7.3	36	5.1	
2	682	18.7	574	19.5	108	15.2	
3	2,623	71.7	2,093	71.1	530	74.5	
4	102	2.8	65	2.2	37	5.2	
Missing	188		119		69		
N stage							< .01
0	2,706	86.7	2,285	90.2	421	71.6	
1	416	13.3	249	9.8	167	28.4	
Missing	723		531		192		
Gleason score							< .01
6	191	5.1	166	5.6	25	3.3	
7	1,257	33.6	1,041	34.9	216	28.5	
8	968	25.9	798	26.8	170	22.4	
9	1,263	33.8	932	31.3	331	43.6	
10	62	1.7	45	1.5	17	2.2	
Missing	104		83		21		
Treatment year							< .01
2010	140	3.6	85	2.8	55	7.1	
2011	322	8.4	234	7.6	88	11.3	
2012	897	23.3	736	24.0	161	20.6	
2013	2,486	64.7	2,010	65.6	476	61.0	
GI procedure 1 year before RT							.14
No	3,639	94.6	2,909	94.9	730	93.6	
Yes	206	5.4	156	5.1	50	6.4	
GU procedure 1 year before RT							.06
No	3,224	83.9	2,587	84.4	637	81.7	
Yes	621	16.2	478	15.6	143	18.3	

Abbreviations: GU, genitourinary; IMRT, intensity-modulated radiation therapy; PO, prostate only; PPLN, prostate and the pelvic lymph nodes; RCS, Royal College of Surgeons; RT, radiation therapy.

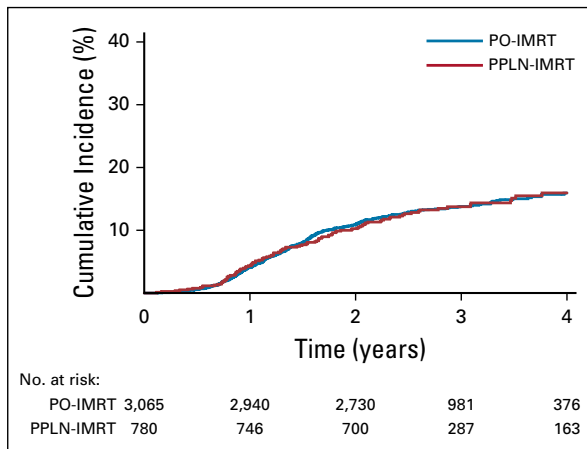


FIG 2. Cumulative incidence curves for GI toxicity after intensity-modulated radiation therapy (IMRT) to the prostate only (PO) or the prostate and pelvic lymph nodes (PPLNs).

respectively) and late grade 3 GI toxicity (7% vs 2%), according to the RTOG scale.^{4,5,16} In contrast, the Groupe Etude des Tumeurs Uro Genitales GETUG-01 RCT, which included 444 patients and was published in 2007, observed similar toxicity (according to the RTOG, Late Effects Normal Tissue Task Force, and Subjective, Objective, Management, Analytic scales), in which the observed increase in grade 2 GI toxicity with PPLN-RT was non-significant.³ A cohort study of 358 patients also showed similar levels of toxicity.¹³ In contrast to our study, these studies included patients treated with older conformal techniques, and therefore the relevance of their results are limited in their ability to inform the toxicity risk for patients treated with IMRT.

A further cohort study of 277 patients, published in 2009, was the first to include IMRT to treat the prostate but the older four-field technique was still used for the PLNs. The

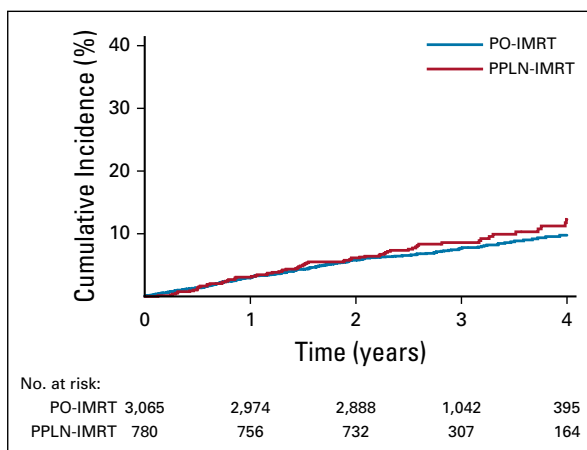


FIG 3. Cumulative incidence curves for genitourinary toxicity after intensity-modulated radiation therapy (IMRT) to the prostate only (PO) or the prostate and pelvic lymph nodes (PPLNs).

