Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2013 March 15; 85(4): 1045–1050. doi:10.1016/j.ijrobp.2012.11.032.

Anatomic Distribution of FDG-Avid Paraaortic Lymph Nodes in Patients with Cervical Cancer¹

Vinita Takiar, M.D., Ph.D.^{*}, Hiral P. Fontanilla, M.D.^{*}, Patricia J. Eifel, M.D.^{*}, Anuja Jhingran, M.D.^{*}, Patrick Kelly, M.D., Ph.D.^{*}, Revathy B. Iyer, M.D.[†], Charles F. Levenback, M.D.[‡], Yongbin Zhang, M.S.[§], Lei Dong, Ph.D.[§], and Ann Klopp, M.D., Ph.D.^{*}

^{*}Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

[†]Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX

[‡]Department of Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

[§]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX

Summary

This study presents a map of PET-positive paraaortic nodes (PAN) in cervical cancer. Available information about the location of PAN metastases in cervical cancer is not adequately detailed to guide treatment planning for highly conformal radiation therapy. Our population based atlas outlines the spatial distribution of these lymph nodes to facilitate target delineation and treatment planning. Suggested clinical target volume contours are included, which provide coverage of PAN nodes for the treatment of cervical cancer.

Purpose—Conformal treatment of paraaortic lymph nodes (PAN) in cervical cancer allows dose escalation and reduces normal tissue toxicity. Currently, data documenting the precise location of involved PAN are lacking. We define the spatial distribution of this high-risk nodal volume by analyzing FDG-avid lymph nodes (LNs) on PET/CT scans in patients with cervical cancer.

Materials/Methods—We identified 72 PANs on pretreatment PET/CT of 30 patients with newly-diagnosed stage IB-IVA cervical cancer treated with definitive chemoradiation. LNs were classified as left-lateral paraaortic (LPA), aortocaval (AC), right paracaval (RPC). Distances from

¹Supplementary material for this article can be found at www.redjournal.org

Corresponding author: Ann Klopp, M.D., Ph.D. Mays Clinic (ACBP1.2839), 1515 Holcombe Blvd. Unit 0097, Houston, TX 77030, Phone: 713-563-2444, Fax: 713 563-6940, aklopp@mdanderson.org.

Portions of this work were presented at the 53rd annual meeting of the American Society of Therapeutic Radiation Oncology, October 1-5, 2011.

Conflicts of Interest Notification: Dr. Lei Dong and Yongbin Zhang: Software licensing of deformable image registration to Varian Medical Systems.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

the LN center to the closest vessel and adjacent vertebral body were calculated. Using deformable image registration, nodes were mapped to a template CT to provide a visual impression of nodal frequencies and anatomic distribution.

Results—We identified 72 PET positive paraaortic lymph nodes (37 LPA, 32 AC, 3 RPC). All RPC lymph nodes were in the inferior 1/3 of the paraaortic region. The mean distance from aorta for all lymph nodes was 8.3 mm (range 3 to 17 mm), and from the inferior vena cava was 5.6 mm (range 2 to 10 mm). Of the 72 lymph nodes, 60% were in the inferior third, 36% were in the middle third and 4% were in the upper third of the paraaortic region. 29/30 patients also had FDG-avid pelvic lymph nodes.

Conclusions—96% of PET positive nodes were adjacent to the aorta; PET positive nodes to the right of the IVC were rare and were all located distally, within 3 cm of the aortic bifurcation. Our findings suggest that circumferential margins around the vessels do not accurately define the nodal region at risk. Instead, the anatomical extent of the nodal basin should be contoured on each axial image in order to provide optimal coverage of the paraaortic nodal compartment.

