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In patients with prostate cancer who have a high risk of pelvic nodal disease, the use of elective whole pelvis radiotherapy is still controversial. Two large, randomised, controlled trials (RTOG 9413 and GETUG-01) did not show a benefit of elective whole pelvis radiotherapy over prostate-only radiotherapy. In 2020, the POP-RT trial established the role of elective whole pelvis radiotherapy in patients who have more than a 35% risk of lymph node invasion (known as the Roach formula). POP-RT stressed the importance of patient selection. In patients with cN1 (clinically node positive) disease or pN1 (pathologically node positive) disease, the addition of whole pelvis radiotherapy to androgen deprivation therapy significantly improved survival compared with androgen deprivation therapy alone, as shown in large, retrospective studies. This patient population might increase in the future because use of the more sensitive prostate-specific membrane antigen PET–CT will become the standard staging procedure. Additionally, the SPORTT trial suggested a benefit of whole pelvis radiotherapy in biochemical recurrence-free survival in the salvage setting. A correct definition of the upper field border, which should include the bifurcation of the abdominal aorta, is key in the use of pelvic radiotherapy. As a result of using modern radiotherapy technology, severe late urinary and intestinal toxic effects are rare and do not seem to increase compared with prostate-only radiotherapy.

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Introduction

Although for many solid tumours, prophylactic elective lymph node irradiation is the standard of care, its use in high-risk prostate cancer is still highly controversial.[1–12] The main reason for this controversy is that none of the randomised controlled trials have shown an overall survival benefit of elective whole pelvis radiotherapy over prostate-only radiotherapy.[9] An exploratory post-hoc analysis of the Medical Research Council PR07 trial[13] confirmed that there was no benefit of whole pelvis radiotherapy. Reasons for this finding might not necessarily be due to the absence of a benefit, but might be the result of incorrect patient selection (in patients with low risk and positive pelvic nodes the benefit of whole pelvis radiotherapy is often absent),[4–6,8,9,11,14–16] inadequate treatment volume definition (not all pelvic nodal regions at risk were considered and consequently not irradiated),[2,4,5,7,9–11,14,15,17,18] inappropriate technology used,[3,10,19] an insufficient dose,[4,10–12,14,15,17,19,20] and inadequate use of concomitant and adjuvant androgen deprivation therapy.[9,11,17,20,21]

In 2014, Dirix and colleagues[2] published a systematic review on this issue, analysing seven contemporary retrospective studies from 2006 to 2011 on elective pelvic radiotherapy. The review suggested that whole pelvis radiotherapy increased disease-free survival in patients with an estimated risk of nodal involvement of 5–35%, according to the Roach formula. However, the three randomised trials analysed by Dirix and colleagues[2] gave insufficient evidence to support the use of prophylactic elective whole pelvis radiotherapy.

The decision to electively irradiate pelvic nodes is often based on a risk calculation using tables and formulas.[12,22,23] Results published from the POP-RT trial[11] in 2021, highlighted the importance of patient selection. This randomised controlled trial encompasses a patient population at high and very high risk of pelvic lymph node disease. Biochemical progression-free survival and distant metastasis-free survival (exploratory endpoints) significantly improved with whole pelvis radiotherapy compared with prostate-only radiotherapy. Notably, all patients who received androgen deprivation therapy were treated for 24 months, and 42 (19%) of 222 patients had an orchiectomy.

The purpose of this Review is to provide an update on the results from reported randomised trials and comment on published data between 2014 and 2021. We also provide advice for the use of radiotherapy in clinical practice.

Oncological outcomes

Table 1 gives an overview of prospective trials evaluating the value of whole pelvis radiotherapy in four different settings: (1) patients with cN0 (clinically node negative) disease and a substantial risk (term varies largely between studies)[1,3,7,8,11,14,20,24] of pathologically involved nodes in the primary setting, (2) patients with cN1 (clinically node positive) disease in the primary setting,[25–31] (3) patients with adjuvant pN1 (pathologically node positive) disease in the postoperative setting,[12,32–37] and (4) patients with pNx (unknown node status) and pN0 (pathologically node negative) disease in the postoperative salvage setting.[38–40]

Patients with cN0 disease in the primary setting

The RTOG 9413 trial[1] published updated results in 2018 and the GETUG-01 trial[7] published updated results in 2016. The primary endpoint of RTOG 9413 was progression-free survival. The 2×2 factorial design was used to evaluate the effect of whole pelvis radiotherapy and the timing of androgen deprivation therapy in patients with risk of lymph node invasion of more than 15%, according to the Roach formula. 1322 patients were randomly assigned to one of four groups: whole pelvis radiotherapy or prostate-only radiotherapy, both groups with 2 months of neoadjuvant androgen deprivation therapy (continued during radiotherapy), or whole pelvis radiotherapy or

