**Critical Review**

# Patterns of Lymph Node Failure in Patients With Recurrent Prostate Cancer Postradical Prostatectomy and Implications for Salvage Therapies

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## Abstract

**Purpose:** There is increasing use of radical prostatectomy to treat patients with high-risk prostate cancer. This has contributed toward a pathologic stage migration, and a greater number of patients are subsequently being diagnosed with biochemical failure. There is increasing use of advanced imaging techniques in the setting of biochemical failure, including positron emission tomography-computed tomography (PET-CT).

**Methods and Materials:** This critical literature review highlights the evidence for PET-CT in postprostatectomy biochemical failure and identifies sites of pelvic lymph node relapse in the setting of biochemical failure and the potential implications that the locations of these relapses may have for salvage therapies. Potential future directions are then considered.

**Results:** The optimal PET-CT tracer remains uncertain but there is increasing use of prostate-specific membrane antigen PET-CT for investigating sites of nodal metastasis at low prostate-specific antigen levels, and this is leading to a blurring of the biochemical and radiologic recurrence phases. The optimal therapeutic approach remains undefined, with current trials investigating postoperative radiation therapy to the whole pelvis in addition to the prostatic fossa, the use of PET-CT in the setting of biochemical recurrence to guide delivery of salvage radiation therapy, and, for patients with node-only relapsed prostate cancer, the addition of whole pelvis radiation therapy to metastasis-directed therapies such as stereotactic ablative radiotherapy.

**Conclusions:** The most appropriate target volume for salvage radiation therapy remains uncertain, and the findings of studies using PET-CT to map nodal recurrences suggest that there could be a role for extending whole pelvis radiation therapy volumes to increase coverage of superior nodal regions. The emerging fields of radiomics and radiogenomics could provide important prognostic information and aid decision making for patients with relapsed prostate cancer.

## Introduction

Prostate cancer (PCa) is the most common cancer in men. Each year in the United States, approximately 30,000 men are diagnosed with high-risk localized or locally advanced PCa (defined using National Comprehensive Cancer Network version 2.2019 criteria).[1,2] Half of the patients with high-risk disease are treated with radical prostatectomy (RP) and a proportion of patients with intermediate-risk PCa at diagnosis may be up-staged owing to adverse pathologic findings at RP.

Historically, RP was discouraged in patients with high-risk PCa because it was considered that the subsequent development of recurrent/metastatic disease was inevitable.[3] Recently, however, there has been increasing use of RP in these patients.[4] There are several reasons for this, including advances in multiparametric magnetic resonance imaging (MRI) providing improved discrimination between tumor, normal prostate, and periprostatic tissues; uptake of robotic assisted laparoscopic technology; and publication of more promising outcomes for high-risk patients treated using RP.[1] In a large retrospective series of 6000 patients with high-risk PCa, cumulative 10-year PCa specific mortality (PCSM) ranged from 3% to 11% depending on the criteria used to define "high-risk."[5]

A persistently rising prostate specific antigen (PSA) greater than 0.2 ng/mL after RP is often considered to indicate biochemical failure.[6,7] It is estimated that 40% to 90% of patients with high-risk features at RP (≥pT3a disease, Gleason score ≥8 [International Society of Urological Pathology (ISUP) grade 4 or 5], high PSA and positive surgical margins) will subsequently develop biochemical failure, with failure rates >50% even in high volume specialist centers.[1,8] In the United States, an estimated 15,000-25,000 patients develop biochemical failure annually.[1] Although only a proportion of patients with biochemical failure will subsequently develop metastatic disease and be at risk of PCSM, the presence of seminal vesicle invasion, Gleason score ≥8, and PSA doubling time <3 months all indicate a higher risk for development of metastases.[9-11]

Metastases may manifest as regional (pelvic) nodal failure after primary treatment.[12-14] It has been observed that the prognosis for patients with lymph node metastases is better than for those with appendicular skeletal or visceral disease (hazard ratio [HR] for appendicular skeletal/visceral vs nodal metastases, 3.6; 95% confidence interval [CI], 1.14-11.9; $P = .03$).[15] Nevertheless, nodal metastases appear to be associated with greater PCSM compared with patients without metastatic disease (HR for nodal metastases vs no metastases, 4.5; 95% CI, 4.2-4.9; $P < .01$), and recently the incidence appears to be increasing.[16] This may reflect increased sensitivity of modern imaging and recommendations against the use of PSA as a screening investigation, meaning that patients may present with more advanced disease.[17]

National Institute for Health and Care Excellence, European Association of Urology, and National Comprehensive Cancer Network guidelines recommend that patients with biochemical failure after RP should be offered salvage radiation therapy (RT) to the prostatic fossa in the absence of imaging-defined metastases.[2,6,18] However, the rate of detection of metastases from computed tomography (CT), MRI, and bone scintigraphy in this setting is poor.[19,20] There is, however, increasing use of positron emission tomography (PET)-CT to identify suitable patients for, and to guide delivery of, salvage treatments. The use of PET-CT with radioactive tracers including carbon 11 (11C) or fluorine 18 (18F) choline, gallium 68 (68Ga) or 18F prostate-specific membrane antigen (PSMA), and 18F fluorocyclobutane-1-carboxylic acid fluciclovine (commonly known as fluciclovine) permits the detection of recurrent disease even at low PSA levels.[21-23] PET-CT may be especially useful in the detection of lymph node disease with superiority in comparison to other imaging modalities such as MRI.[24]

Where PCa recurs in a limited number of nodal sites after primary treatment (so-called *oligorecurrence*), there is ongoing investigation of treatments including stereotactic ablative radiotherapy (SABR), salvage pelvic lymph node dissection (PLND), and whole pelvis RT (WPRT). These salvage therapies have the potential to improve outcomes and possibly cure a proportion of patients.[25-29]

Understanding the patterns of spread for nodal disease in recurrent PCa is important to ensure sufficient coverage by WPRT or to ensure that PLND is provided to nodal stations that may be PET-CT negative but nonetheless harbor a risk of micrometastases.[30] Furthermore, there is a paucity of evidence regarding whether use of advanced imaging techniques for recurrence detection results in improved patient outcomes. A number of prospective trials are underway that aim to determine the effect of PET-CT-guided treatment planning on outcomes and may provide insight into this area (Clinicaltrials.gov NCT01666808, NCT03762759, NCT03525288, NCT03582774).

This critical literature review summarizes the evidence for PET-CT in postprostatectomy biochemical failure and identifies the patterns of nodal recurrence post-RP as

evaluated by PET-CT studies. Implications for salvage therapies and potential future directions are then considered.