Keywords

Intensity-modulated radiation therapy (IMRT); cervical cancer contouring; nodal clinical target volume (CTV); PET positive lymph nodes; paraaortic lymph node location

Introduction

Definitive chemoradiation therapy remains the standard of care for locally advanced cervical cancer. Standard pelvic radiation fields include treatment of the external and internal iliac, obturator, and presacral lymph nodal basins. Patients with involved upper common iliac or paraaortic lymph nodes require treatment of the paraaortic nodal region(1). Inclusion of the paraaortic nodes increases acute and late radiation-induced toxicity as compared to pelvic radiation alone(2, 3). Intensity-modulated radiation therapy (IMRT) has the potential to reduce normal tissue toxicity and allow for dose escalation necessary for grossly involved lymph nodes. For successful treatment with conformal radiation, precise delineation of the lymph node region at risk is critical. Currently available information on the location of paraaortic lymph nodes at risk is based on the anatomical distribution of normal lymphatics as well as the distribution of metastatic disease based on surgical and pathologic studies (4-6). However, surgical studies lack the precise anatomic distribution of information that is required for target volume delineation, and grossly involved lymph nodes may not be equally distributed over the region of normal lymphatics.

To address this limitation of current studies, we have previously investigated the distribution of 2-deoxy-2-¹⁸F fluorodeoxyglucose positron emission tomography (FDG-PET) positive pelvic lymph nodes in patients with cervical cancer.(Ref XX) FDG-PET has been shown repeatedly to be highly sensitive and specific in detecting metastatic lymphadenopathy in cervical cancer.(7-14) In this study, we analyze paraaortic lymph nodes which were FDG-avid on PET/computed tomography (PET/CT) to outline the spatial and probabilistic distributions of positive paraaortic lymph nodes, providing data for an evidence-based approach to paraaortic radiotherapy field design, particularly guiding conformal therapy.

Methods and Materials

Patients

We retrospectively reviewed the records of patients treated with definitive chemoradiation for locally advanced cervical cancer at XX's Department of Radiation Oncology Clinic from 2006 to 2011. This study was approved by the Institutional Review Board at XX. We identified 30 patients with FDG-avid paraaortic lymph nodes (superior to aortic bifurcation) on pretreatment PET/CT scans. Six patients had stage IB, twelve had stage II (IIA-2, IIB-10), eight had stage IIIB, and four had stage IV (IVA-3, IVB-1) disease. These patients were collectively analyzed for this study.

Lymph node characterization, distribution, mapping and contouring

Each patient's PET/CT images were transferred to a Pinnacle treatment planning system (Philips Healthcare, Andover, MA). FDG-avid lymph nodes were contoured onto the individual PET/CT scans by two radiation oncologists (XX, YY). Each contour was then verified by a diagnostic radiologist with expertise in the imaging of gynecologic malignancies (ZZ). Positive lymph nodes in our study were included based on the FDG avidity and CT appearance of the node, therefore no standard SUV cut off was utilized.

The volumetric center of each lymph node was identified and used for subsequent characterization of location. FDG-avid paraaortic lymph nodes were characterized as to the left of the aorta (left paraaortic or LPA), between the aorta and inferior vena cava (aortocaval or AC), or to the right of the inferior vena cava (right paracaval or RPC). Given the anatomic variation with regards to the location of the bifurcation between patients, on each individual PET/CT scan, the distance from the aortic bifurcation to the top of the T12 vertebral body was measured and this dimension was divided into thirds; lymph nodes were thereafter classified in the cephalad-caudad dimension as present in the superior, middle, or inferior third of the paraaortic region. The distance from the volumetric center of each LN to the lateral edge of the closest vessel (aorta or inferior vena cava (IVC)) was tabulated. The lateral distance from midline (at mid-vertebral body) and the anterior-posterior distance to the anterior border of the vertebral body were also calculated for each LN. The method for measuring these dimensions is illustrated in Figure S1.