	Study design	Number of patients	Lymph node invasion risk	Treatment groups	Primary endpoint	Median follow-up, months
Patients with cN0 disease in the primary setting						
RTOG 9413 trial[1]	RCT	1322	All patients >15% (Roach formula)	2 × 2 design, neoadjuvant hormonal treatment versus adjuvant hormonal treatment and whole pelvis radiotherapy versus prostate-only radiotherapy	Progression-free survival	108
GETUG-01 trial[7]	RCT	446	45% patients >15%	Whole pelvis radiotherapy versus prostate-only radiotherapy, 4–8 months of hormonal treatment	Event-free survival	104
POP-RT trial[11]	RCT	224	All patients >20% (Roach formula), median risk 38%	Whole pelvis radiotherapy versus prostate-only radiotherapy, 24 months of hormonal treatment	Biochemical progression-free survival	68
Tharmalingam et al[14]	Cohort	812	Not specified	Brachytherapy boost after prostate-only radiotherapy versus whole pelvis radiotherapy, hormonal treatment variable	Biochemical progression-free survival	56
PIVOTAL trial[3]	RCT	124	All patients ≥30% (Roach formula)	Prostate-only radiotherapy versus whole pelvis radiotherapy, 6–9 months of hormonal treatment	Toxicity, quality of life	24
Morris et al[24]	RCT	398	Not specified	Whole pelvis radiotherapy plus boost (external beam radiotherapy *vs* low-dose rate brachytherapy), 12 months of hormonal treatment	Biochemical progression-free survival	78
Amini et al[20]	Retrospective	14 817	Not specified	Whole pelvis radiotherapy versus prostate-only radiotherapy (with or without brachytherapy), hormonal treatment variable	Overall survival	81
Sandler et al[8]	Retrospective	1170	17% in the companion cohort (Gleason grade group 5)	Whole pelvis radiotherapy versus prostate-only radiotherapy (with or without brachytherapy), hormonal treatment variable	Biochemical relapse-free survival, distant metastasis-free survival, and prostate cancer-specific survival	61 (without brachytherapy); 76 (with brachytherapy)
Patients with cN1 disease in the primary setting						
Lin et al[25]	Retrospective	3540	..	Hormonal treatment with or without whole pelvis radiotherapy	Overall survival	62 (2004–06); 32 (2004–11)
Bryant et al[26]	Retrospective	648	..	Hormonal treatment with or without whole pelvis radiotherapy, hormonal treatment variable	Prostate cancer-specific survival and overall survival	62
Seisen et al[27]	Retrospective	2967	..	Local radical prostatectomy or local radiotherapy with or without hormonal treatment	Overall survival	50
Tsuchida et al[28]	Retrospective	51	..	Whole pelvis radiotherapy (single arm), hormonal treatment variable	Biochemical progression-free survival, distant metastasis-free survival, prostate cancer-specific survival, and overall survival	88
Mallick et al[29]	Retrospective	61	..	Whole pelvis radiotherapy (single arm), 24–36 months of hormonal treatment	Toxicity, biochemical progression-free survival, and overall survival	48
Telkhade et al[30]	Retrospective	60	..	Whole pelvis radiotherapy (single arm; 57 of 60 patients), hormonal treatment variable	Biochemical progression-free survival, disease-free survival, and overall survival	30
James et al[21]	Cohort	721	..	Hormonal treatment with or without whole pelvis radiotherapy	Failure-free survival and overall survival	17

(Table 1 continues on next page)

prostate-only radiotherapy, both followed by 4 months of adjuvant androgen deprivation therapy. Dose prescription was standard at the start of the study: prostate to 70·2 Gy (39 fractions) and pelvis to 50·4 Gy (28 fractions).[1] After a median follow-up of nearly 9 years, all groups had low 10-year estimates of progression-free survival, and the highest progression-free survival (30%) was with prostate-only radiotherapy plus adjuvant androgen deprivation therapy. However, neoadjuvant androgen deprivation therapy plus whole pelvis radiotherapy and adjuvant androgen deprivation therapy plus prostate-only radiotherapy had significantly better 10-year progression-free

	Study design	Number of patients	Lymph node invasion risk	Treatment groups	Primary endpoint	Median follow-up, months
(Continued from previous page)						
Patients with pN1 disease in the primary setting						
Touijer et al[32]	Retrospective	1338	..	Radical prostatectomy plus pelvic lymph node dissection plus observation versus hormonal treatment versus external beam radiotherapy and hormonal treatment	Overall survival	69
Gupta et al[33]	Retrospective	8074	..	Radical prostatectomy plus pelvic lymph node dissection plus observation versus hormonal treatment versus whole pelvis radiotherapy and hormonal treatment	Overall survival	52
Jegadeesh et al[34]	Retrospective	2569	..	Radical prostatectomy plus hormonal treatment with or without whole pelvis radiotherapy	Overall survival	53
Van Hemelryk et al[35]	Retrospective	69	..	Pelvic lymph node dissection plus radiotherapy (plus whole pelvis radiotherapy, if pN1)	Biochemical progression-free survival, clinical progression-free survival, and prostate cancer-specific survival	60
Poelaert et al[36]	Retrospective	154	..	Pelvic lymph node dissection plus prostate-only radiotherapy plus hormonal treatment (pN0) versus pelvic lymph node dissection plus whole pelvis radiotherapy plus hormonal treatment (pN1)	Biochemical relapse-free survival	55
Abdollah et al[37]	Retrospective	1107	..	Radical prostatectomy plus pelvic lymph node dissection plus hormonal treatment with or without whole pelvis radiotherapy	Prostate cancer-specific survival and overall survival	85
Blanchard et al[12]	RCT	413	..	Hormonal treatment versus hormonal treatment plus chemotherapy, pelvic lymph node dissection plus prostate-only radiotherapy (pN0) or whole pelvis radiotherapy (pN1)	Biochemical progression-free survival	38
Postoperative salvage setting						
Song et al[38]	Retrospective	163	..	Radical prostatectomy followed by salvage radiotherapy; prostate bed radiotherapy versus whole pelvis radiotherapy	Biochemical progression-free survival	57
Ramey et al[39]	Retrospective	1861	..	Radical prostatectomy with or without pelvic lymph node dissection then salvage radiotherapy; prostate bed radiotherapy with or without hormonal treatment versus whole pelvis radiotherapy with or without hormonal treatment	Biochemical progression-free survival and distant metastasis-free survival	51
Pollack et al[40]	RCT (abstract)	1792	..	Prostate bed radiotherapy versus prostate bed radiotherapy plus short-term hormonal treatment versus whole pelvis radiotherapy plus prostate bed radiotherapy plus short-term hormonal treatment	Failure-free survival	65