## Methods and Materials

Literature searches were performed using PubMed (National Center for Biotechnology Information) for terms relating to, but not restricted to, recurrent PCa post-RP, pelvic lymph node mapping, PET-CT and salvage PLND and WPRT. Further articles were identified by manually searching reference lists of relevant publications. To identify a relatively homogenous patient group, this review was restricted to studies that examined nodal recurrence in the post-RP setting only. We excluded detailed review of studies that did not provide a precise breakdown of pelvic nodal locations. Given the breadth of the subject and the existence of multiple systematic reviews/meta-analyses concerning PET-CT in PCa, a systematic review was purposely not undertaken. Where there were large numbers of studies that addressed a particular topic (eg, diagnostic accuracy of particular PET-CT tracers), the findings of review articles, systematic reviews, and meta-analyses are presented as a summary of the best available evidence.

## Comparison of PET tracers

11C and 18F choline, 68Ga and 18F PSMA and 18F fluciclovine PET-CT are commonly used in the recurrent PCa setting. Multiple systematic reviews and meta-analyses addressing the diagnostic performance of these tracers have been performed in the setting of biochemical recurrence after primary treatment. This section presents a summary of performance data and available comparisons between tracers in the recurrent PCa setting, and a summary is provided in Table 1.

It has generally been observed in systematic reviews and prospective studies comparing 68Ga PSMA and choline PET-CT that 68Ga PSMA is superior for the detection of metastases in the setting of biochemical failure.[22,23,31-35] A meta-analysis of choline PET-CT for detection of recurrent disease calculated pooled sensitivity and specificity as 85% and 88% respectively.[36] However, the mean PSA of patients in the included studies was 7.9 ng/mL, which is higher than the typical level at which biochemical recurrence would be investigated in current practice using PET-CT.[21] Pooled detection rates for recurrent nodal disease by choline PET-CT in another meta-analysis were 36%.[37] A further meta-analysis of studies before salvage PLND concluded that choline PET-CT lesion-based sensitivity was 56%.[38] Although both 11C and 18F choline tracers are available, according to another meta-analysis, there does not appear to be a significant difference in detection rates between the 2 tracers.[39] However, the detection of recurrent disease by choline PET-CT declines substantially at low PSA levels, especially <1 ng/mL, and with slower PSA kinetics, where detection rates may be <30% in comparison with rates >50% with a PSA of 2 ng/mL.[22] There is also a risk of false positive uptake in regions of inflammation, and false negative results may occur in the presence of micrometastatic disease (<2 mm diameter).[21]

The results from systematic reviews and prospective studies of fluciclovine and choline PET-CT suggest that fluciclovine performs better than choline PET-CT, especially at low PSA levels.[22,40,41] Three meta-analyses calculated the pooled sensitivity and specificity for detection of recurrent disease by fluciclovine PET-CT as 76.5% to 87% and 66% to 89%, respectively (although the meta-analysis by Laudicella et al combined studies evaluating fluciclovine PET-CT in both the primary and recurrent disease setting in their analysis).[40,42,43] Recently, prospective studies have directly compared fluciclovine and 68Ga PSMA PET-CT in single center patient cohorts with biochemical recurrence with contrasting results. Calais et al[12] reported significantly better performance with 68Ga PSMA PET-CT in patients with PSA <2 ng/mL, with overall detection rates of 56% with 68Ga PSMA versus 26% with fluciclovine (P = .0034). In contrast, Pernthaler et al[44] studied a cohort with a wider PSA range (median, 4.1 ng/mL), but, when limited to patients with a PSA <2 ng/mL, they observed less varied detection rates: fluciclovine 42% versus 68Ga PSMA PET-CT 53%.[44]

Meta-analyses of 68Ga PSMA report sensitivity and specificity per lesion of 75% to 80% and 97% to 99%, respectively.[33,34] 68Ga PSMA PET-CT appears to be particularly effective at low PSA levels, with a meta-analysis calculating pooled detection rates of 94% with PSA >2 ng/mL and 63% for PSA <2 ng/mL.[45] 68Ga PSMA PET-CT may even detect recurrent disease post-RP in 33% to 42% of patients at PSA levels <0.2 ng/mL, below the level when salvage RT to the prostate bed would typically be initiated.[21,33,34]

## Lymph node mapping by PET-CT

Several studies have evaluated lymph node mapping using PET-CT in the setting of biochemical failure after primary treatment with RP (Table 2). Figure 1 illustrates lymph node positions in relation to WPRT volumes.

De Bruycker et al[46] mapped nodes in 82 patients (mostly treated with RP or RP plus salvage RT) with biochemical failure using choline PET-CT. Forty-nine percent of nodes were observed in the true pelvis, within the external iliac (43% of nodes), internal iliac/obturator (30%), presacral/perirectal/perivesicle regions (18%), and a combination of these in 11% of 158 PET-avid lesions. Ten percent of lesions were observed in the common iliac

**Table 1**  Summary of performance characteristics of available PET-CT tracers from prospective comparative studies and meta-analyses

