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Original Report

Anatomic distribution of [^{18}F] fluorodeoxyglucose-avid lymph nodes in patients with cervical cancer

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Abstract

Purpose: Current information about the anatomic distribution of lymph node (LN) metastases from cervical cancer is not precise enough for optimal treatment planning for highly conformal radiation therapy. To accurately define the anatomic distribution of these LN metastases, we mapped [^{18}F] fluorodeoxyglucose positron emission tomography (FDG PET)-positive LNs from 50 women with cervical cancer.

Methods and Materials: Records of patients with cervical cancer treated from 2006 to 2010 who had pretreatment PET/computed tomography (CT) scans available were retrospectively reviewed. Forty-one consecutive patients (group 1) with FDG-avid LNs were identified; because there were few positive paraortic LNs in group 1, 9 additional patients (group 2) with positive paraortic LNs were added. Involved LNs were contoured on individual PET/CT images, mapped to a template CT scan by deformable image registration, and edited as necessary by a diagnostic radiologist and radiation oncologists to most accurately represent the location on the original PET/CT scan.

Results: We identified 190 FDG-avid LNs, 122 in group 1 and 68 in group 2. The highest concentrations of FDG-avid nodes were in the external iliac, common iliac, and paraortic regions. The anatomic distribution of the 122 positive LNs in group 1 was as follows: external iliac, 78 (63.9%); common iliac, 21 (17.2%); paraortic, 9 (7.4%); internal iliac, 8 (6.6%); presacral,

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2 (1.6%); perirectal, 2 (1.6%); and medial inguinal, 2 (1.6%). Twelve pelvic LNs were not fully covered when the clinical target volume was defined according to Radiation Therapy Oncology Group guidelines for intensity modulated radiation therapy for cervical cancer.

Conclusions: Our findings clarify nodal volumes at risk and can be used to improve target definition in conformal radiation therapy for cervical cancer. Our findings suggest several areas that may not be adequately covered by contours described in available atlases.

Introduction

Radiation therapy is the standard treatment for locally advanced cervical cancer[1,2] and requires comprehensive treatment of lymph nodes (LNs) at risk of harboring occult disease.[3] Standard radiation therapy fields for cervical cancer include the whole pelvis including the external iliac, internal iliac, and presacral lymph nodes. Compared with standard radiation therapy, highly conformal therapy such as intensity modulated radiation therapy (IMRT) has the potential to reduce radiation-induced toxicity.[4-6] However, the quality of highly conformal therapy depends on accurate delineation of regions at risk. The current definitions of the nodal basins at risk in cervical cancer are based on pathologic analyses of the anatomic distribution of LN metastases and the locations of normal pelvic and paraortic LNs.[7-11] However, these analyses do not provide the detailed information on the spatial location of positive LNs that is needed for highly conformal radiation treatment planning; further, differences in nomenclature among the previous reports make interpretation difficult.[12]

The 2-deoxy-2-[^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) is extremely useful in the detection of LN metastases from cervical cancer, with a sensitivity of 82% and specificity of 95% reported in a meta-analysis.[13,14] In an effort to improve targeting for highly conformal radiation therapy for cervical cancer, we reviewed PET images from patients with cervical cancer to identify the anatomic distribution of FDG-avid LNs. An additional goal of our study was to evaluate the adequacy of recent consensus guidelines for contouring of nodal clinical target volume for IMRT as developed by the Radiation Therapy Oncology Group (RTOG).[15-17]

Methods and materials

Patients

This retrospective analysis was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. We reviewed the records of patients who had been treated for cervical cancer at the Department of Radiation Oncology at MD Anderson Cancer Center from 2006 to 2010 who had pretreatment PET/computed tomography (CT) scans available for review. First, we identified 41 consecutive patients who had FDG-avid LNs on pretreatment PET/CT images (group 1). Next, because there were few positive paraortic LNs in that initial group, we identified 9 additional patients who had positive paraortic LNs (group 2). These 50 patients were the subjects of the current study.