RCT=randomised controlled trial. cN0=clinical node negative. cN1=clinical node positive. pN1=pathological node positive.

Table 1: **Overview of trials on whole pelvis radiotherapy in different settings**

survival than adjuvant androgen deprivation therapy plus whole pelvis radiotherapy and neoadjuvant androgen deprivation therapy plus prostate-only radiotherapy.

GETUG-01 randomly assigned 446 patients with T1–T3N0 disease to either whole pelvis radiotherapy or prostate-only radiotherapy, plus 4–8 months of androgen deprivation therapy for both groups. 203 (45%) of 446 in the trial population had a lymph node invasion risk of more than 15%. The decision to start androgen deprivation therapy was at the discretion of the physician and was initiated in 199 (56%) of 354 patients at high risk. After a median follow-up of 11·4, there was no difference in overall survival (75% with whole pelvis radiotherapy *vs* 74% with

prostate-only radiotherapy) or the primary endpoint, which was event-free survival (58% *vs* 56%).[7]

Recently, the oncological results and data on late toxicity from the POP-RT trial were published.[10,11] This trial, in which 224 patients were enrolled and randomly assigned (1:1) to receive either prostate-only radiotherapy or whole pelvis radiotherapy, might help to inform which patients benefit the most from whole pelvis radiotherapy. The inclusion criteria differed from the RTOG 9413 and GETUG-01 trials in that patients were eligible only if the risk of nodal involvement—calculated using the Roach formula—exceeded 20%. The median risk of pelvic lymph node involvement was 38% (IQR 25–53). Almost half (103 [46%]) of 222 patients had more than 40% risk of pelvic nodal involvement, reflecting the very high risk population enrolled in this study. Another difference compared with the RTOG 9413 and GETUG-01 trials was the long-term use of androgen deprivation therapy (24 months). Notably, 42 (19%) patients received an orchiectomy which might introduce bias, although patients were stratified based on the type of androgen deprivation therapy. Although we support the use of long-term androgen deprivation therapy in these patients, orchiectomy should no longer be considered as the standard of care in view of the severe morbidity resulting from lifelong castration.[41] After a median follow-up of 68, biochemical progression-free survival was significantly longer with whole pelvis radiotherapy than with prostate-only radiotherapy (95% *vs* 81%; p<0·0001). A similar significant difference was observed for disease-free survival (90% with whole pelvis radiotherapy *vs* 77% with prostate-only radiotherapy; p=0·002) and distant metastasis-free survival (95% *vs* 88%; p=0·01). Notably, most patients (80%) included in this trial were staged with prostate-specific membrane antigen (PSMA) PET–CT.[11]

A prospective, multicentre, cohort study analysed 812 patients, who received high-dose rate brachytherapy (single fraction of 15 Gy). Before the high-dose rate boost application, group A received prostate-only radiotherapy (37·5 Gy in 15 fractions) and group B received additional whole pelvis radiotherapy (46 Gy in 23 fractions). Patients who received whole pelvis radiotherapy (286 [71%] of 401) had treatment with androgen deprivation therapy for substantially longer (>18 months) than those who received prostate-only radiotherapy (194 [47%] of 411).[14] After a median follow-up of 4·7 years, high-risk patients who received whole pelvis radiotherapy had a significantly better 5-year biochemical progression-free survival than did patients who received prostate-only radiotherapy (84% *vs* 77%; p=0·001). This benefit was not maintained in the intermediate-risk group (91% *vs* 90%; p=0·92).