LN mapping

The individual nodal contours were subsequently mapped onto an integrated "template" CT image using both bony and soft tissue anatomic landmarks and a deformable registration algorithm. This technique uses a variation of the "demons" algorithm as previously described.(15) This algorithm uses CT number information for automatic registration between CT images from a reference (template) patient and a test patient to reduce the mean-square gray-value difference between the 2 images. First, manual rigid bony (pelvis and vertebral body) anatomy is used to align the individual-patient CT scan with the template CT dataset. Subsequently, the individual LN contours are deformably mapped onto the template CT dataset using a multithreaded parallel implementation on a Dell Precision workstation (Model T7400 with two 3.0-GHz Xeon E5472 processors).

All mapped LN locations were individually reviewed and edited to most precisely represent the corresponding location on the original PET/CT scan by a radiologist (XX) and by 2 radiation oncologists (YY, ZZ). Figure S2 illustrates our LN mapping result for a representative patient. Most cases required only minimal editing, largely to ensure that the transferred nodal contours excluded normal tissues. A volume probability map was then generated with nodal volumes and displayed on the template CT for a visual representation of the axial density of distribution. The center of each LN was identified and expanded to a 2 cm sphere to minimize the impact of nodal volume on the probability map. A single probability map was generated for all LNs at a single vertebral body. Suggested paraaortic nodal clinical target volume contours were generated by radiation oncologists specializing in treatment of gynecologic malignancies based on the anatomical distribution of FDG-avid paraaortic nodes. (YY, UU).

Results

Patient Information

The median age of the 30 patients included in this study was 49 years (range, 28-74). Twenty-five patients had squamous cell carcinoma, 4 had adenocarcinoma, and one had an undifferentiated carcinoma. The median primary tumor size was 6 cm (range 2.5-8). The median number of positive paraaortic lymph nodes per patient was 1.5.

Anatomic location of FDG-avid paraaortic lymph nodes

A total of 72 FDG-avid paraaortic lymph nodes were identified from 30 patients. Axial images demonstrating the anatomic distribution of all of these lymph nodes is shown in Figure 1. Figures 2a and 2b present composite coronal and sagittal views of the volumetric centers of all identified PET-positive paraaortic lymph nodes. 37 (51%) PET-positive lymph nodes were classified as left paraaortic (LPA), 32 (44%) were classified as aortocaval (AC) and 3 (4%) were classified as right paracaval (RPC) (Figure 2c). The mean distance from the vessel to the volumetric center of the LN was 7.1 mm (range 2 to 17 mm). The mean distance from the LN center to the aorta was 8.3 mm (range 3 to 17 mm), while the mean distance from the LN center to the IVC was 5.6 mm (range 2 to 10 mm) (Table 1).

Figure 3a uses a color gradient to depict the probability of a positive paraaortic LN in a given location in our study. Of the 72 lymph nodes identified, 43 (60%) were in the inferior third of the paraaortic region, 26 (36%) were in the middle third, and 3 (4%) were in the upper third (2-T12, 3-L1, 19-L2, 34-L3, 14-L4). Notably, all right paracaval lymph nodes were limited to the inferior 1/3 of the paraaortic region, at or below L3, and within 3 cm of the aortic bifurcation. The location of aortic bifurcation did vary with respect to skeletal anatomy between patients with bifurcation at L3 for 2 patients, L3/L4 for 3 patients, L4 for 19 patients, L4/L5 for 3 patients, and L5 for 3 patients. Positive LNs were located 0.1-11.5 cm superior to the aortic bifurcation and 0.1 to 15.4 cm superior to the L4/L5 interspace. Thirty-four lymph nodes were to the right of midline, 1 was at midline, and 37 lymph nodes were to the left of midline. The mean distance from midline was 1.0 cm (range 0.1 to 2.6 cm) for right sided and 1.9 cm for left sided (0.6 to 2.9 cm) nodes. (Figure 3b) Most positive lymph nodes were anterior to the anterior aspect of vertebral body (59 of 72 LN, 82%), 8

(11%) were posterior to the anterior aspect of the vertebral body, and 5 (7%) were at the anterior edge of the vertebral body. Twenty-nine of 30 patients also had involved pelvic lymph nodes.

