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Clinical Investigation: Genitourinary Cancer

Value of PET/CT and MR Lymphography in Treatment of Prostate Cancer Patients With Lymph Node Metastases

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Summary

A total of 29 prostate cancer (PCa) patients underwent MRL and ^{11}C-choline PET/CT. Both molecular imaging techniques can detect lymph node (LN) metastasis without using the size criteria. This resulted in the detection of metastases in normal-size LNs and suspicious LNs outside the conventional CTV. Potentially, these findings allow us to individualize treatment selection and enable image-guided radiotherapy for patients with PCa LN metastases.

Purpose: To determine the clinical value of two novel molecular imaging techniques: ^{11}C-choline positron emission tomography (PET)/computed tomography (CT) and ferumoxtran-10 enhanced magnetic resonance imaging (magnetic resonance lymphography [MRL]) for lymph node (LN) treatment in prostate cancer (PCa) patients. Therefore, we evaluated the ability of PET/CT and MRL to assess the number, size, and location of LN metastases in patients with primary or recurrent PCa.

Methods and Materials: A total of 29 patients underwent MRL and PET/CT for LN evaluation. The MRL and PET/CT data were analyzed independently. The number, size, and location of the LN metastases were determined. The location was described as within or outside the standard clinical target volume for elective pelvic irradiation as defined by the Radiation Therapy Oncology Group. Subsequently, the results from MRL and PET/CT were compared.

Results: Of the 738 LNs visible on MRL, 151 were positive in 23 of 29 patients. Of the 132 LNs visible on PET/CT, 34 were positive in 13 of 29 patients. MRL detected significantly more positive LNs ($p < 0.001$) in more patients than PET/CT ($p = 0.002$). The mean diameter of the detected suspicious LNs on MRL was significantly smaller than those detected by PET/CT, 4.9 mm and 8.4 mm, respectively ($p < 0.0001$). In 14 (61%) of 23 patients, suspicious LNs were found outside the clinical target volume with MRL and in 4 (31%) of 13 patients with PET/CT.

Conclusion: In patients with PCa, both molecular imaging techniques, MRL and ^{11}C-choline PET/CT, can detect LNs suspicious for metastasis, irrespective of the existing size and shape criteria for CT and conventional magnetic resonance imaging. On MRL and PET/CT, 61% and 31% of the suspicious LNs were located outside the conventional clinical target volume.

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Therefore, these techniques could help to individualize treatment selection and enable image-guided radiotherapy for patients with PCa LN metastases.

Keywords: Ultra-small super-paramagnetic iron-oxide nanoparticles, Lymph node, Magnetic resonance imaging, MRI, Prostate cancer, Positron emission tomography, Computed tomography, ^{11}C-choline PET/CT

Introduction

Prophylactic whole pelvic radiotherapy (WPRT) is often given for high-risk and unfavorable intermediate-risk prostate cancer (PCa) patients, in addition to hormonal therapy. However, the outcome has been variable. Two main reasons for this could be differences in patient selection, variability in the a priori risk of lymph node (LN) involvement, and variability in the radiation fields (1, 2). The need for an accurate target volume for LN RT was recently underlined by Ganswindt *et al.* (3), who presented an anatomic atlas of prostate sentinel LNs. They found 66% of patients had sentinel LNs outside the standard target volume used. The findings of Ganswindt *et al.* (3) suggest that geographic miss is a substantial problem in WPRT and that more accurate methods for imaging LN metastases are needed. Also, the use of more accurate imaging techniques could improve patient selection for WPRT.

Equations and nomograms that predict the risk of LN involvement for patient selection are based on the prostate-specific antigen (PSA) value and Gleason grade. In the detection of local recurrence, PSA kinetics can be useful; however, they have limited value for predicting LN involvement (4). The nodal risk formula overestimates LN involvement, leading to significant overtreatment (5). Nomograms have to be used, because morphologic imaging techniques, such as conventional magnetic resonance imaging (MRI) or computed tomography (CT), are not sufficiently sensitive nor sufficiently specific in the detection of LN metastasis. A meta-analysis by Hövels *et al.* (6) in 2008 showed a pooled sensitivity of 0.42 and 0.39 and a pooled specificity of 0.82 and 0.82 for CT and MRI, respectively. Invasive surgical standard pelvic LN dissection also underestimates LN involvement in high-risk and unfavorable intermediate-risk PCa patients (1). A reason for underestimating LN metastases could be that 40%−50% of the positive LNs are found outside the surgical standard pelvic LN dissection field. Furthermore, sensitivity is lacking for the standard cytopathologic evaluation, resulting in a false-negative rate of $\leq$30%, mainly because of micrometastasis (1). Thus, limited information is available about the correct number, size, and location of metastatic LNs.