Patients with cN1 disease in the primary setting

When suspected positive pelvic nodes are present on CT imaging, adding whole pelvis radiotherapy to androgen deprivation therapy significantly improves survival.[25–27,31] With the advent of modern biological imaging techniques, such as PSMA PET–CT, the likelihood that pelvic nodes will be found earlier, more frequently, and will be more widespread is high, as shown in several trials.[27,42–45] In patients with cN1 disease in the primary setting, androgen deprivation therapy is standard management and, in our opinion, whole pelvis radiotherapy should always be added, including the application of a simultaneously integrated boost to PSMA PET-positive nodes. Concerning future trials and clinical applications, there seems to be a relationship between the dose to the enlarged pelvic nodes, long-term progression-free survival, and distant metastasis-free survival. A dose of more than 60 Gy in 2 Gy fractions is recommended.[28]

Patients with pN1 disease in the postoperative setting

Despite technological improvements in diagnostic imaging, an extended pelvic lymph node dissection is still the most accurate staging procedure after radical prostatectomy,[4,12,23,35,46–48] as mentioned in the European Association of Urology guidelines.[49] When a pelvic lymph node dissection reveals pathologically positive lymph nodes, the prognosis worsens and, in our opinion, postoperative whole pelvis radiotherapy should be added to androgen deprivation therapy,[12,32–34] especially for patients with between two and four positive nodes after nodal dissection.[37] Prostate cancer-specific survival and overall survival are significantly increased when androgen deprivation therapy is combined with whole pelvis radiotherapy compared with androgen deprivation therapy alone.[33,34,37] When volumetric-modulated arc therapy plus 24–36 months of androgen deprivation therapy were given to patients with pN1 disease, the median biochemical progression-free survival was 88 months and clinical progression-free survival was 92 months, and the toxicity was acceptable. Moreover, relapses in the irradiated pelvic lymph node areas were absent.[36] Patients presenting with two or less pathologically positive pelvic lymph nodes had similar biochemical and clinical progression-free survival compared with high-risk patients with pN0 disease, whereas prostate cancer-specific mortality did not differ between patients with pN0 and pN1 disease.[35] Severe toxicity was not higher with whole pelvis radiotherapy than with prostate-only radiotherapy.[12,35]

The postoperative salvage setting

In cases of biochemical recurrence after prostatectomy and in the absence of distant metastasis, early salvage radiotherapy is the only treatment that has proven to be effective.[38,39] Several published retrospective and prospective trials[38–40] advocate to include pelvic nodes in the salvage radiation field. Song and colleagues[38] reported a 20% increase in biochemical progression-free survival with salvage whole pelvis radiotherapy compared with prostate-bed radiotherapy in patients receiving salvage radiotherapy after radical prostatectomy (prostate-specific antigen [PSA] ≥0·4 ng/mL). Ramey and colleagues[39]

reported a similar benefit in 5-year biochemical progression-free survival with salvage whole pelvis radiotherapy. Results from the NRG Oncology/RTOG 0534 SPPORT trial,[40] published as an abstract, indicate that whole pelvis radiotherapy in addition to androgen deprivation therapy is superior to prostate bed irradiation (hazard ratio [HR] 0·51 for 5-year distant metastases-free survival; p=0·014).

Toxicity of radiotherapy

Theoretically, whole pelvis radiotherapy might lead to increased toxicity compared with prostate-only radiotherapy.[50] However, data are conflicting[51] with some studies reporting no significant difference—even when using conventional technology—in late genitourinary toxic effects with prostate-only radiotherapy versus whole pelvis radiotherapy at an intermediate dose,[1,7,52] whereas another study[14] reported increased late genitourinary toxic effects by 40% with whole pelvis radiotherapy. The same inconsistencies exist with late gastrointestinal toxic effects. Although the GETUG-01 trial[7] did not report any excess late gastrointestinal toxic effects, the RTOG 9413 trial[1] reported significantly worse gastrointestinal toxic effects with whole pelvis radiotherapy versus prostate-only radiotherapy (5·1% *vs* 1·9%). Tharmalingam and colleagues[14] confirmed this significant increase in late gastrointestinal toxic effects (grade 2 or higher). Data on haematological toxic effects are sparse, and there were no grade 3 or higher toxic effects in the RTOG 9413 trial.[1] Absolute lymphocyte and white blood cell counts can remain lower than the baseline 1 year after whole pelvis radiotherapy, particularly in smokers and in patients presenting with low baseline lymphocytes. In these cases, the volume of ilium bone marrow receiving 40 Gy is a strong predictor for developing late lymphopenia.[53] Whole pelvis radiotherapy increased late grade 2 or higher haematological toxic effects, although absolute numbers remained low (29 [5%] of 570 patients) compared with prostate bed radiotherapy (27 (2%) of 1125 patients).[40] Using patient-reported toxicity scoring, whole pelvis radiotherapy seemed to induce more frequent bowel movements, loose stools, faecal urgency, and gas passage.[50]

PIVOTAL, a phase 2 randomised trial[3] comparing prostate-only radiotherapy with whole pelvis radiotherapy using intensity-modulated radiotherapy investigated whether modern radiotherapy could further reduce acute and late toxic effects (primary endpoint). Biological dose to the pelvic nodes was 55·0 Gy, which is substantially higher than the 50·4 Gy dose applied in the RTOG 9413 trial.[1] With a median follow-up of 37·6 months, there was no difference in late gastrointestinal and genitourinary toxic effects (grade 2 or higher) at 24 months between the two groups. Additionally, the crude incidence remained low. Even when using the more stringent Common Terminology Criteria for Adverse Events (version 4.0) score, grade 3 or higher gastrointestinal and genitourinary toxic effects were rarely observed (3% in the prostate-only group *vs* 0% in the whole pelvis radiotherapy group).