LN mapping

To map the location of the positive LNs, PET/CT images from each patient were transferred to a Pinnacle treatment planning system (Philips Healthcare, Andover, MA). FDG-avid LNs (those identified as positive on the PET/CT report or by a diagnostic radiologist with expertise in gynecologic malignancies [RI]) were contoured on the individual PET/CT scans. The individual node contouring was performed by 2 radiation oncologists (AK, HF). Each contour was evaluated by a diagnostic radiologist. The positive lymph nodes in our study were included based on the FDG avidity and CT appearance of the node. No standard SUV cutoff was utilized. Nodal contours were then mapped to the corresponding location on a single "template" CT image set using bony and soft-tissue landmarks, including relationship to pelvic vessels and musculature, and a deformable image registration algorithm.[18] Briefly, this technique uses a variation of the "demons" algorithm[18] in which CT number information is used for automatic registration between the CT images from a test patient and those of the reference (template) patient to minimize the mean-square gray-value difference between 2 images. In the current study, manual rigid bony (pelvic and femoral head) alignment was first used to align the individual patient CT scan with the template CT data set. The individual LN contours were then deformably mapped onto the template CT data set using a multi-threaded parallel implementation on a Dell Precision workstation (Model T7400 with two 3.0-GHz Xeon E5472 processors; Dell Inc, Round Rock, TX).

The mapped LN locations were individually reviewed and edited to most accurately represent the corresponding location on the original PET/CT scan by a radiologist (RI) and by radiation oncologists specializing in gynecologic malignancies. Fig e1 (available online only at www.practicalradonc.org) illustrates our LN mapping method in a representative patient. Most cases required only minimal

Table 1 Patient and tumor characteristics

Characteristic	All patients (N = 50)	Mean no. of +LNs per patient	Group 1 (consecutively identified) (n = 41)			Group 2 (+PA LNs) (n = 9)		
			No. of patients	No. of +pelvic LNs	No. of +PA LNs	No. of patients	No. of +pelvic	No. of LNs +PA LNs
Disease stage [a]								
IA2	1	1	1	1	0	0	—	—
IB1	1	2	1	1	1	0	—	—
IB2	14	3.0	14	41	1	0	—	—
IIA	4	3.5	4	14	0	0	—	—
IIB	16	5.3	10	25	1	6	35	23
IIIA	0	—	0	—	—	0	—	—
IIIB	11	3.2	10	27	5	1	1	2
IVA	2	2.7	1	4	1	1	0	3
IVB	1	4.0	0	—	—	1	2	2
Totals		3.8	41	113	9	9	38	30

LNs, lymph nodes; +, positive; PA, paraortic; SCC, squamous cell carcinoma.
[a] 2003 International Federation of Gynecology and Obstetrics staging system.

editing, mostly to ensure that the transferred nodal contours excluded normal tissues.

A volume probability map was generated with isotropic nodal volumes by identifying the center of each LN and expanding it to a 1-cm diameter sphere. This approach minimizes the impact of the volume of each LN on the overall probability map.

LN distribution by nodal region

For the first 41 patients (group 1), the percentages of positive LNs along major blood vessels and in the presacral (subaortic) and perirectal regions were calculated. The nomenclature used to describe pelvic lymphatics varies considerably in published reports[11,12,19]; the primary-echelon nodes for the cervix are called inter-iliac and obturator, among other names. We defined nodal regions on the basis of lymphatic and vascular anatomy, which we considered the most appropriate approach given that our primary goal was to identify anatomic locations of LNs to facilitate radiation treatment planning. External, internal, and common iliac and paraortic LNs were defined as those within a 3-cm radial margin of the corresponding blood vessel visible on the template CT scan. According to this definition, internal iliac LNs included the lateral parametrial LNs. Medial inguinal LNs were defined as those caudal to the inguinal ligament. Areas of overlap among LN regions were modified as anatomically appropriate.