| Study (first author) | Type of study | Type of PET-CT | Population studied | Endpoints | Results |
|---|---|---|---|---|---|
| Emmett[31] | Prospective cohort study | 68Ga PSMA vs 18F choline | Biochemical recurrence post-RP | Detection rates at median PSA of 0.42 ng/mL | 68Ga PSMA: 42% 18F choline: 32% |
| Morigi[32] | Prospective cohort study | 68Ga PSMA vs 18F choline | Biochemical recurrence postprimary treatment | Detection rates | 68Ga PSMA: 50% when PSA <0.5 ng/mL 86% when PSA >2 ng/mL 18F choline: 12.5% when PSA <0.5 ng/mL 57% when PSA >2 ng/mL |
| Calais[12] | Prospective cohort study | 68Ga PSMA vs Fluciclovine | Biochemical recurrence post-RP | Detection rates with PSA <2 ng/mL | 68Ga PSMA: 56% Fluciclovine: 26% |
| Pernthaler[44] | Prospective cohort study | 68Ga PSMA vs Fluciclovine | Biochemical recurrence postprimary treatment | Detection rates with PSA <2 ng/mL | 68Ga PSMA: 53% Fluciclovine: 42% |
| Nanni[41] | Prospective cohort study | Fluciclovine vs 11C choline | Biochemical recurrence post-RP | Sensitivity and specificity at median PSA 3.35 ng/mL | Fluciclovine: Sensitivity 37% Specificity 67% 11C choline: Sensitivity 32% Specificity 40% |
| Umbehr[36] | Meta-analysis | 11C and 18F choline | Biochemical recurrence postprimary treatment | Pooled estimates for sensitivity and specificity at mean PSA 7.9 ng/mL | Sensitivity 85% Specificity 88% |
| Fanti[37] | Meta-analysis | 11C choline | Biochemical recurrence postprimary treatment | Pooled detection rates, sensitivity, and specificity estimates | Detection rate 62% Sensitivity 89% Specificity 89% |
| Evangelista[38] | Meta-analysis | 11C and 18F choline | Biochemical recurrence postprimary treatment | Pooled sensitivity and specificity estimates | Sensitivity 86% Specificity 93% |
| von Eyben[39] | Meta-analysis | 11C and 18F choline | Biochemical recurrence postprimary treatment | Pooled detection rate estimates at mean PSA 3.6 ng/mL | 11C choline: 30% 18F choline: 39% |
| Perera[33] | Meta-analysis | 68Ga PSMA | Biochemical recurrence postprimary treatment | Predicted positivity by meta-regression analysis | 48% where PSA 0.2 ng/mL 56% where PSA 0.5 ng/mL 70% where PSA 1 ng/mL |
| Perera[34] | Meta-analysis | 68Ga PSMA | Biochemical recurrence postprimary treatment | Pooled estimates for percentage positivity | 33% where PSA <0.2 ng/mL 59% where PSA 0.2-0.5 ng/mL 75% where PSA 1-2 ng/mL 95% where PSA >2 ng/mL |

**Table 1** (*continued*)

| Study (first author) | Type of study | Type of PET-CT | Population studied | Endpoints | Results |
|---|---|---|---|---|---|
| Hope[45] | Meta-analysis | 68Ga PSMA | Biochemical recurrence postprimary treatment | Pooled detection rate estimates | 63% where PSA <2 ng/mL 94% where PSA >2 ng/mL |
| Laudicella[40] | Meta-analysis | Fluciclovine | Primary staging and biochemical recurrence postprimary treatment | Pooled estimates for sensitivity and specificity | Sensitivity 86% Specificity 76% |
| Kim[42] | Meta-analysis | Fluciclovine | Biochemical recurrence postprimary treatment | Pooled estimates for sensitivity and specificity | Sensitivity 79% Specificity 69% |
| Ren[43] | Meta-analysis | Fluciclovine | Biochemical recurrence postprimary treatment | Pooled estimates for sensitivity and specificity | Sensitivity 87% Specificity 66% |

*Abbreviations:* 11C choline = carbon 11 choline; 18F choline = fluorine 18 choline; 68Ga PSMA = gallium 68 prostate specific membrane antigen; PET-CT = positron emission tomography-computed tomography; PSA = prostate specific antigen; RP = radical prostatectomy.

and retroperitoneal regions and 31% were found in a combination of these regions and true pelvis. Sobol et al[47] also mapped nodes using choline PET-CT in patients with biochemical failure (median PSA, 2.3) post-RP but excluded patients treated with salvage RT/androgen deprivation therapy (ADT). Of 202 patients with PET-avid disease, pelvic and retroperitoneal nodes were seen in 37% and 10% of patients, respectively. Twenty-one percent of patients had nodal disease distal to the aortic bifurcation, 37% had disease distal to the common iliac bifurcation, and 9% had perirectal disease. Hegemann et al[48] also reviewed patients with biochemical failure post-RP (median PSA, 3.1) using choline PET-CT. Positive lymph nodes were identified within the common iliac (25% of nodes), external iliac (23%), internal iliac (14%), para-aortic (20%), presacral (3%), and perirectal/vesicle (7%) nodal regions. Parker et al[49] evaluated choline PET-CT in 41 patients in the setting of biochemical failure postsalvage RT to the prostate bed. They reported 86% of 121 lesions relapsed out of the previous radiation field with 47% of these occurring in lymph nodes. The sites of involvement identified included internal iliac (12% of nodes), external iliac (22%), obturator (5%), common iliac (20%), presacral (2%), and retroperitoneal (21%).

In most of the PET-CT mapping studies, the majority of patients had high-risk primary disease (eg, extraprostatic disease [≥T3a] and/or Gleason score ≥8) and the type of PLND performed at the time of RP was often poorly described. It is not known whether the extent of PLND performed at RP influences oncological outcomes or patterns of further nodal failure. More extensive dissections are associated with greater detection of positive nodes but also increased morbidity.[50] The patterns of recurrent disease in the setting of biochemical failure may

also differ depending on whether salvage RT/ADT was used, but this was not consistently described. Nehra et al[51] observed that administration of salvage RT in 550 patients before choline PET-CT appeared to alter the distribution of PET-positive lesions. In this study, after salvage RT was delivered to the prostatic fossa, either alone or in combination with ADT, most recurrences occurred outside the treated volume. Administration of ADT without salvage RT was associated with the highest proportion of locally recurrent disease, suggesting that prostatic fossa RT reduces the risk of locally recurrent PCa. Patterns of recurrence may also differ depending on hormone sensitivity. Grazini et al[52] reviewed choline PET-CT images from 3200 patients: in patients with PSA progression on ADT, indicating castrate-resistant disease, there were more positive choline PET-CT examinations and increased likelihood of distant metastatic disease.

Given the known limitations of choline PET-CT, other studies have used 68Ga PSMA PET-CT for nodal mapping. Devos et al[53] reported 55 of 78 patients (71%) with biochemical failure post-RP had nodal recurrence identified by 68Ga PSMA PET-CT. Incorporating patients with relapses at multiple sites, positive nodes were identified in the external/internal iliac (53% of patients), common iliac/presacral (15%), retroperitoneal (10%), and perirectal (5%) regions. In this study, median PSA was 2.6 ng/mL, and most patients had received post-RP prostatic fossa RT or ADT before imaging. 68Ga PSMA PET-CT may be effective at identifying nodal disease at very low PSA values. Calais et al[54] reported nodal mapping post-RP before salvage RT or ADT using 68Ga PSMA PET-CT at a median PSA of only 0.48 ng/mL, and 61% of patients had high-risk disease. One hundred and thirty-two patients (49%) had a positive scan with 304 lesions

identified. Of these, 57% were lymph nodes, which were found in the internal iliac (11% of nodes), external iliac (15%), obturator (8%), common iliac (9%), retroperitoneal (5%), and presacral (7%) nodal regions. Schiller et al[55] also evaluated biochemical recurrence before any salvage therapy using 68Ga PSMA PET-CT. In their study, median PSA was 0.71 and 94% of patients were high-risk. Thirty-one patients had PET-avid disease with 50 nodal lesions identified. Lesions were found in the internal iliac (28% of nodes), external iliac (14%), obturator (6%), common iliac (12%), retroperitoneal (2%), presacral (8%), and perirectal (20%) nodal regions.