These physicians' reported data were confirmed by patient-reported outcomes, which did not show a significant difference between the two treatment groups.[3]

POP-RT also used intensity-modulated radiotherapy to deliver 50 Gy in 25 fractions to the pelvic nodes and a biological dose of 80 Gy to the prostate, delivered in 25 fractions.[11] The results from POP-RT suggest a significant increase in late grade 2 or higher late genitourinary toxic effects with whole pelvis radiotherapy (20% *vs* 9% with intensity-modulated radiotherapy; p=0·02). Late grade 2 or higher gastrointestinal toxic effects were not different between the two groups. Grade 4 toxic effects were not observed (Radiation Therapy Oncology Group [RTOG] scale).[11] Quality of life questionnaires did not show any significant change in functional or symptom domains.[10] Upper borders of the treatment fields are defined differently in each trial (figure 1; table 2).

Interpretation of trial results

When a tumour spreads in an orderly and contiguous manner, elective nodal irradiation might improve outcomes.[2] Whether prostate cancer follows such a predictable pattern is still not clear,[2] which might be one of the reasons why elective pelvic irradiation did not show a survival benefit versus prostate-only radiotherapy. Lymphatic drainage of the prostate is complex and lymph node metastases are found in hypogastric and internal iliac nodes (lateral pathway), obturator fossa nodes (inferior pathway), external iliac nodes (ascending pathway), presacral nodes (posterior pathway), and in the common iliac nodes.[2,5,17–19] However, the proPSMA trial[42] showed that in some cases uptake in the nodes was outside the traditional boundaries of an extended pelvic

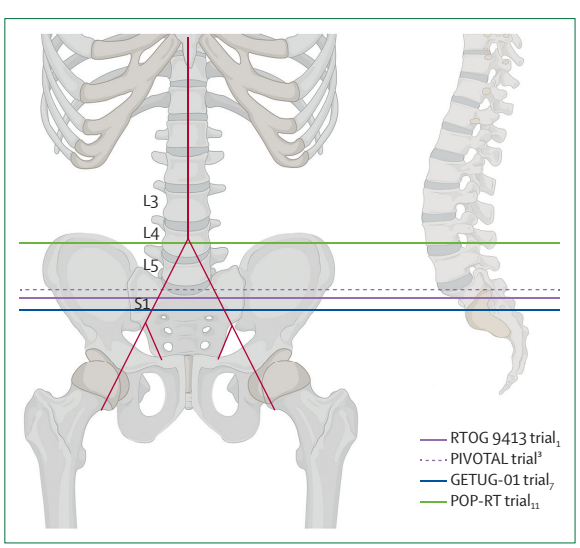

Figure 1: **Comparison of radiation treatment upper borders in different randomised trials**

Figure created with BioRender. Upper borders of the pelvic treatment fields used in different trials. The arterial vasculature of the abdomen and pelvis depicted in relation to the bony anatomy (red). Exact description of the respective upper borders is shown in table 2.

	RTOG 9413 trial[1]	GETUG-01 trial[7]	PIVOTAL trial[3]	POP-RT trial[11]
Pelvic upper limit	L5–S1	S1–S2	Lower border L5 on sagittal CT	L4–L5, common iliac nodes included
Prostate prescription dose, Gy	70·2 (1·8 Gy per fraction)	66–70 (1·8–2 Gy per fraction)	74 (2 Gy per fraction)	68 (2·68 Gy per fraction)
Prostate biologically effective dose, Gy	112	106–112	123	129
Pelvic prescription dose, Gy	50·4 (1·8 Gy per fraction)	46 (2 Gy per fraction)	60 (1·6 Gy per fraction)	50 (2 Gy per fraction)
Pelvic biologically effective dose, Gy	81	77	92	83
Radiotherapy technique	Conventional, 4D box	3D conformal radiotherapy	Intensity-modulated radiotherapy	Intensity-modulated radiotherapy
Androgen deprivation therapy, months	4	4–8	6–9	≥24

Biologically effective dose (calculated for an α/β of 3). 3D=three dimensional. 4D=four dimensional.

Table 2: **Comparison of radiation treatments**

lymph node dissection. Translating this finding to the radiation–oncology community implies the use of vascular anatomy instead of the bony anatomy and inclusion of common iliac nodes, which has also been proposed in published reviews.[16,54] This increasing knowledge also led to an adaptation in the RTOG delineation guidelines[55] for pelvic nodal areas. These guidelines stress the importance of the upper (should include common iliac arteries and veins) and lower delineation limits (should include presacral nodes to the bottom of the third sacral vertebra).

The GETUG-01 trial[7] did not show any benefit of whole pelvis radiotherapy, and the small whole pelvis radiotherapy volume (also known as the mini-pelvis) was probably the main reason for this finding.[51] Because the upper border excludes common iliac nodes and parts of the external iliac and presacral nodes,[7] major lymph node areas at risk were missed for the whole pelvis radiotherapy group,[5] with only 33% of these areas covered when compared with the location of lymph node metastases in patients with pelvic nodal recurrences after radical local treatment.[17,18] Even when the upper border was set at the L5–S1 interspace (same as in the RTOG 9413 trial), only 42% of patients with nodal disease would have complete coverage; hence this coverage is probably insufficient to show any benefit from whole pelvis radiotherapy. Conversely, raising the upper limit of whole pelvis radiotherapy to the L4/L5 interspace could have prevented more than 90% of the nodal recurrences after definitive radiotherapy, according to a retrospective analysis on 2694 patients at Memorial Sloan Kettering Cancer Center (New York, NY, USA).[17] The RTOG 0924 trial, for which enrolment was closed in June, 2019, is evaluating the benefit of whole pelvis radiotherapy with extended superior coverage to L4–5 compared with prostate-only radiotherapy.