Molecular imaging techniques, such as ferumoxtran-10−enhanced magnetic resonance lymphography (MRL) and ^{11}C-choline PET/CT (PET/CT), with the ability to visualize specific cell or tissue function, can potentially improve the accuracy for assessing the LN status.

Magnetic resonance lymphography is a molecular imaging technique capable of separating normal functioning LN tissue from LN tissue invaded by metastasis by labeling the macrophages in normal LNs with ferumoxtran-10. MRL does not rely on the conventional size and shape criteria to detect LN metastases. Several studies have indicated that the diagnostic performance of MRL in pretreatment patients varies from 88% to 90% and 96% to 98% for sensitivity and specificity, respectively (7−9).

^{11}C-choline is a PET agent that is incorporated into tumor cells after phosphorylation by choline kinase (10). PET/CT is an accurate and sensitive imaging method for the staging of pelvic LNs (11). The reported performance of PET/CT for LN metastasis detection varies from 60% to 64% for sensitivity and 90% to 98% for specificity on a patient-by-patient analysis, respectively (12, 13).

Because these molecular imaging modalities appear to be more accurate for the detection of LN metastases than conventional imaging, they might have a potential role in the workup of PCa patients, who might be candidates for WPRT. Thus, the aim of the present study was to evaluate the findings of MRL and PET/CT within the same patient group in terms of the number, size, and location of positive LNs to evaluate their potential clinical use for patient selection and target volume determination for LN RT.

Methods and Materials

Patients

A group of 29 patients with either primary PCa or recurrent disease, who were referred for MRL at our institution in 2005 to

Table 1 Patient characteristics and demographics pertaining to PET/CT and MRL imaging

Characteristics and demographics	Value
Patients (*n*)	29
Age (y)	
Mean ± SD	63 ± 9
Range	48−79
PET/CT and USPIO MRL performed (*n*)	
Before local therapy	7
After radical prostatectomy with increasing PSA level	9
After radical prostatectomy combined with HT	7
After HT	5
After HIFU combined with HT	1
Patients receiving HT (*n*)	13
PSA value at diagnosis (ng/mL)	
Mean ± SD	9.9 ± 13.9
Range	0.6−58
Gleason score	
Median	8
Range	5−9
Interval between PET/CT and USPIO MRL (d)	36 ± 52

Abbreviations: CT = computed tomography; HIFU = high-intensity ultrasound; HT = hormonal therapy; MRL = magnetic resonance lymphography; PET = positron emission tomography; PSA = prostate-specific antigen; USPIO = ultra-small super-paramagnetic iron-oxide nanoparticles.