## Implications of lymph node patterns of failure for salvage therapies

In addition to describing the location of nodal recurrences, studies that have investigated PET-CT in the recurrent PCa setting have discussed the implications of these lymph node maps for salvage therapies. Relationships between nodal relapses and different WPRT and PLND templates are discussed here.

### Identification of oligometastatic nodal disease

The use of restaging imaging in the setting of biochemical failure increasingly identifies patients with limited sites of metastatic (oligometastatic) disease, including nodal disease, but the optimum therapeutic approach and the clinical benefits of such interventions remain undefined. There is ongoing investigation of metastasis-directed therapies, including SABR, to treat nodal disease. At present, the evidence to support this approach is derived from early phase studies, although phase III trials are recruiting.[26,28,29,56,57] Targeting only macroscopically involved nodes using SABR risks further relapse adjacent to the treated site, which could compromise the delivery of further radiation owing to the tolerances of surrounding organs at risk.[58] The concern regarding treatment of only the involved nodes is supported by the PET-CT mapping studies evaluated in this review. One, 2, 3, and ≥4 nodes were identified in 27% to 60%, 17% to 35%, 5% to 25%, and up to 12% of patients, respectively.[46-49,53] Most of these studies used choline PET-CT and imaged patients at a median PSA of 3.1 ng/mL, which is higher than the typical value at which biochemical recurrence would be investigated in current practice. At low PSA values, choline PET-CT has limited value, especially in the detection of micrometastatic disease, which risks understaging the true extent of disease. A greater proportion of patients with multiple positive nodes might be identified using 68Ga PSMA PET-CT, even at lower PSA levels. This raises the question as to whether there might be a benefit in treating regions of potential micrometastatic disease using WPRT with a boost to involved node(s) compared with SABR to the involved node alone. A recent multicenter study of 506 patients compared elective nodal RT with SABR and found that elective nodal RT was associated with fewer further nodal relapses including in pelvic nodes, although there was a higher incidence of early and late toxicities.[59] This approach is currently being evaluated in the phase II Salvage Treatment of OligoRecurrent Nodal Prostate Cancer Metastases (STORM) trial.[25]

It remains unclear how many macroscopically involved nodes can be treated by metastasis-directed therapies such as SABR with or without WPRT while maintaining clinical utility. Previous authors have reported that survival outcomes were associated with the number of metastatic lesions identified, although they did not discriminate between the type of metastasis (nodal, skeletal, or visceral) in this analysis, and PET-CT was not used to stage all patients. Ost et al[15] reported 5-year estimates for PCa specific survival of 90% for patients with a single metastasis versus 32% for those with multiple lesions (P = .005). Schweizer et al[60] observed superior overall survival for patients diagnosed with ≤3 versus >3 metastases (HR, 0.5; 95% CI, 0.29-0.85; P = .012). A limit of 3 metastases was used in the phase II study of metastasis-directed therapy by Ost et al.[26] However, it has been observed that survival is superior for patients with nodal disease compared with those with skeletal or visceral metastases.[15] This could be because the clinical behavior of nodal metastases differs compared with bone or visceral lesions.[61] Previously, the perception existed that regional lymph node metastases were an essential intermediate step between clinically localized disease and subsequent distant metastases. However, recent genomic data suggest that nodal metastases may not necessarily be a precursor to distant osseous or visceral spread but rather could represent a distinct biological and clinical entity.[62,63] Therefore, it is theoretically possible that there could still be a clinical benefit in radically treating patients with multiple nodal lesions that remain confined to the pelvis in comparison with patients with multiple extrapelvic nodal or non-nodal metastases.

### Elective nodal RT volumes

Elective nodal RT volumes have generally followed the template established by the Radiation Therapy Oncology Group (RTOG), and recently the Prostate and PelvIc Versus prOstaTe ALone (PIVOTAL) trial, where the distal common iliac, external iliac, internal iliac, obturator, and presacral S1-3 nodal regions are included.[64,65] The superior border of the WPRT volume corresponds to the L5/S1 interspace and inferior border of L5 for the RTOG and PIVOTAL templates, respectively. The inferior border of the external iliac nodal region is the superior aspect of the femoral heads.

**Table 2**   Summary of imaging-based lymph node mapping studies

| Study | Type of imaging | Number of patients | Post-RP treatment | T stage (%) | PSA ng/mL at time of imaging | Gleason score | Number of lesions |
|---|---|---|---|---|---|---|---|
| De Bruycker[46] | Choline PET-CT | 82 | 68% had salvage RT with/without ADT | pT1-2 40 (49%) pT3-4 42 (51%) | Median 3.1 | ≤7 55 (67%) ≥8 27 (33%) | 158 |
| Sobol[47] | Choline PET-CT | 202 | None | pT2 95 (53%) pT3-4 84 (47%) | Median 2.3 | ≤7 130 (64%) ≥8 72 (36%) | |
| Hegemann[48] | Choline PET-CT | 87 | Not stated | pT2 15 (25%) pT3-4 72 (75%) | Median 3.1 | ≤7 44 (51%) ≥8 43 (49%) | 161 |
| Parker[49] | Choline PET-CT | 41 | 100% had salvage RT | 13 (32%) | Median 3.1 | ≤7 25 (61%) ≥8 16 (39%) | 121 |
| Devos[53] | 68Ga PSMA PET-CT | 78 | 15% had salvage RT/ADT 17% had ADT alone | pT1-2 29 (37%) pT3-4 40 (63%) | Median 2.6 | ≤7 39 (50%) ≥8 28 (36%) Not known 11 (14%) | 141 |
| Calais[54] | 68Ga PSMA PET-CT | 270 | None | pT2 99 (37%) pT3-4 144 (53%) Unknown 27 (10%) | Median 0.44 | ≤7 168 (62%) ≥8 86 (32%) Not known 16 (6%) | 304 |
| Schiller[55] | 68Ga PSMA PET-CT | 31 | None | pT2 9 (29%) pT3-4 22 (71%) | Median 0.71 | ≤7 20 (66%) ≥8 11 (34%) | 50 |
| Joniau[96] | Sentinel lymph node mapping | 74 | Not applicable | pT1-2 20 (27%) pT3-4 54 (73%) | Median 10.4 | ≤7 42 (57%) ≥8 32 (43%) | 470 |
| Ganswindt[73] | Sentinel lymph node mapping | 61 | Not applicable | T2 40 (66%) T3-4 (34%) | Median 20.9 | ≤7 39 (64%) ≥8 22 (36%) | 324 |

*Abbreviations:* 68Ga PSMA = gallium 68 prostate specific membrane antigen; ADT = androgen deprivation therapy; CI = common iliac; EI = external iliac; II = internal iliac; Ob = obturator; PET-CT = positron emission tomography-computed tomography; PS = presacral; PSA = prostate specific antigen; RP = radical prostatectomy; RT = radiation therapy.