Additionally, results from the RTOG 9413 trial are difficult to interpret because of the complex design.[12] Although interaction mechanisms between androgen deprivation therapy and radiation volume have been used to explain these results, we see the estimated 10-year progression-free survival of 30% as disappointing. Furthermore, patients included in this trial should be considered high risk, and for this subgroup there is level 1 evidence to apply long-term androgen deprivation therapy (ie, 18–36 months).[21] Therefore, the 4 months of androgen deprivation therapy received by patients in the RTOG 9413 trial, independently from randomisation, should be considered insufficient and might explain the high progression rate.

As also pointed out by Sandler and colleagues,[8] the benefit of whole pelvis radiotherapy might have been diluted because both randomised trials[1,7] included patients at low risk of pelvic nodal involvement.[4,5,17] Results from patients with high risk of pelvic nodal involvement have been conflicting. Although in patients with a Gleason score of 5, whole pelvis radiotherapy did not improve distant metastasis-free survival or prostate cancer-specific survival,[8] other studies[4,5] stated that the benefit of pelvic elective nodal radiotherapy is mostly present in patients with a high risk of developing positive pelvic nodes. Within this discussion, the recently published randomised POP-RT study paves the way for future clinical studies in this setting.[11] In patients with a 20% or higher risk of pelvic lymph node disease, biochemical progression-free survival, disease-free survival, and distant metastasis-free survival were significantly improved with whole pelvis radiotherapy compared with prostate-only radiotherapy. There was no improvement in overall survival, which could be because the median follow-up was too short (68 months).[11] But, because distant metastasis-free survival is a strong surrogate for overall survival,[56] the distant metastasis-free survival benefit might translate into an overall survival benefit with longer follow-up.

There are multiple reasons why this trial[11] achieved the primary (biochemical progression-free survival) and secondary endpoints. First, patients belonged to high-risk and very-high-risk groups (table 1). Half of patients (109 [49%] of 222) had a Gleason grade group of 4 or 5, almost 50% had a risk of pelvic lymph node involvement of more than 40%, and the median PSA was 28 ng/mL. Patients with a substantial risk of having positive pelvic nodes probably benefit the most from whole pelvis radiotherapy.[11] Notably, for this group of patients, an extended pelvic lymph node dissection is the treatment of choice after a radical prostatectomy, according to the European Association of Urology guidelines.[49] Lestingi and colleagues[46] recently published the outcomes of the first randomised controlled trial that compared limited pelvic lymph node dissection with extended pelvic lymph node dissection in patients with intermediate or high risk prostate cancer. Although there was no difference in biochemical recurrence-free survival at 5 years for the entire cohort, patients with an International Society of Urologic Pathology score of 3–5 had better 5-year

biochemical recurrence-free survival with extended pelvic lymph node dissection than with limited pelvic lymph node dissection (HR 0·48; p=0·024). This finding confirms the conclusions that only patients with a substantial risk of pathological pelvic nodes benefit from extended therapy (extended pelvic lymph node dissection or whole pelvis radiotherapy, or both). Although this cutoff is arbitrary, we want to suggest a cutoff value of 35% for lymph node invasion to enable whole pelvis radiotherapy to be done electively. This 35% cutoff is based on the median risk of lymph node invasion of 38% shown in the POP-RT trial. Additionally, in intermediate-risk patients, staging, treatment, or both, of the pelvic nodes can be omitted.[11,46]

Second, the POP-RT trial protocol adequately covers pelvic lymph node regions with the upper border set at the L4–L5 junction, thus adequately including the common iliac nodes and resulting in 93% coverage. This definition of the upper border is an important difference compared with the randomised controlled trial by Murthy and colleagues.[11] Lastly, the biological dose to the prostate used in POP-RT is sufficient to optimise local control.[11] Indeed, local control plays an important role in optimising progression-free survival and metastasis-free survival,[11,15] and is linked to the dose delivered to the prostate.[24,57] Both the RTOG 9413 and GETUG-01 trials had this issue;[4] taking into account current knowledge, the dose delivered in these two studies was too low to guarantee sufficient local control. Consequently, the rate of local relapse was substantial and led to a second wave of distant metastasis,[15] which diluted the potential benefit of whole pelvis radiotherapy.[1,7,14] Results from Sandler and colleagues[8] confirmed that only when the primary tumour is controlled, whole pelvis radiotherapy might affect the outcome. Indeed, biochemical control and distant metastasis-free survival were better when a brachytherapy boost was added to external-beam radiotherapy,[8] an approach which was also proposed by others.[4,14,24] The randomised PIVOTALboost trial[58] will build on the retrospective results obtained by Sandler and colleagues.[8] A phase 2 trial[59] using whole pelvis radiotherapy reported better disease-specific survival in patients receiving a higher dose of 55–60 Gy to the pelvic nodes than those receiving 50 Gy. HRs for 5-year disease-free survival with higher pelvic doses were 0·71 for the cohort receiving 55 Gy and 0·45 for those receiving 60 Gy.