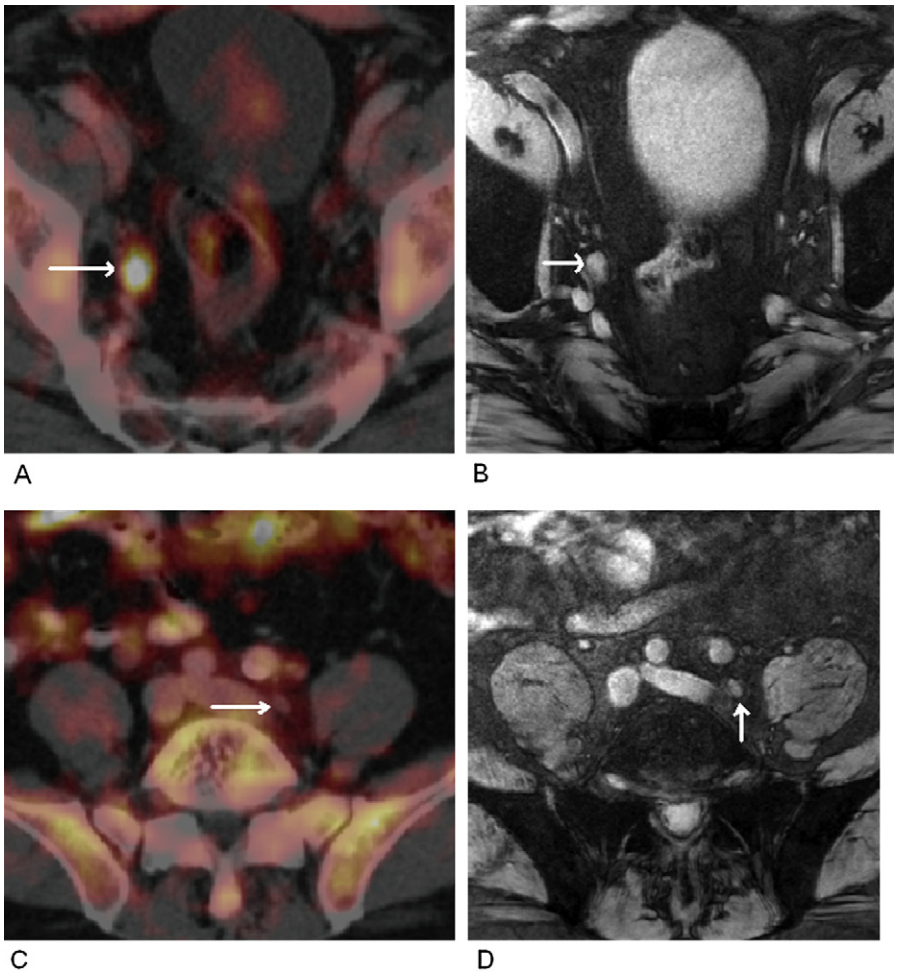

Fig. 1. Post-treatment patient. On both positron emission tomography/computed tomography (PET/CT) (A) and magnetic resonance lymphography (MRL) (B), 9-mm positive lymph node (LN) (arrow) detected in right internal iliac region. MRL, however, also demonstrated high-signal intensity 4-mm suspicious LN in left common iliac region (D, arrow), which was negative on PET/CT (C).

2006 and who had also undergone PET/CT at their referring institution were included. Of the 29 patients, 22 presented with recurrent disease and 7 had been referred before their initial treatment. All patients gave informed consent for the intravenous injection of the LN contrast and the use of the obtained data for research purposes. The patient characteristics and demographics are listed in Table 1.

Imaging and interpretation

The 29 PET/CT examinations were performed at four different institutions using an identical integrated PET/CT system (Siemens Healthcare, Erlangen Germany). All PET/CT Digital Imaging and Communications in Medicine images were reconstructed in the axial, coronal, and sagittal views and corrected for attenuation. Two experienced nuclear medicine specialists (S.N.R., with 18 years' experience, and C.S., with 2 years' experience) qualitatively reviewed the images retrospectively to anatomically localize the sites of pathologic ^{11}C-choline uptake. LNs with increased tracer uptake were considered suspicious for metastatic spread, and LNs without detectable tracer uptake were considered nonsuspicious.

Magnetic resonance lymphography was performed at a field strength of 1.5 Tesla (2 of 29) and 3.0 Tesla (27 of 29) using a pelvic phased array coil (Sonata/Symphony and Trio, Siemens, Erlangen, Germany). Two-dimensional magnetic resonance images were acquired of the pelvis, extending from the renal artery to the pubic bone 24 hours after the intravenous drip infusion of ferumoxtran-10 (2.6 mg ferritin/kg); 20–35-nm particle size (Guerbet, Paris, France), as described by Harisinghani *et al.* (7) and Heesakkers *et al.* (8). All MRL images were analyzed by 2 experienced uroradiologists (J.O.B. and S.T., with 11 and 2 years' experience for evaluating MRL, respectively). A LN was considered suspicious for metastasis if the entire LN or a focal area did not show a low signal on the ferumoxtran-10–sensitive images. A LN was considered normal if it showed a homogeneous low signal.

The size of the positive LNs on both modalities was determined. Their location was registered in relation to the clinical target volume (CTV) for elective pelvic RT as defined by the Radiation Therapy Oncology Group (14) by 2 independent researchers (A.S.F. and H.J.M.M.).

The PET/CT and MRL images were evaluated by the imaging specialists who were unaware of the outcomes from the other modality and independent of each other.