In the primary disease setting, WPRT was not associated with improved outcomes over prostate-only RT in 2 randomized trials. There has been criticism of the RTOG 9413 and Genitourinary Group (GETUG)-01 methodologies, including inadequate power to compare the treatment arms (RTOG 9413) and overrepresentation of low- and intermediate-risk patients (who might be less likely to benefit from WPRT [GETUG-01]).[66] However, it has also been suggested that inadequate coverage of superior nodal regions might be another reason for the apparent absence of improved outcomes for patients treated with WPRT over prostate-only RT. In RTOG 9413 and GETUG-01, the superior border was set at L5/S1 and S1/2, respectively.[67,68] The RTOG 0534 Short Term Androgen Deprivation With Pelvic Lymph Node or Prostate Bed Only Radiotherapy (SPPORT) study of WPRT in the setting of post-RP biochemical recurrence also used L5/S1 as the superior border for the elective volume.[69] However, because a superior border at L5/S1 may not cover all common iliac nodes, the recently closed RTOG 0924 trial of WPRT in high-risk primary disease increased the superior border to L4/5.[70] It may be more appropriate to use vascular anatomy to demarcate the extent of nodal regions rather than bony landmarks because nodal metastases appear closely localized to major blood vessels.[71] Two ongoing trials of WPRT in the oligorecurrent PCa setting, Salvage Radiotherapy Combined With Hormonotherapy in Oligometastatic Pelvic Node Relapses of Prostate Cancer (OLIGO-PELVIS) (ClinicalTrials.gov identifier: NCT02274779) and STORM (ClinicalTrials.gov identifier: NCT03569241), identify the superior border of the elective nodal volume as the level of the aortic bifurcation rather than a vertebral interspace.[25,72]

## Determining the optimal elective nodal RT volume

Several studies have evaluated the effect of imaging on nodal coverage by WPRT fields. Ganswindt et al[73] used a sentinel node technique and reported that 30% of nodes found were outside the standard WPRT template, with the highest proportions in the external iliac, perirectal, and para-aortic regions. Parker et al[49] evaluated the location of recurrences after post-RP RT using choline PET-CT and found that 43% and 63% of recurrences would be within

**Table 2**  (continued)

| Obturator (%) | II (%) | EI (%) | CI (%) | Presacral (%) | Perirectal (%) | Aortic bifurcation | Para-aortic (%) |
|---|---|---|---|---|---|---|---|
| Number of nodes: 15 (9%) | 15 (9%) | 45 (28%) | 38 (24%) | 2 (1%) | 10 (6%) | | 30 (19%) |
| Number of patients: (distal to CI bifurcation) 74 (37%) | | | 43 (21%) | | 18 (9%) | | 21 (10%) |
| Number of nodes: II/Ob 30 (14%) | II/Ob 30 (14%) | 48 (23%) | 52 (25%) | 6 (3%) | 7 (3%) | | 42 (20%) |
| Number of nodes: 6 (5%) | 15 (12%) | 27 (22%) | 24 (20%) | 3 (2%) | 6 (5%) | | 26 (21%) |
| Number of patients: (distal to CI bifurcation) 41 (53%) | | | CI and PS 12 (15%) | CI and PS 12 (15%) | 4 (5%) | | 15 (19%) |
| Number of nodes: 24 (8%) | 32 (11%) | 45 (15%) | 26 (9%) | 22 (7%) | 25 (8%) | | |
| Number of nodes: 3 (6%) | 14 (28%) | 7 (14%) | 6 (12%) | 4 (8%) | 10 (20%) | | 1 (2%) |
| Number of sentinel nodes: 78 (17%) | 107 (23%) | 77 (16%) | 88 (19%) | 35 (7%) | 14 (3%) | 17 (4%) | 49 (10%) |
| Number of sentinel nodes: II/Ob 58 (18%) | II/Ob 58 (18%) | 111 (34%) | 41 (13%) | 28 (9%) | 20 (6%) | | 38 (11%) |

WPRT fields with the superior border at L5/S1 and the aortic bifurcation, respectively. Lesions not covered by these radiation fields included para-aortic, perirectal, and some presacral nodes. De Bruycker et al[46] used choline PET-CT to compare nodal positions with WPRT fields. They adapted the PIVOTAL trial volumes by extending the superior border to the aortic bifurcation (approximately L4/5). Using this approach, almost all nodes between the aortic bifurcation and iliac bifurcation were covered. However, coverage of pelvic nodes was 80%. Most of the pelvic nodes not covered by the WPRT volume were within the external iliac region. The authors suggested that extending the external iliac volume distally to the level of the midfemoral head would cover almost all external iliac nodes. Inadequate coverage of nodal regions superior to L5/S1 seen in the post-RP recurrence setting were also observed in a mapping study of nodal recurrence patterns after primary prostate-only RT.[68] Coverage of nodal regions by WPRT with the superior border at L5/S1 was only 42% in comparison to 93% by raising the border to L4/5. Many of the studies that compared patterns of relapse to WPRT/PLND templates found metastases in regions that could not be covered without risking excess toxicity, such as perirectal nodes.[46] The optimum superior limit for WPRT fields remains uncertain. With intensity modulated RT (IMRT), elective nodal volumes can be safely extended into the lower para-aortic region (as far as L2/3).[74] A study of patterns of failure after RP plus postoperative RT or prostate-only RT using choline PET-CT identified that an elective nodal volume extended to L2/3 would potentially cover 95% of at-risk nodal regions.[75] However, at present there is uncertainty regarding the management of patients with relapsed para-aortic nodal disease given the perception that there is a high risk of further metastases and there is a risk of understaging the burden of metastases, even with PET-CT.[76] A single-arm phase II study (NCT03079323) is currently investigating the addition of para-aortic RT to WPRT for pathologically node positive patients after RP and PLND. In this study, the superior border is at the level of the renal vessels (approximately L2/3). Although there might be a clinical benefit in improving coverage of the para-aortic nodal region, this ultimately requires validation within a randomized study.