Evaluation of LN coverage according to RTOG consensus guidelines

We also evaluated the coverage of PET-positive LNs by standard pelvic radiation therapy fields for cervical cancer and target definition contours according to the RTOG consensus guidelines for pelvic IMRT.[15,20] Of note, the RTOG guidelines were published to be used with accompanying protocol, not intended for the patients in this study. Moreover, the RTOG guidelines recommend that the CTV be extended to include any adjacent visible or suspicious lymph nodes in the contours. The RTOG-defined nodal target volumes were contoured on the template CT scan by a radiation oncologist (AK) according to the images published in the online atlas (where the textual description and images did not match, we used the images). Contouring was done without visualization of the mapped FDG-avid LN contours and the CTV was not modified to include enlarged LNs. The superior border of the RTOG-defined contour was extended to cover the paraortic region; the inferior border was placed at the level of the superior femoral heads. All LNs were displayed as 1-cm-diameter spheres expanding from the LN center, and a node was considered inadequately covered if >50% of this volume was outside the RTOG contours. For standard radiation therapy fields, we evaluated coverage of PET-positive LNs by pelvic fields with superior borders at the aortic bifurcation, L4/L5, or L5/S1.

Results

Patient information

The median age of the 50 patients in the study was 50 years (range, 28-74). Thirty-nine patients had squamous cell carcinoma, 10 had adenocarcinoma, and 1 had adenosquamous carcinoma. The median primary tumor size was 6 cm (range, 1-8). The distribution of patients by disease stage is shown in Table 1.