study authors reported an increased rate of acute GI toxicity (CTCAE) with PPLN-RT (75% vs 49% for grade 1 and 18% vs 7% for grade 2).⁹ There was no difference in late toxicity (90 days or more) after a median of 30 months, and severe toxicity was rare with only one patient experiencing late grade 3 toxicity. With exclusively IMRT and a much larger patient population, our findings indicate that severe toxicity (grade 3 or greater) is much more prevalent, and they highlight the strength of using robust outcome measures from routine data over the potential under-reporting of clinical measures.

Initial, small-scale, noncomparative reports of PPLN-IMRT of 40 and 70 patients have shown its favorable tolerability with no severe toxicity observed (acute or late).^{10,11} Results from a PPLN-IMRT dose-escalation study of 447 patients further indicate its safety.¹⁵ The authors found similar GI toxicity (grade 2 or greater) compared with the toxicity observed in men undergoing PO-IMRT in other study cohorts.

Several studies have used patient-reported outcome measures (PROMs) to compare toxicity in men undergoing PPLN-RT or PO-RT. First, the GETUG-01 RCT found that quality of life, according to PROMs taken at 12 and 24 months after conformal RT, was similar in both groups.³ Second, a prospective matched-pair cohort study of 120 patients (published in 2011) used the Expanded Prostate Cancer Index-26 (EPIC-26) questionnaire 16 months after conformal RT. The study found that bowel function scores were eight points lower on a scale from 0 to 100 in the PLN group than in the PO group and, although this was statistically significant, it did not represent a clinically significant difference.¹⁴ Third, a PROMs cohort study of 120 patients (published in 2014) compared patients who had PLN-IMRT in addition to conventional conformal RT to the prostate with those who had PO-RT. According to the University of California, Los Angeles Prostate Cancer Index, urinary and bowel function were worse for the PPLN group at 3 months, but they were comparable by 12 months.¹² This likely represents an increase in mild or moderate toxicity in the acute period with PPLN-RT that resolves over time. Our results indicate that in a large United Kingdom population with national coverage, not only is the 3-year risk of severe GI and GU toxicity the same, irrespective of treatment region, but the cumulative incidence as a function of time from the start of treatment is also similar.

Strengths of this population-based study include the relatively high volume of patients ($n = 3,845$), making it the largest comparative study to date assessing the toxicity of PPLN-RT and, to our knowledge, the first to include IMRT exclusively. Findings are also representative of real-world practice across England because our data included all National Health Service RT providers in the country. Patients who underwent RT in the private sector were not

TABLE 2. Adjusted Outcomes for GI and GU Toxicity After PO-IMRT or PPLN-IMRT

Toxicity Site	3-Year Cumulative Incidence (%)	95% CI	Rate (total events/100 person-years)	sHR	95% CI	P
GI toxicity						
PO-IMRT	13.8	12.6 to 15.2	5.05	1		—
PPLN-IMRT	13.8	11.4 to 16.5	4.89	1.00	0.80 to 1.24	.97
GU toxicity						
PO-IMRT	7.7	6.7 to 8.8	2.70	1		—
PPLN-IMRT	8.6	6.7 to 10.9	3.16	1.10	0.83 to 1.46	.50

Abbreviations: GU, genitourinary; IMRT, intensity-modulated radiation therapy; PO, prostate only; PPLN, prostate and the pelvic lymph node; sHR, subdistribution hazard ratio.