PSMA PET-CT may be more effective than other PET-CT tracers for mapping nodal recurrences before
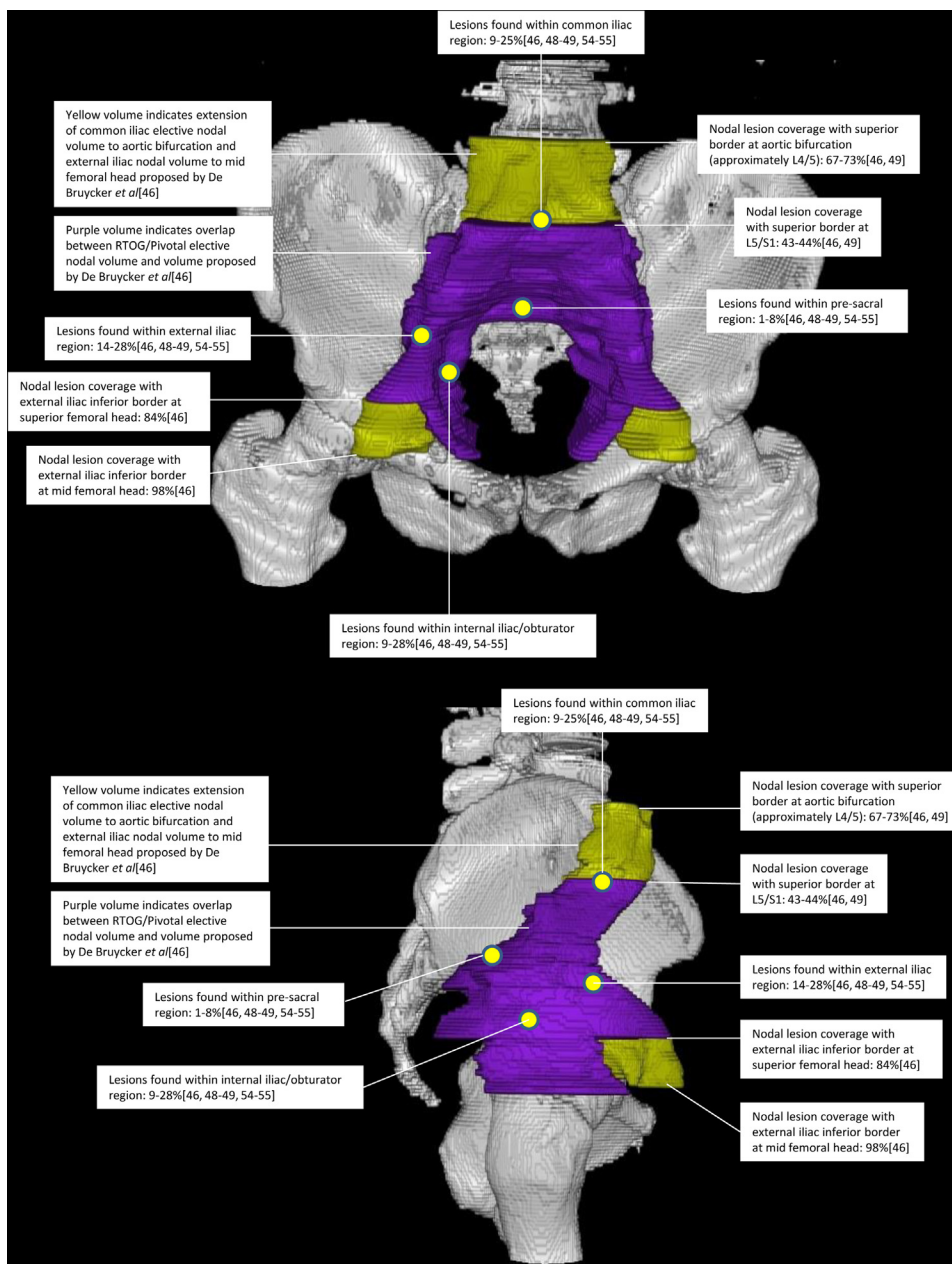
**Figure 1**   Anterior and right lateral views of the pelvis illustrating the locations of nodal metastases evaluated by imaging series in relation to whole pelvis radiation therapy volumes. The purple radiation therapy volume represents the overlap between the Radiation Therapy Oncology Group/Prostate and PelvIc Versus prOstaTe ALone (PIVOTAL) trial volume and the volume recommended by de Bruycker et al. The yellow volume represents the extension of this volume in the common iliac/external iliac nodal regions recommended by de Bruycker et al.[46]

salvage WPRT, especially at low PSA values in the post-RP biochemical recurrence setting. Previous studies have reported that 68Ga PSMA PET-CT before salvage RT resulted in changes to treatment, including modification of radiation fields, dose escalation to PET-CT positive lesions, and addition of ADT.[77-79] Currently, there are ongoing prospective randomized studies in the setting of post-RP biochemical failure (Clinicaltrials.gov NCT01666808, NCT03762759, NCT03525288)

including 1 phase III study (NCT03582774). These compare the current standard of care (salvage RT to prostatic fossa) with PSMA/fluciclovine PET-CT-guided salvage RT (either to prostatic fossa alone or with the addition of pelvic lymph nodes, depending on PET-CT findings). However, general implementation of PET-CT before salvage RT should be guided by results from phase III trials, such as NCT03582774, given that "blind" prostate fossa salvage RT remains an effective treatment.

In addition, there remain limitations to the size of nodal metastases that can be confidently detected as well as false positive results, even with PSMA PET-CT, especially at the very low PSA levels at which salvage RT is initiated.[80] A further consideration is the optimum management for patients with biochemical failure post-RP who have low volume metastatic disease detected by PSMA PET-CT at low PSA levels.[81] It is uncertain if changes in management based on such imaging findings alter the overall disease course. Despite these questions, the ability of novel imaging technologies such as PSMA PET-CT to detect metastatic disease at very low PSA levels appears to be blurring the distinction between the biochemical and radiologic recurrence phases.[53]

The question of whether improved coverage of nodal regions by WPRT in the recurrent PCa setting translates into better oncological outcomes also remains unanswered. There is a strong theoretical rationale for treating both macroscopic oligometastatic disease and adjacent microscopic disease using SABR and WPRT if oligometastatic disease represents an intermediate state between localized and widely disseminated disease.[58] However, although phase II studies are investigating this, phase III trials are needed to determine the actual clinical benefits compared with standard of care (ADT) and to study the increasingly popular use of SABR to the involved node alone without WPRT.[25,72]