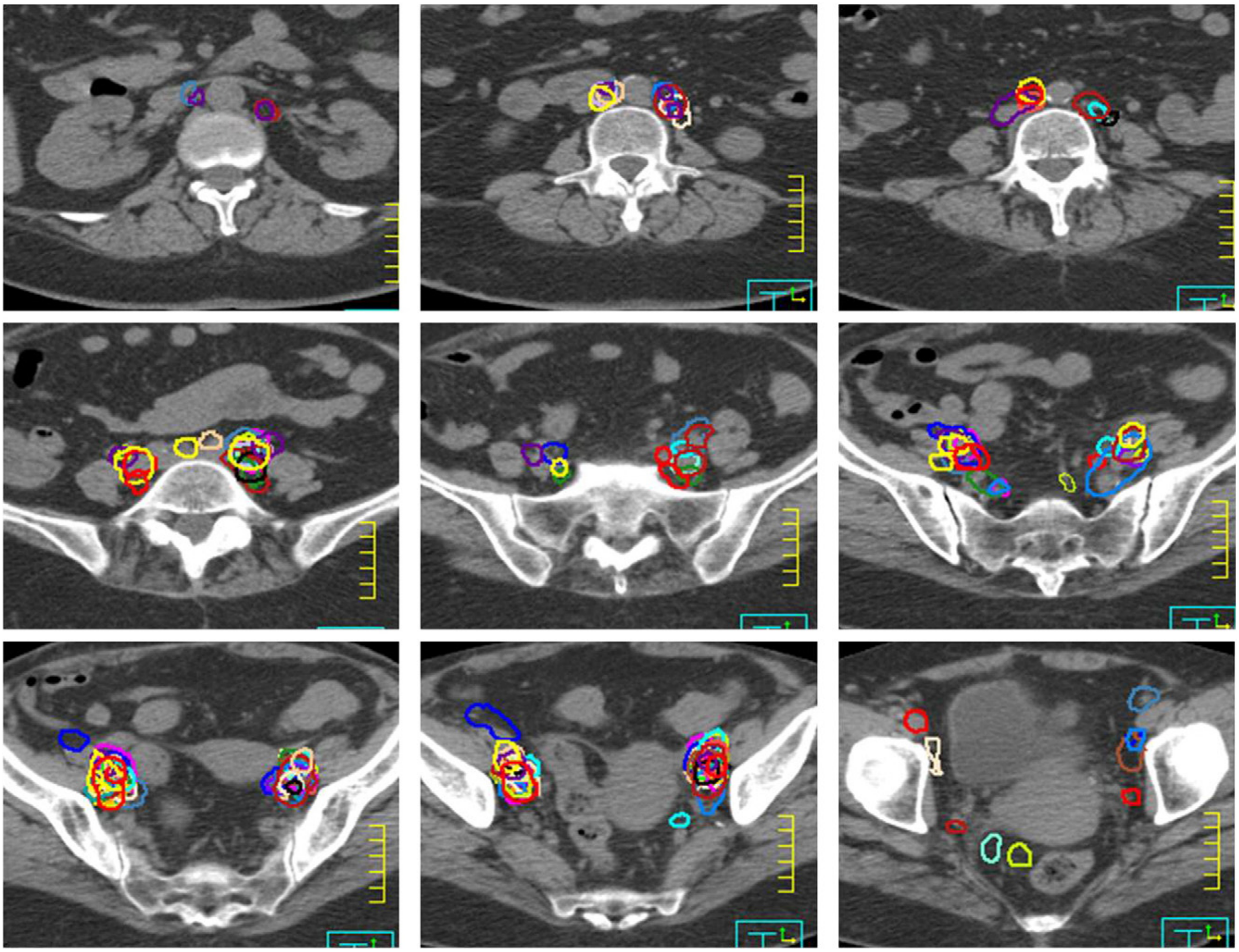

Figure 1 "Atlas" of positron emission tomography (PET)-positive LNs. Representative axial images (superior to inferior) showing the location of all 190 identified PET-positive lymph nodes. All nodes from each patient are contoured in the same color; each color is used for 2 patients.

We identified 190 FDG-avid LNs; 122 in group 1 (the 41 consecutive initially identified patients) and 68 in group 2 (the additional 9 patients with positive paraortic LNs). The median number of positive LNs per patient was 3 (range, 1-6) in group 1 and 5 (range, 3-17) in group 2. The distribution of FDG-avid LNs by disease stage is shown in Table 1.

Anatomic distribution of FDG-avid LNs

Axial images depicting the anatomic distribution of all 190 FDG-avid LNs (from groups 1 and 2) are shown in Fig 1. There were 94 external iliac lymph nodes, 40 common iliac lymph nodes, and 2 parametrial lymph nodes in groups 1 and 2 combined. Our mapping analysis revealed that most PET-positive nodes were located around major vessels, between the psoas muscle and the vascular bundle as seen in Fig 1. The FDG-avid external iliac nodes were generally posterior to the external iliac vessels and extended laterally to the pelvic musculature or bones. Several FDG-avid LNs were located posterior and caudal to the distal external iliac vessels, classically defined as the medial external iliac nodes; these LNs extended just inferior to the level of the superior femoral heads. Two FDG-avid parametrial nodes were noted and these were primarily lateral, most likely because of the difficulty of identifying distinct nodal volumes in the vicinity of the primary tumor. There were also multiple positive common iliac nodes located between the common iliac vein and psoas muscle, extending posteriorly between the psoas muscle and the sacrum. Positive common iliac nodes were also noted lateral to the vessels and anterior to the psoas muscle.

The anatomic distribution of positive LNs in group 1 is summarized in Table 2 and Fig 2. The most common locations of positive LNs were the external iliac region (63.9% of positive LNs) and the common iliac region (17.2%). In group 1, all 41 patients had at least 1 positive distal pelvic LN (ie, at or distal to the bifurcation of the common iliac vessels). Sixteen of the 41 patients (39%)

Table 2 Anatomic distribution of 122 positron emission tomographic-positive lymph nodes in 41 consecutive patients (group 1) with cervical cancer

Lymph node region	No. (%) of positive lymph nodes
Paraortic	9 (7.4)
Common iliac	
	Left 18 (14.8)
	Right 3 (2.5)
External iliac	
	Left 42 (34.4)
	Right 36 (29.5)
Internal iliac	
	Left 4 (3.3)
	Right 4 (3.3)
Presacral	2 (1.6)
Perirectal	2 (1.6)
Medial inguinal (right)	2 (1.6)

had positive common iliac nodes, and 7 of 41 (17%) had positive paraortic nodes. Only 1 patient, from group 2, had positive paraortic nodes without positive pelvic nodes; this patient had stage IVA disease with bladder involvement. Two patients had positive medial inguinal nodes; both had stage III disease, but neither had distal vaginal involvement. Two patients had positive perirectal LNs; 1 (with stage IIIB disease) had anterior rectal involvement on magnetic resonance imaging, and the other (with stage IIA disease) had no evidence of rectal or posterior vaginal involvement on imaging or physical examination. All patients who had positive LNs in low-frequency regions (presacral, perirectal, and medial inguinal) had additional distal pelvic LNs larger than 2.5 cm.