Although toxicity rates are acceptable even with conventional radiotherapy technology, trials using intensity-modulated radiotherapy or volumetric modulated arc therapy report very low rates of severe toxicity even when a higher dose to the pelvic nodes is applied.[3,4,14,50,52,59] Moreover, side-effects settle rapidly.[59] The doubling of late genitourinary toxic effects in the POP-RT trial is linked to the higher dose to the pelvis. Nevertheless, no grade 4 or higher toxic effects occurred, and grade 3 toxic effects occurred in less than 2% of patients (two of 112), independently of the treatment group.[11] This low rate of grade 3 or higher toxic effects has been confirmed by other studies.[4,12] Whether dosimetric superiority of new radiation approaches, such as intensity-modulated proton therapy, will further reduce late toxic effects is still unknown. Planning studies showed that intensity-modulated proton therapy significantly reduced the dose to the bladder, small bowel, large bowel, and rectum compared with volumetric arc therapy.[60,61]

A reduction of the small bowel volume from 20 Gy to 50 Gy is predictive for the development of bowel toxic effects.[14,50,51] A registry study which included patients treated with pelvic proton therapy showed that intestinal and urinary toxic effects were infrequent after a short follow-up of 14 months.[51] The dose distribution of an intensity-modulated proton therapy plan, volumetric arc

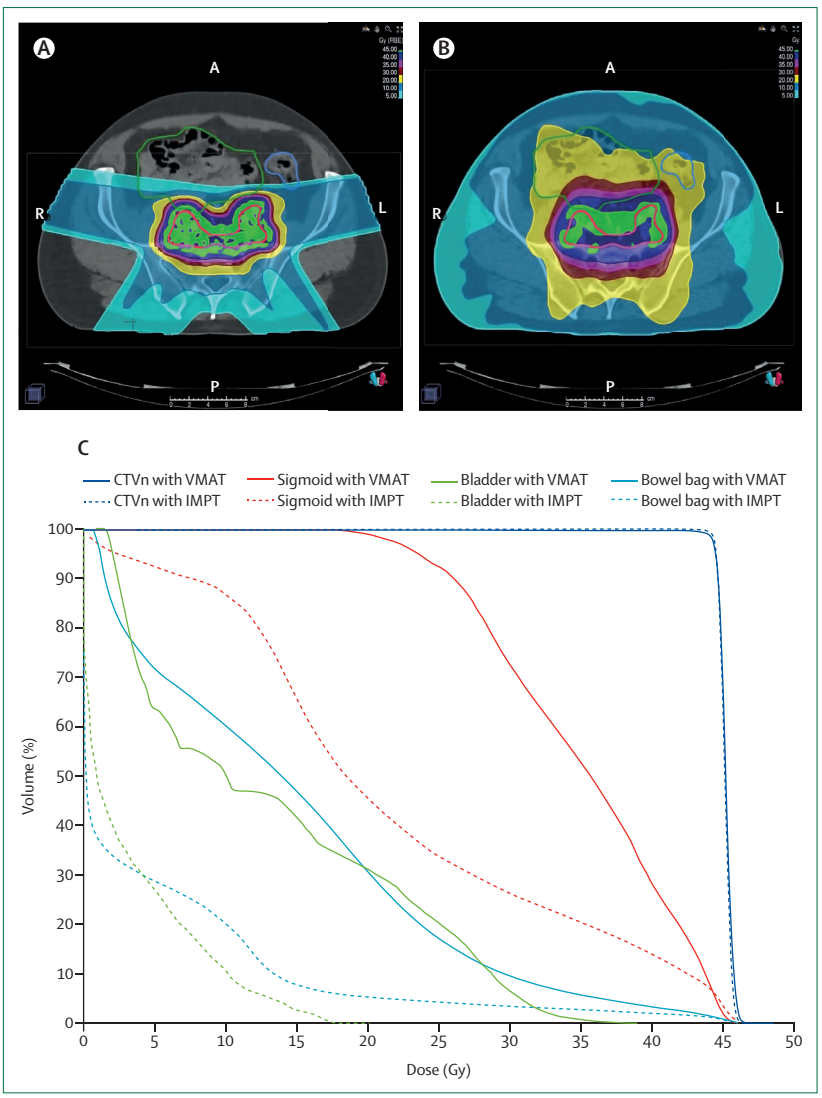

Figure 2: **Transverse dose distribution for two different modalities for whole pelvis radiotherapy**
IMPT plan (A) and VMAT plan (B). The planning target volume (pink area), bowel bag (green area), and sigmoid (blue area). (C) A dose–volume histogram for the CTVn and for organs at risk with IMPT plan and VMAT plan. CTVn=nodal clinical target volume. IMPT=intensity-modulated proton therapy. RBE=relative biological effectiveness. VMAT=volumetric modulated arc therapy.

therapy-generated dose distribution, and dose–volume histograms of different planning techniques are shown in figure 2.