A further consideration with WPRT, especially with extended fields, is the potential for increased toxicity. However, with IMRT, significant late genitourinary and gastrointestinal toxicities can be minimized.[82] In the recent first report of RTOG 0534 SPPORT, 87% of patients received IMRT and ≥grade 3 late genitourinary and gastrointestinal toxicities were observed in 6% and 1.1% of patients, respectively.[69] Developments in IMRT and image guided RT suggest that dose escalation to involved nodes and hypofractionated regimens can also be safely and effectively delivered.[66] However, expanding coverage of nodal regions for all patients could risk excess toxicity and compromise the delivery of dose escalated radiation to sites of macroscopic disease. Individualized elective target volumes that include only those nodal regions identified using imaging as at-risk of involvement could be a solution. Radiologic investigations such as sentinel lymph node mapping using Single Photon Emission Computed Tomography (SPECT) and magnetic resonance lymphography may help identify both positive nodes and at-risk nodal regions.[83] In the future, the prediction of at-risk nodal regions from radiologic examinations could be further refined through the use of radiomics and machine learning algorithms.[66]

In summary, it should be acknowledged that questions remain regarding the clinical benefits and the timing/trigger for PET-CT guided interventions, especially at very low PSA levels or for sites of micrometastatic nodal disease. Further uncertainties exist concerning the optimum intervention, its timing, and whether elective treatment of nodal regions should be performed instead of metastasis-only therapies and, if so, which nodal regions should be included.[81] Patients should be informed of these uncertainties and encouraged to enter clinical trials to determine the optimum therapeutic approach.

## Future directions: Radiomics, radiogenomics, and the RT pathway

Currently, interpretation and reporting of medical imaging are generally restricted to qualitative descriptions of tumor location, size, and shape and features such as necrosis, patterns of enhancement, and relationships to surrounding structures.[84] In contrast, the rapidly evolving field of radiomics uses computer algorithms to extract quantitative data from CT, MRI, and PET, including information not discernible by human observation. It has been identified that many clinically significant tumors, including PCa, exhibit intratumoral heterogeneity as a result of genomic instability.[85] This produces clonogenic subpopulations within the primary tumor and between metastatic sites, with the potential for more aggressive behavior and greater treatment resistance. Radiomics assumes that characteristics of tumor heterogeneity and variations within the tumor microenvironment correspond to particular imaging features, known as habitats.[85,86] By extracting geometric, textural (analysis of individual voxel intensities), and statistical information, radiomics offers the potential to develop imaging biomarkers or radiomic feature signatures that reflect the heterogeneity of underlying tumor genomics, biology, and behavior, which could provide important prognostic information.[87] The additional functional information provided by multiparametric MRI and PET-CT, for example concerning cellular density, vascularity, hypoxia, and metabolism, could be especially valuable.[86]

Given the increasing number of imaging examinations that are performed, there is the potential to combine this information with clinical, histopathologic, and genomic data to create integrated diagnostic databases containing vast amounts of data derived from large patient numbers. This could be key in the development of personalized precision medicine.[84,85,88] As well as providing a valuable resource, such databases could be used for machine learning algorithm training (a subset of artificial intelligence) with the intention of automating radiomic analyses, increasing disease detection, monitoring changes in multiple lesions and/or in response to treatment, reducing errors, and predicting outcomes based on comparisons with large numbers of previously treated patients. In the future, it is possible that imaging could be integrated with measurement of circulating tumor DNA to provide near real-time tracking of tumor activity.[84] Such developments

could well influence our understanding of when and how to intervene in the management of patients with node-only relapsed PCa. However, considerable challenges remain regarding routine clinical use of radiomics and artificial intelligence. These include variations in imaging techniques and equipment as well as a need to standardize data collection, image curation, and reporting. In addition, it is necessary to standardize and validate methods of tumor segmentation and radiomic feature extraction and to overcome barriers to data sharing and address information governance concerns.[84,88,89]

Radiogenomics is an emerging field investigating how individual genetic variation is associated with the development of early and late RT toxicities, outside of differences in RT dose/fractionation, technique, concurrent therapies, smoking, and comorbidities.[90] The increasing availability of whole genome sequencing means that, in the future, RT toxicity risk could be estimated using predictive models and treatment tailored accordingly. This means that radiogenomics could contribute toward decision making regarding whether SABR, WPRT, salvage PLND, or another approach is most appropriate for patients with pelvic nodal PCa relapses. In patients considered to have low risk of RT toxicity, dose escalation, more extensive volumes (eg, the addition of an elective nodal volume), and reirradiation strategies could be considered whereas alternative treatments (eg, surgery) may be more appropriate for those considered high-risk.[91]

## Limitations of current evidence

There is considerable heterogeneity in the published literature concerning the diagnostic performance of PET-CT tracers in recurrent PCa. Relatively few prospective comparative studies between different PET tracers have been performed, and there is an absence of phase III evidence in this setting.[35,41,44] Assessment of the diagnostic performance as well as comparisons between tracers are limited by the quality of much of the published literature. Many of the studies contained within systematic reviews and meta-analyses are retrospective, potentially selective single center studies, often with small patient numbers, no histopathologic correlation of PET-CT positive lesions, heterogenous patient populations (eg, different risk categories of PCa and PSA values), and different injected activities of the tracer.[23] In addition, the detection of recurrent disease, and hence diagnostic performance, by PET-CT depends on PSA level, doubling time and velocity, size of the involved lymph node, receipt of anticancer therapy (eg, ADT), and Gleason score.[22] It has also been suggested that greater standardization in the reporting of PET-CT examinations is required.[92] The result of all these factors is that variable diagnostic performance statistics have been reported for the different PET

tracers.[23] A further consideration is whether performance is reported per patient or per lesion. Because it may frequently be impractical to obtain histologic confirmation for all lesions visualized on PET-CT, nonhistopathologic methods for confirming presence of recurrent disease (such as interval imaging or serial PSA measurement) may be used, but this approach is subject to examination bias.[12,23,93] This lack of histopathologic confirmation means that many studies report detection rates rather than sensitivity/specificity values, which are commonly used to describe performance of diagnostic investigations, and there is also a risk of false positive results as a consequence.[21] There is a need for more robust sensitivity and specificity data to better understand the diagnostic performance of PET tracers in the recurrent PCa setting.[34] These uncertainties and the absence of clinical trial data/direct comparisons between PET-CT tracers mean that there are unanswered questions concerning the optimum PET-CT tracer, the timing/trigger for imaging, and the clinical benefit of identifying sites of disease in the biochemical recurrence setting. These limitations also extend to studies that used PET-CT to map patterns of nodal failure and to guide delivery of salvage therapies. Further variation exists between studies as to whether patients treated with salvage RT to the prostate bed and/or ADT before PET-CT are included. The type and extent of PLND performed at the time of RP was often poorly described. In addition, studies differ as to which precise subdivisions of pelvic/extrapelvic nodal regions they include within their analyses and whether the location of nodes is described per patient or per lesion.