Anatomic distribution of FDG-avid LNs in relation to treatment planning guidelines

The location of the aortic bifurcation by vertebral body was L3 in 5 patients, L3/L4 in 5 patients, L4 in 32 patients, L4/L5 in 7 patients, and L5 in 1 patient. Fig 3 shows the distribution of FDG-avid LNs in relation to conventional pelvic radiation fields for cervical cancer treatment with the superior border at L4/L5. Twenty-one pelvic LNs in 13 patients were not fully covered with the superior border at L4/L5 (11 LNs in 8 patients from group 1 and 10 LNs in 5 patients from group 2). With the border at L5/S1, 40 pelvic LNs in 21 patients were not fully covered (24 LNs in 15 patients from group 1 and 16 LNs in 6 patients from group 2). Of the 34 patients without positive paraortic LNs, pelvic LNs were not fully covered in 5 patients (15%) with superior border at L4/L5 and in 10 patients (29%) with border at L5/S1.

When target volumes were contoured using the RTOG consensus guidelines for pelvic IMRT,[15] most PET-positive LNs were adequately covered (Fig 4). However, 12 LNs (average size 1.4 cm; range, 0.7 to 2 cm) were

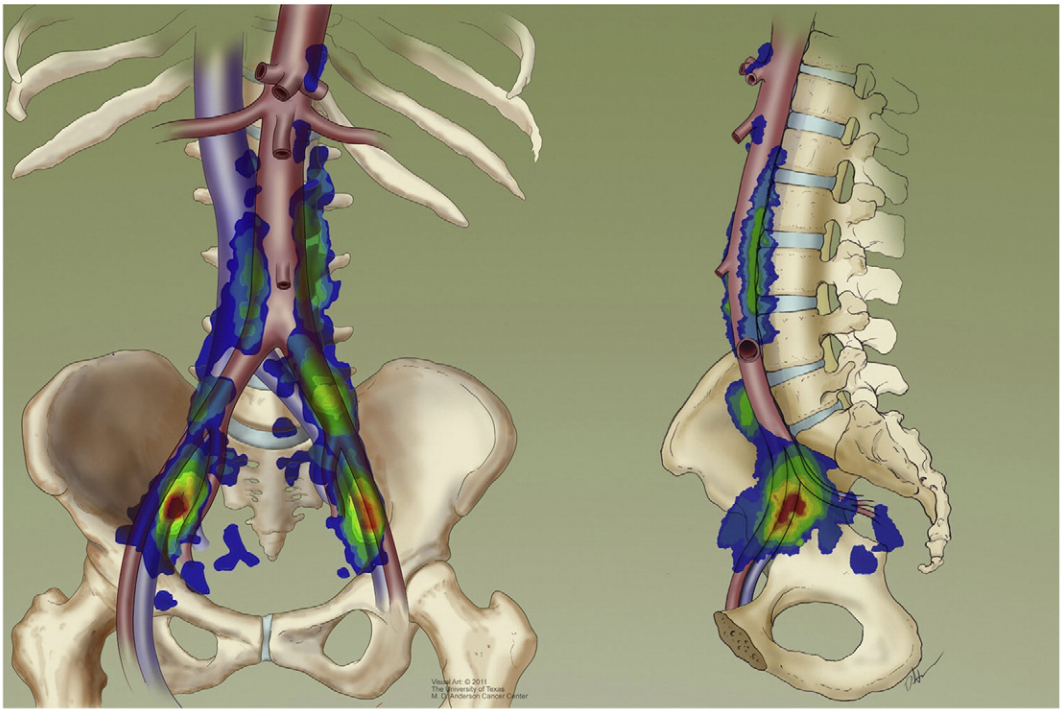

Figure 2 Anatomic distribution of positron emission tomography-positive lymph nodes (LN) based on a volume probability map. A color gradient corresponding to the visible-light spectrum is used to indicate the frequency of LN involvement. (Red, high frequency; green, moderate frequency; blue, low frequency.)