Another change within the radiation–oncology community is the implementation of hypofractionated radiotherapy in treating node-negative prostate cancer.[62,63] Although still in early development, hypofractionated and ultra-hypofractionated whole pelvis radiotherapy is currently widely investigated.[6,15,29,30] Despite short follow-up, preliminary results suggest that these approaches are safe[29,30] without affecting quality of life.[6]

None of the randomised trials considered locoregional salvage treatment for isolated pelvic lymph node recurrence in patients receiving prostate-only radiotherapy, which is the most dominant site of recurrence.[64] These patients have a better outcome compared with patients presenting with bone or visceral metastasis.[16,44,65] The optimal salvage approach has not been defined, but a combination of minimally invasive extended salvage lymph node dissection, modern adjuvant pelvic radiotherapy, and a period of androgen deprivation therapy might result in the best outcomes by increasing 5-year relapse-free survival without increasing toxic effects.[43,65–68] Therefore, the European Association of Urology guidelines have incorporated salvage lymph node dissection as a possible treatment option.[49] Another, non-surgical, approach is the administration of salvage whole pelvis radiotherapy in combination with androgen deprivation therapy and a simultaneous integrated boost to PET–CT positive nodes.[64] This treatment seems to be well tolerated in terms of physician-derived and patient-derived toxicity scores. There was no decrease in quality of life 12 months after treatment with salvage whole pelvis radiotherapy.[69] An update of this study, published as an abstract, reported a 2-year progression-free survival of 78% after a median follow-up of 34 months. Grade 2 or higher urinary toxic effects were observed in 10% of patients and intestinal toxic effects in 2% of patients.[70] By contrast, patients who received salvage whole pelvis radiotherapy regretted the decision more frequently than those who received prostate bed-only salvage radiotherapy.[71] Whether salvage stereotactic ablative radiotherapy to macroscopically involved nodes (visible on biological imaging, such as PSMA PET–CT) will be as effective as salvage whole pelvis radiotherapy is a matter of debate. However, when using the salvage stereotactic ablative radiotherapy approach, there is a substantial risk of disease relapse adjacent to the treated node, making reirradiation nearly impossible.[16,43,64] Moreover, metastasis-free survival at 3 years was significantly better with salvage whole pelvis radiotherapy than with salvage stereotactic ablative radiotherapy, especially in patients presenting with one nodal recurrence in whom the treatment is more effective, but there are increased toxic effects.[64] Results from the STORM trial[72] might show which radiation mode should be preferred, but, for now, we advocate salvage whole pelvis radiotherapy, including a simultaneous integrated boost to the involved lymph nodes, in combination with long-term androgen deprivation therapy, although this approach is still not supported by the European Association of Urology guidelines.[49] Delineation guidelines in this setting have been described by Achard and colleagues,[73] although we would advocate the same recommendation concerning the upper limit as that proposed by Hall and colleagues.[55]

Clinical research on expanding radiation fields to include retroperitoneal lymph nodes in cases of pathologically positive lymph nodes during lymph node dissection is ongoing.[23] This type of research was initiated because a substantial number of nodal recurrences occur in the retroperitoneal nodes.[16,45,54]

Search strategy and selection criteria

We searched PubMed for literature on elective lymph node irradiation using the terms "prostate cancer", "elective pelvic radiotherapy", "whole pelvis radiotherapy", "positive lymph nodes", "randomized trial", "proton therapy", "salvage lymph node dissection", and "PSMA PET-CT". Only articles in English were reviewed, and the articles that encompassed the purpose of this Review were identified. We then reviewed full articles in detail as a second selection. The search was restricted to reviews, original articles, and editorials, for papers published between Jan 1, 2014, and Jan 26, 2021. Papers providing details on the technology used without data on oncological outcome or toxicity, or both, were excluded except for planning studies evaluating theoretical benefits of proton therapy.

Conclusion

New data suggest a substantial benefit for elective nodal radiotherapy in patients with high risk of pathologically positive pelvic lymph nodes. Although a clear cutoff is still not decided, we propose that a risk of lymph node invasion more than 35%, using the Roach formula, should lead to elective nodal radiotherapy. The biological dose to the prostate and seminal vesicles should be at least 78 Gy. A biological dose of 50 Gy should be considered for the pelvic nodal areas. The upper border of the pelvic field should encompass the bifurcation of the abdominal aorta.

When modern radiotherapy is applied to deliver pelvic radiotherapy, there are nearly no grade 3 or higher toxic effects. Patients who present with pathologically involved lymph nodes benefit from the addition of postoperative pelvic radiotherapy to systemic treatment with androgen deprivation therapy. Regarding modern imaging, PSMA PET–CT might become the new standard staging procedure in high-risk patients. Patients presenting with enlarged nodes on imaging would benefit from the addition of radiotherapy to androgen deprivation therapy.

Contributors

GDM did the literature search, data collection and interpretation, wrote the first manuscript, made the decision on coauthors, and rewrote the manuscript. CB did the literature search, data interpretation, and figures. ABr and KD did the critical review and gave advice on surgical items and references. CV did the critical review and gave advice on systemic

treatment items and references. JM did the critical review, reviewed grammar and semantics, and gave advice on radiation oncology items. SJ and AML did the critical review and gave advice on surgical items. CC did the critical review and gave advice on radiation oncology items and references. KR did the critical review, figures, and submitted the manuscript. VF and ODH did the critical review and gave advice on radiation oncology items. ABo did the critical review, data interpretation, made the decision on coauthors, rewrote the manuscript after comments from coauthors, and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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