Table 2 Node detection and characteristics for MRL and PET/CT

Variable	MRL	PET/CT	*p*
Total nodes (n = 29 patients)	738	132	
Nodes/patient (n)			<0.0001*
Mean	25	4.4	
Range	4–76	1–26	
Nodal size range (mm)	2–20	4–19	
Positive nodes (n)	151 (n = 23 patients)	34 (n = 13 patients)	0.002†
Short diameter (mm)			<0.0001*
Mean	4.9	8.4	
Range	2–20	4–19	
Positive node cutoff = 7 mm			
<7	125	12	
≥7	26	22	
Negative nodes (n)	587	98	

Abbreviations: MRL = magnetic resonance lymphography; PET = positron emission tomography; CT = computed tomography.
* Paired *t* test.
† McNemar test.

Statistical analysis

The number, size, and location of the positive LNs using PET/CT and MRL were compared and correlated by a third independent radiologist (W.M.L.L.G.D.). The outcome was evaluated on a patient and node analysis level. As a cutoff level for diameter analysis, we used 7 mm, the minimal short-axis diameter for malignant LN on plain MRI (15). For statistical analysis, the paired *t* test was used: (*1*) to quantify the discordance between the number of suspicious LNs found on PET/CT and MRL, and (*2*) to evaluate the discordance between the axial diameter of the suspicious LNs found on PET/CT and MRL. To evaluate the discordance at the patient level, the McNemar test was performed. The analyses were performed using Statistical Package for Social Sciences, version 16.0, for Windows (SPSS, Chicago, IL).

Results

On MRL, 738 LNs were visible, of which 151 were suspicious for metastasis in 23 of 29 patients. On PET/CT, 132 LNs were visible, with 34 suspicious for metastasis in 13 of 29 patients. Positive LNs on both MRL and PET/CT are shown in Fig. 1A,B, with LNs positive only on MRL are shown in Fig. 1C,D. Differences in the number of positive LNs ($p < 0.0001$) and positive patients ($p = 0.002$) were significant (Table 2).

The mean diameter of detected positive LNs on MRL and PET/CT was significantly different at 4.9 mm and 8.4 mm, respectively ($p < 0.001$; Table 2). Figure 2 illustrates the size distribution of the positive LNs.

Magnetic resonance lymphography detected positive LNs in 10 of 29 patients with initial negative PET/CT findings and thus changed the outcome of LN assessment from normal to positive. Of these 10 patients, 3 presented before their initial treatment. In these 10 patients, the all positive LNs were <7 mm (2 mm in 2, 3 mm in 14, 4 mm in 18, 5 mm in 7, and 6 mm in 5; Table 2 and Fig. 2). In the 13 of 29 patients with positive findings on both MRL and PET/CT, MRL detected 71 more positive LNs than PET/CT. All 71 LNs were <7 mm (2 mm in 13, 3 mm in 20, 4 mm in 19, 5 mm in 13, and 6 mm in 6; Tables 2 and 3).

On MRL, 125 of 151 positive LNs were <7 mm and only 26 were ≥7 mm. On PET/CT, 12 of 34 positive LNs were <7 mm and 22 were ≥7 mm (Table 2 and Fig. 2).

The MRL and PET/CT findings showed 67 of 151 and 10 of 31 positive LNs in 14 (61%) of 23 and 4 (31%) of 13 patients outside the CTV, respectively (Figs. 1D and 3 and Table 3).

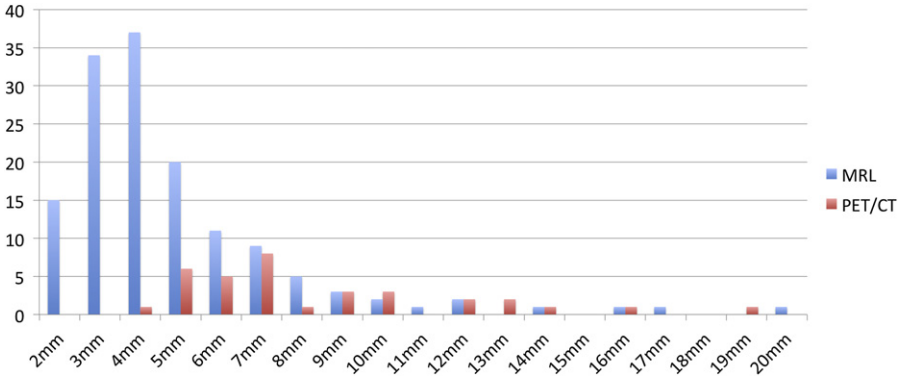

Fig. 2. Overview of axial lymph node diameter of positive lymph nodes. MRL = number of found lymph nodes with corresponding axial diameter on magnetic resonance lymphography; PET/CT = number of found lymph nodes with corresponding axial diameter on positron emission tomography/computed tomography.