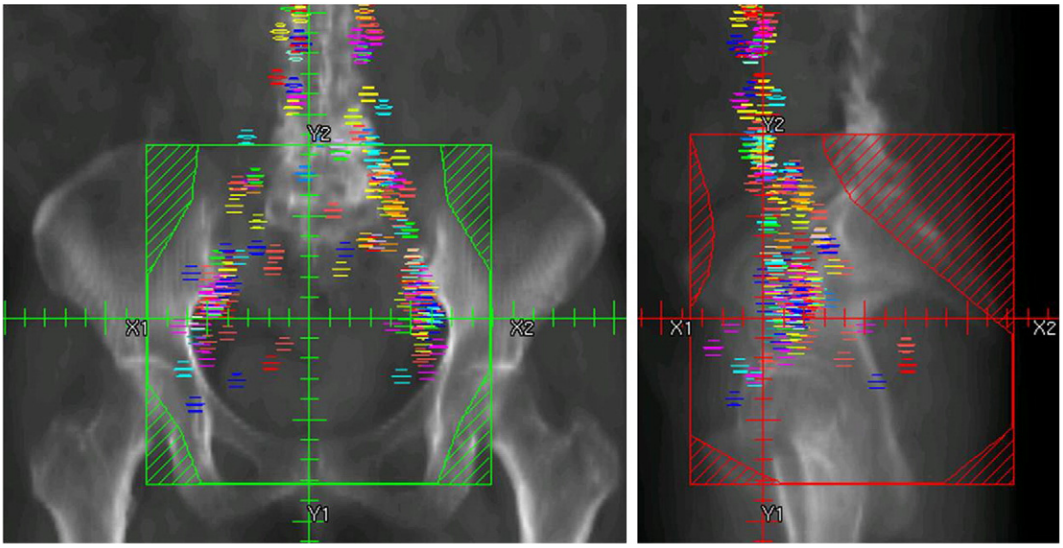

Figure 3 Coverage of (PET)-positive lymph nodes (LNs) by conventional treatment fields. Anterior-posterior (left panel) and lateral (right panel) views show conventional pelvic radiation therapy fields used in cervical cancer treatment, with the superior border at the L4/L5 interspace. PET-positive LNs (n = 190) are shown as 1-cm-diameter spheres expanding from the center of the original node.

inadequately covered: 4 common iliac nodes anterior to the psoas muscle (lateral to the contours); 2 external iliac nodes medial to vessels (inferior or medial to the contours); 1 external iliac node posterior to vessels (inferior to the contours, classically defined as a medial external iliac node); 1 internal iliac node (inferior to the contours, likely a lateral parametrial node); 2 perirectal nodes; and 2 medial inguinal nodes.