## Priorities for current/future studies

Given the increased use of RP in patients with high-risk PCa, it is a priority to establish the optimal role of PET-CT and the best PET tracer for staging patients with biochemical failure post-RP. Table 3 summarizes ongoing randomized trials investigating the use of PET-CT in this setting to guide salvage RT (Clinicaltrials.gov NCT01666808, NCT03762759, NCT03525288, NCT03582774). These studies, especially the phase III trial NCT03582774, could provide evidence to support PET-CT as an aid to decision making regarding RT delivery to the prostatic fossa and/or pelvic lymph nodes. However, the need remains for phase III studies that directly compare choline, fluciclovine, and/or PSMA to determine the optimum PET tracer for use in the recurrent PCa setting post-RP. The question of whether delivering WPRT in addition to prostatic fossa RT influences the pattern of further nodal failure and longer term oncological outcomes could be answered by the analysis of mature data in studies such as RTOG 0534 SPPORT.[69] However, the timing of postoperative RT (either immediate or salvage) has been controversial, and whether the

**Table 3**   A summary of randomized clinical trials currently investigating PET-CT directed radiation therapy in the recurrent PCa setting

| Study | Location | Study dates | Study type | Study purpose | Intervention | Study population | Endpoints |
|---|---|---|---|---|---|---|---|
| NCT03582774 | Los Angeles, USA | 2018-2024 | Randomized phase III study | To investigate 68Ga PSMA PET-CT directed RT post-RP | 68Ga PSMA PET-CT before prostatic fossa with/without WPRT | Post-RP detectable PSA | Primary: Biochemical progression-free survival Secondary: Metastasis-free survival and additional PCa therapy initiation-free survival |
| NCT01666808 | Atlanta, USA | 2012-2022 | Randomized phase II study | To investigate fluciclovine PET-CT vs conventional imaging directed RT post-RP | Fluciclovine PET-CT before prostatic fossa with/without WPRT | Post-RP detectable PSA | Failure-free survival at 3 years |
| NCT03762759 | Atlanta, USA | 2019-2025 | Randomized phase II study | To investigate fluciclovine vs 68Ga PSMA PET-CT directed RT post-RP | Fluciclovine or 68Ga PSMA PET-CT before prostatic fossa with/without WPRT | Post-RP detectable PSA | Primary: Disease-free survival Secondary: RT decision making and dosimetric endpoints |
| NCT03525288 | Montreal, Canada | 2018-2026 | Randomized phase II study | To investigate 18F PSMA PET-CT vs conventional imaging directed RT for high-risk primary, post-RP, or oligometastatic PCa | 18F PSMA PET-CT before RT to prostate gland/prostatic fossa plus up to 5 sites of metastasis | High-risk primary, post RP, or oligometastatic PCa | Failure-free survival at 5 years |

*Abbreviations:* 18F PSMA = fluorine 18 prostate specific membrane antigen; 68Ga PSMA = gallium 68 prostate specific membrane antigen; PCa = prostate cancer; PET-CT = positron emission tomography-computed tomography; PSA = prostate specific antigen; RP = radical prostatectomy; RT = radiation therapy; WPRT = whole pelvis radiation therapy.

presence of high-risk features, a particular PSA level, or a positive PET-CT examination should be used as the trigger for intervention remains unanswered. The initial results from the Radiation Therapy and Androgen Deprivation Therapy in Treating Patients Who Have Undergone Surgery for Prostate Cancer (RADICALS-RT) trial (International Standard Randomized Controlled Trial Number: ISRCTN40814031) and the Adjuvant or Salvage Radiotherapy for the Treatment of Localized Prostate Cancer (ARTISTIC) meta-analysis of the RADICALS-RT, Genitourinary Group and French Association of Urology (GETUG-AFU) 17 (NCT00667069), and Comparing Adjuvant Radiotherapy

(RT) With Early Salvage RT in Patients With Positive Margins or Extraprostatic Disease Following Radical Prostatectomy (RAVES) (NCT00860652) trials were recently presented, which suggest that early salvage RT may be preferable to adjuvant RT because no significant difference in biochemical progression-free survival was observed between adjuvant RT and salvage RT triggered by a PSA rise (PSA $\geq$0.2 ng/mL or 3 consecutive rises).[94,95] However, it has been observed that PSMA PET-CT may be positive at PSA <0.2 ng/mL.[21,33,34] For patients with established oligometastatic nodal disease, ongoing phase II studies could provide preliminary evidence as to whether delivering WPRT in addition to a

boost to macroscopically involved nodes influences longer term outcomes.[25,72] There remains a need for phase III trials in this setting. The optimum nodal volume, especially regarding the level of the superior border, also remains uncertain. Whether fewer further relapses are seen within superior nodal regions in ongoing studies that used L4/5 (or aortic bifurcation) for the superior border of the clinical target volume, as opposed to L5/S1, could provide evidence to help answer this question.[25,72]

## Conclusions

With increasing use of RP to treat patients with high-risk PCa, nodal relapse within the pelvis is increasingly common. Relapses are frequently observed in superior nodal regions, which could limit the efficacy of current salvage WPRT and PLND templates. There is increasing use of PET-CT to restage patients with biochemical failure, especially with PSMA PET-CT, and subsequently an increase in the identification of sites of nodal metastasis at low PSA levels after RP. This is leading to a merging of the biochemical and radiologic recurrence phases, but the optimal therapeutic approach remains undefined. Current trials are investigating postoperative RT to the whole pelvis in addition to the prostatic fossa, the use of PET-CT in the setting of biochemical recurrence to guide delivery of salvage RT, and, for patients with node-only relapsed PCa, the addition of WPRT to metastasis-directed therapies. The most appropriate target volume for salvage RT remains uncertain. Although the findings of studies using PET-CT to map nodal recurrences suggest that there could be a role for extending WPRT volumes to increase coverage of superior nodal regions, the clinical effect of doing so remains undefined. Patients should be informed of these uncertainties and encouraged to enter clinical trials.

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