Table 3 Node detection in individual patients

	LN MRL			LN PET/CT		
Pt. No.	Negative	Positive	Positive outside CTV	Negative	Positive	Positive outside CTV
1 P	16	0		3	0	
2 R	31	1		0	0	
3 R	32	2		3	0	
4 R	9	5	1	3	1	
5 R	13	5	2	5	0	
6 R	22	1		1	2	
7 P	33	0		7	0	
8 R	32	1		0	1	
9 R	1	3	3	0	1	1
10 R	26	1		1	0	
11 R	16	0		3	0	
12 P	9	5	1	1	0	
13 R	70	6		7	0	
14 P	13	4		4	0	
15 R	9	11	1	3	5	1
16 R	0	3	1	0	1	
17 R	13	18	9	0	9	4
18 R	12	10	8	4	0	
19 R	15	0		2	0	
20 R	11	9	7	3	1	
21 P	26	4		1	0	
22 P	22	23	8	6	3	
23 R	25	16	12	13	3	
24 R	31	8	2	3	2	
25 P	17	0		3	0	
26 R	41	0		3	0	
27 R	5	4	4	5	4	4
28 R	0	3		0	1	
29 R	30	8	8	8	0	

Abbreviations: P = before initial treatment; R = recurrent disease, LN MRL = number of lymph nodes found on magnetic resonance lymphography; LN PET = number of lymph nodes found on positron emission tomography/computed tomography.

Positron emission tomography/CT showed suspicion of bone metastases in 1 patient. MRL showed no relevant additional findings.

Discussion

As molecular imaging techniques, both PET/CT and MRL can detect LNs suspicious for metastasis without using the size criteria and thus allows the detection of metastasis in small normal size LN (<7 mm) on conventional MRI and CT.

The present study showed that more positive LNs were detected with MRL than with PET/CT ($p < 0.0001$). The positive LNs on MRL were smaller ($p < 0.0001$), and positive LNs were detected in more patients ($p = 0.002$). ^{11}C-choline is a functional technique that requires a minimal amount of tracer in viable malignant tissue. MRL labels normal macrophages in the LNs. Thus, it does not depend on the functional activity of cancer in the LNs themselves. Furthermore, MRL has greater spatial resolution. These differences explain why more and smaller positive LNs can be detected with MRL. Harisinghani *et al.* (7) reported that with MRL, 30% of metastases found in LNs are <5 mm and in 70% are <10 mm. The detection rate in that study was slightly greater (125 of 151; 83% <7 mm). This minimal difference can be explained by the predominantly greater field strength used in that study. A greater field strength has been reported to improve the visibility of small LNs on MRL (16). On PET/CT, the mean diameter of positive LNs was 8.4 mm and varied from 4 to 19 mm. This agrees with the reported data, in which the mean diameter of missed (false-negative) LN metastasis on ^{11}C-choline PET/CT varied from 4 to 6 mm (12, 13). The mean number of detected LNs on PET/CT in the published data ranged from 1 to 6 LNs and 0.2 to 2 LN metastasis/patient (11, 12), in agreement with our findings. PET/CT and MRL detected 22 and 26 positive LNs that were ≥7 mm, respectively, and therefore the findings substantially agree (Fig. 2 and Table 2). For LNs with an axial diameter of ≤6 mm, however, the difference between the two modalities was significant. Thus, the difference between these two molecular imaging techniques lies in the ability of MRL to detect LNs of ≤6 mm.

Histologic confirmation of the positive LNs was not possible in our group as presented. The lack of histologic confirmation was a limitation of our study. However, our results are in line with in the previously cited data (7–9, 11–13, 16) and the expectations based on the differences in the modalities.

Both PET/CT and MRL could have a role in the workup of PCa patients. For primary PCa, pelvic LN dissection can be omitted if the a priori risk of LN involvement is <5% (17). Based on the reported high sensitivity (88%–90%) and negative predictive