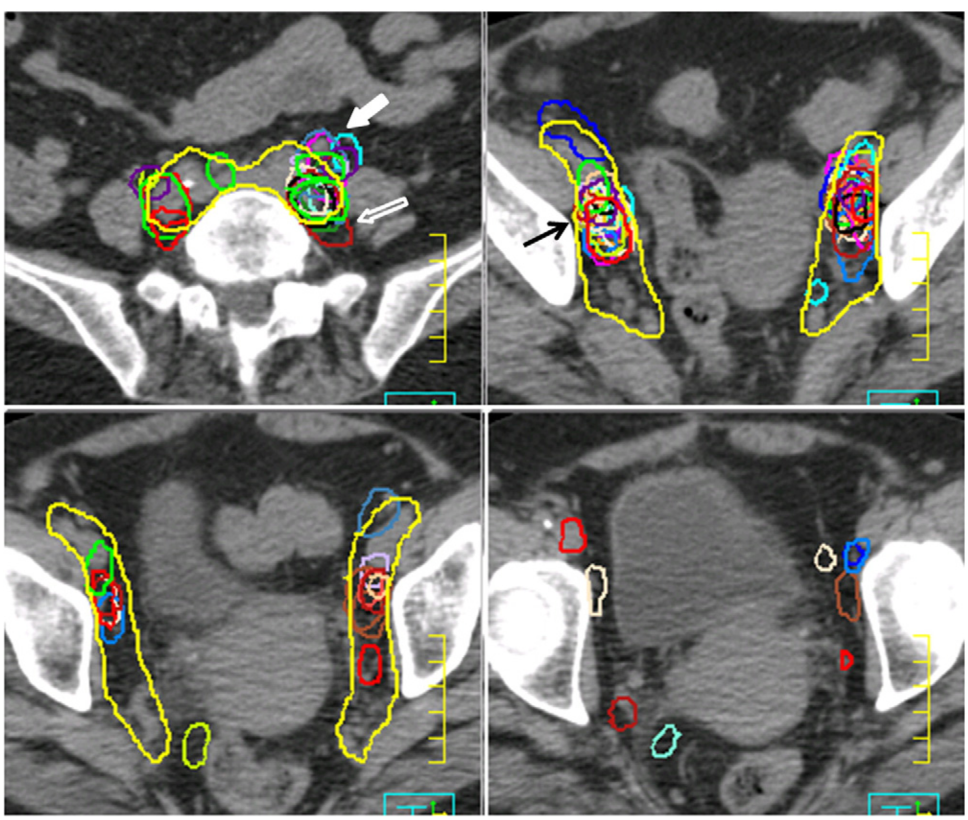

Figure 4 Representative axial images showing coverage of positron emission tomographic (PET)-positive lymph nodes (LNs) when the nodal target volume is contoured according to Radiation Therapy Oncology Group consensus guidelines (yellow). Majority of PET-positive LNs were adequately covered. Generous coverage is required in areas of high frequency of nodal involvement, including common iliac nodes anterior to the psoas muscle (solid white arrow), posteriorly between psoas and sacrum (open white arrow), and external iliac nodes (thin black arrow). Lymph nodes inferior to the contours were not covered (lower right image).

Discussion

With the increasing use of conformal radiation therapy for the treatment of cervical cancer, appropriate target definition is critical; however, little information is available on the precise location of at-risk nodal regions. This study uses PET scans to describe the anatomic distribution of positive pelvic and paraortic LNs in patients with cervical cancer on axial imaging.

Consistent with conventional knowledge and data from sentinel LN evaluation,[21] we found considerable overlap among patients in the location of involved LNs, and the frequency of positive nodes was highest in the primary and secondary echelons of drainage (Figs 1 and 2). We defined nodes near the external iliac vessels as external iliac nodes although these are variably referred to as inter-iliac or obturator nodes in the surgical and radiology literature.[11,12,19] Our finding that the positive external iliac nodes were most often posterior to the vessels and extended laterally to the pelvic musculature and bones suggests that target volumes in this region should not cover a fixed margin around the vessels but rather generously cover this space, which is at the highest risk of micrometastasis. Similarly, our finding that many positive common iliac nodes extended posteriorly between the psoas muscle and the sacrum, laterally and anteriorly to the psoas muscle, indicates that a target volume that encompasses only the common iliac artery and vein and intervening lymphatic tissue could miss many positive common iliac nodes. Small increases in the margins in highest risk regions can reduce the potential for near-miss which must be balanced with the increased bone marrow toxicity that may result from the larger target volumes.[4]

We found that most PET-positive paraortic LNs were lateral to the aorta or aortocaval; there were relatively few paracaval LNs. These findings support the appropriateness of the conventional practice of aligning field borders with the vertebral bodies, providing a margin around the aorta but not around the inferior vena cava. Further analysis of additional patients would clarify the anatomic distribution of paraortic nodes and whether the contours for conformal treatment should be uniform around the 2 vessels.

Although conventional fields based on bony landmarks generously cover the primary tumor and distal pelvic LN basins, the superior border of the pelvic fields varies among radiation oncologists. In patients without LN metastases, or with metastases only in distal pelvic LNs, the upper border is generally extended to approximately the junction of L4/L5, which includes only the distal common iliac LNs. Similarly, the superior border of the RTOG consensus contours is 7-mm below the L4/L5 interspace.[15] In our study, 15% of patients with negative paraortic nodes had common iliac nodes superior to a radiation field border at L4/L5, and 29% had nodes superior to a radiation field border at L5/S1. These findings are consistent with reports of cervical cancer recurrence at the superior edge of the conventional field, which may be a consequence of common iliac node metastasis.[3] In our study, 39% of patients in group 1 had positive common iliac nodes, all of whom also had other positive distal pelvic LNs. These findings suggest that the common iliac nodes should be covered entirely for patients with any PET-positive LNs. To fully cover this region, the common iliac nodes should be contoured to the bifurcation of the aorta, with the contour extending from psoas muscle to psoas muscle.