included, but they represent less than 10% of the case load nationally.²⁹

The indicators we used have been specifically developed and validated to identify RT-related complications severe enough to require a procedure (grade 3 or greater), which allowed us to measure toxicity at a specific severity level. The use of both diagnosis and procedure codes improved the validity of our indicators allowing us to better identify true toxicity. Previous studies using routine data, comparing IMRT with conformal RT, were limited by their use of only individual diagnosis, procedure, or claim codes to report toxicity.³⁰⁻³² Other strengths include the validated method to identify comorbidities in the HES record, which aids the reliability of our adjusted study estimates.²⁵ In addition, adjustments for previous GI and GU procedures allowed us to account for baseline procedures, which is often problematic when using routine data. All regression analyses were therefore adjusted for potential measurable confounders. Residual confounding could still be present, but given the small impact of adjusting for a wide range of confounders, this is likely to be minimal. Specific examples of unmeasurable factors associated with increased toxicity include anticoagulant use and treatment volumes, but because they are unlikely to vary between study groups, the potential bias from their exclusion is small.

The data collected in the RTDS was detailed regarding RT doses and patient attendances. We therefore only included men with a recognized RT regimen to ensure that the groups were comparable. A limitation of the RTDS is that it does not provide the exact RT dose administered to the PLNs, only the overall total dose. The PLN dose can vary among patients, but given that this variation is restricted to patients who underwent PPLN-IMRT, this variation is not a confounding factor for the difference between PO-IMRT and PPLN-IMRT groups.

A final limitation is the relatively short follow-up time. We demonstrated that GU toxicity rates are similar in patients who had PPLN-IMRT and PO-IMRT at 3 years after treatment. Additional GU toxicity events are likely to occur in later years, but this will introduce differences between the groups only if the occurrence of later toxicity events

depends on whether PPLN-IMRT or PO-IMRT was given. The short follow-up is a direct consequence of the inclusion of a contemporary population from 2010 onward to ensure that all patients were receiving IMRT. Using an earlier population with a longer follow-up would have included a number of patients who had 3D conformal RT, which could have confounded our results.

We did not find evidence that PPLN-IMRT leads to more severe GI and GU toxicity than PO-IMRT for men with high-risk or locally advanced prostate cancer. This indicates that PLN-RT should be considered for treating these men in line with current guidelines.¹ This is particularly relevant, given the recent evidence suggesting that the pattern of relapse after RT is more nodal-centric than previously thought, which emphasizes the importance of extending the treatment field to include the PLNs.³³ However, we do not know whether extending the radiation field leads to an increased rate of secondary malignancy. Because this long-term outcome requires more than 10 years of follow-up, we are unable to comment on this, but it is certainly an area for additional research.³⁴

Advances are currently being made in this area of RT. Phase II trials have already confirmed the tolerability of dose escalation and hypofractionation in PPLN-IMRT.^{15,35} More importantly, there are three RCTs being undertaken using IMRT that will confirm the definitive role of PLN irradiation in terms of cancer control, but these studies do not have sufficient statistical power to compare toxicity rates.⁶⁻⁸ Observational research can provide important information on adverse effects because it is likely to meet the underlying assumption that the allocation of patients to certain groups is unrelated to the occurrence of adverse effects, given that these are often unintended and unpredictable.³⁶

In conclusion, including PLNs in radiation fields for high-risk or locally advanced prostate cancer is not associated with increased GI or GU toxicity at 3 years and should be considered in this patient group. Follow-up beyond 3 years is required to answer questions about its impact on late GU toxicity. Definitive evidence in favor of better cancer control with PPLN-RT is needed to fully define its role.

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EQUAL CONTRIBUTION

M.G.P. and A.S. contributed equally to this work as first authors. J.v.d.M. and A.A. contributed equally to this work as senior authors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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All patient data used are fully anonymized and are therefore exempt from United Kingdom National Research Ethics Committee (NREC) approval. The use of English Cancer Registry data, the National Radiation Therapy Data Set and Hospital Episode Statistics was approved by the Confidentiality Advisory Group of the NHS Health Research Authority for the purpose of national clinical audit and health service evaluation (CAG 8-03[PR9]/2013).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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