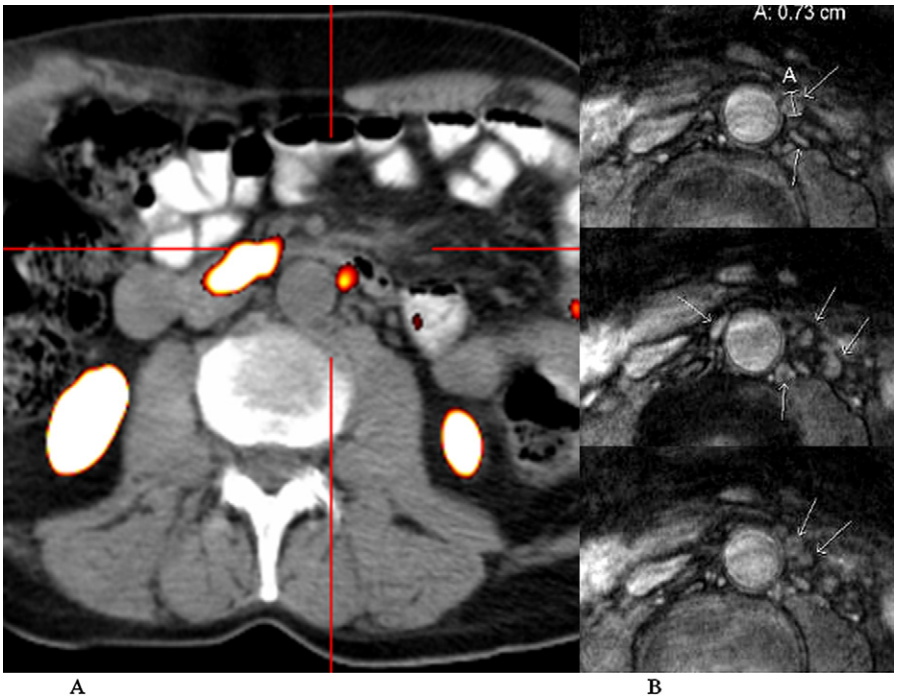

Fig. 3. Post-treatment patient with positive lymph nodes outside clinical target volume. Positron emission tomography/computed tomography (A) detected one and magnetic resonance lymphography (B) detected multiple positive para-aortal lymph nodes outside clinical target volume (arrows). These lymph nodes showed no signal drop on ferumoxtran-10–sensitive images and were thus white.

value (97%–98%) of MRL, this is possible if the MRL findings are negative (7, 8). This was the case for 3 of 7 patients. Thus, 4 of the 7 patients were upstaged. With the use of PET/CT, it is less safe to omit pelvic LN dissection, because the sensitivity (41%–64%) and negative predictive value (72%–97%) in the published data on a nodal basis are too low to ensure a sufficiently low a priori risk (12, 13). Only 1 of 7 patients had LN metastasis on PET/CT (and MRL as well). Two of the patients who were only positive on MRL had their LNs outside the CTV (Table 3).

In the workup of recurrent PCa patients, more accurate imaging methods for determining LN status before local salvage therapy might be even more important. Pelvic LN dissection is usually not performed in patients with recurrent disease, and no nomograms are available to predict the risk of LN involvement. In the present study, 22 of 29 patients developed a PSA relapse after the initial treatment (Table 3). Of these 22 patients, 12 had positive LNs on both MRL and PET/CT, and 7 had positive LNs on MRL only. Of the patients with recurrence, 4 and 8 had positive LNs outside the CTV on PET/CT and MRL and on MRL alone, respectively (Table 3 and Fig. 3).

When no LN or distant metastases are present, a PSA relapse is likely to be caused by local recurrence only and, thus, local therapy is indicated. However, if LN metastases are present, usually systemic hormonal therapy without or with RT is given. The latter group seems to have better survival (18).

Magnetic resonance lymphography detected positive LNs outside the CTV in 14 (61%) of 23 of all positive patients and in 12 (63%) of 19 positive patients with PSA relapse. Preventing geographic miss by knowledge of the LN metastasis location could improve target volume definition and therefore the outcomes of WPRT. Furthermore, recent research toward treating known positive LNs has been encouraging. Recent research showing MRL-guided boost RT to positive LNs to be feasible has been encouraging (19). MRL-guided hypofractionated intensity-modulated RT in patients with known positive LNs seems to be safe and has shown promising results in follow-up (20).

Conclusion

In patients with PCa, both molecular imaging techniques, MRL and PET/CT, can detect LNs suspicious for metastasis, irrespective of the existing size and shape criteria for CT and conventional MRI. However, MRL seems superior to PET/CT in detecting positive LNs <7 mm. On MRL and PET/CT, positive LNs were located outside the conventional CTV in 14 (61%) of 23 and 4 (31%) of 13 positive patients, respectively. Thus, MRL and PET/CT might help to individualize treatment selection and enable image-guided RT.

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