The RTOG recently published consensus guidelines for contouring nodal target volumes for the postoperative treatment of cervical cancer,[15,16] and although these guidelines are not intended for patients with grossly positive LNs and recommend that any suspicious LNs should be included in the contours, they do aim to cover the LN basin at risk. Although most PET-positive nodes in our study occurred well within the RTOG contours, in several cases, positive common iliac nodes were anterior to the psoas muscle, somewhat lateral to the RTOG nodal contours. Generous coverage with larger margins in areas of highest risk of lymph node involvement is warranted, including in the common iliac region where the contours should be extended more posteriorly and anteriorly around the psoas muscle bilaterally. In addition, a few external iliac and internal iliac LNs were located inferior to the RTOG contours, which extend to the level of the femoral heads. This area is generously covered by conformal fields designed to cover the primary tumor and parametria, but it could be at risk for undertreatment, particularly if IMRT is used. However, care must be taken with significant expansion of the target volume as larger margins may increase dose to normal tissues including the bowel and bone marrow. In particular, larger expansions around the psoas muscle may increase dose to the bone marrow which may impact hematologic toxicity.[4]

We also identified regions where PET-positive LNs were uncommon; the presacral, perirectal, and medial inguinal regions. However, 3 of the 4 patients with positive perirectal and medial inguinal nodes did not have primary tumor involvement of adjacent structures that would have predicted metastasis to these nodal regions. Presacral and perirectal LNs are generously covered by conventional therapy and it is unclear if specific targeting with conformal therapy is warranted considering the low risk of positivity. The medial inguinal nodes are not routinely covered in the conventional fields, and because we found a low risk of involvement in those nodes, prophylactic treatment of this region should be weighed against potential added toxicity. In 1 series, 6% of recurrences occurred in the medial inguinal region, but only 1% of recurrences were isolated inguinal recurrences.[3] In our study, all patients with positive LNs in generally low-frequency regions had additional pelvic LNs larger than 2.5 cm; this factor could potentially be used to identify patients who are at higher risk of nodal involvement in these regions.

Our study had several limitations. Although the specificity of PET/CT in the detection of LN metastases from cervical cancer is 95% in a pooled meta-analysis, there is a considerable range in the published sensitivities and specificities of PET/CT in detecting pelvic lymph nodes.[13,14,22-29] Without pathologic evidence we cannot be certain that all of the mapped LNs contained metastases. Furthermore, because these FDG-avid nodes were grossly enlarged, we cannot be certain what constitutes adequate coverage for nonenlarged LNs with micrometastatic disease. We attempted to minimize the impact of LN volume by evaluating each LN as a 1-cm sphere expanded from LN center for analysis of treatment coverage. The presence of grossly enlarged LNs may also affect lymphatic drainage in unpredictable ways. Our evaluation of coverage by RTOG contours is limited because these contours were intended for use in postoperative treatment and not for patients with grossly positive LNs; the RTOG also recommends that any suspicious LNs should be included in the contours. Despite these limitations, we believe that our study extends the understanding of the nodal regions at highest risk for metastasis from cervical cancer. Considering the significant overlap that we observed in regions of involved LNs, even for patients with only a few positive LNs, these areas with high rates of LN positivity likely indicate the typical drainage pattern in patients with cervical cancer.

Conclusions

Understanding the anatomic location of PET-positive LNs in cervical cancer is useful for identifying nodal regions at particular risk of harboring metastatic disease. The probability map we created can help define targets for conformal radiation therapy and guide changes in conventional radiation therapy techniques. The external iliac and common iliac nodal regions had particularly high numbers of positive LNs, and thus these areas require generous coverage, especially between the vasculature and the psoas muscle.

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