Discussion

Optimal conformal radiation therapy of the paraaortic lymph node region requires precise target identification and delineation to minimize toxicity. Safe use of IMRT to treat regional lymphatics at risk depends on accurate clinical delineation of the nodal compartment. Due to inadequate data on the anatomical distribution of involved lymph nodes, target volumes are often defined primarily on the basis of the distribution of normal lymphatics or by vascular and bony landmarks which have been traditionally used for field design.

The central aim of this study was to use PET scans to characterize the axial distribution of lymph node positivity in patients with paraaortic lymph node involvement and use this evidence to suggest contours which would potentially improve conformal treatment in this patient population (Figure 4). There is an increased risk of involvement of the paraaortic lymph nodes to the left of the aorta or the aortocaval nodes relative to nodes to the right of the vena cava, demonstrating that there is an asymmetric distribution of paraaortic lymph node involvement in cervical cancer. The majority (96%) of the lymph nodes identified were immediately aortocaval or in the left paraaortic region. Only 3 (4%) of the lymph nodes identified were in the paracaval region, to the right of the IVC, and all of these were in the lower 1/3 of the retroperitoneum, within 3 cm of aortic bifurcation. A similar distribution was noted in a study of PAN node distribution in Stage II seminoma patients (16). These similarities in nodal distribution were noted despite the distinct nodal drainage pattern in seminoma and cervical cancer. Our findings suggest that uniform circumferential margins around the aorta and vena cava do not accurately define the nodal region at risk. Instead, the anatomical extent of the nodal basin should be contoured to include the LPA and AC nodes in the upper paraaortic nodes. The contour should broaden to cover the region to the right of the IVC as it approaches the bifurcation. Proposed contours to cover these regions are shown in Figure 4. The volume treated with these contours is consistent with traditional field designs which generally were drawn to give symmetrical margins around the vertebral bodies, usually to the edge of the transverse processes of T12-L3. These fields provided significant margin around the aorta (which is approximately centered on the vertebral bodies at this level; Figure 3a), but not the inferior vena cava which is well to the right of midline. In regards to the superior and inferior treatment borders required for paraaortic node coverage, treating only the lower paraaortic nodes would likely result in reduced toxicity. However, based on a surgical series by Frumovitz et al, which suggests that patients without FDG-avid paraaortic nodes above the inferior mesenteric artery still harbor microscopic disease in this location, it is our clinical practice to treat the entire paraaortic nodal volume in any patient with positive paraaortic lymph nodes.(17)

There are limitations to our approach in this study. Our findings are based on interpretation of PET/CT data, not on pathologic assessment, and therefore we cannot prove that all of the identified FDG-avid lymph nodes are contain metastatic disease. Nevertheless, PET/CT is generally reported to have a high rate of sensitivity and specificity in this setting.(7-12, 14)

We were only able to identify 30 patients with FDG-avid paraaortic disease, which yielded 72 lymph nodes for the present analysis. Fortunately, the location of these nodes was highly reproducible as illustrated by the volume probability maps in Figure 3, suggesting that our sample size is sufficient to propose the axial contours depicted in Figure 4. Finally, we use enlarged and FDG-avid lymph nodes to determine areas of frequent lymph node involvement, and this may not accurately reflect the location of non-enlarged nodes which harbor micrometastatic disease. This limitation is partially addressed by identifying the volumetric center of each lymph node to measure distances to adjacent structures. We believe that this study contributes novel, patient population-based data regarding the anatomic distribution of positive paraaortic lymph nodes to generate a PAN node contour that may serve as a “template” to guide clinical target volume delineation during conformal treatment planning.

Conclusions

Optimal dose delivery to involved nodal basins in cervical cancer is contingent upon accurate target delineation. This is particularly important when paraaortic involvement is suspected as extended treatment fields correlate with significant morbidity. In this study, we present a probability map demarcating areas with the greatest incidence of paraaortic lymph node involvement that may be used to refine target volumes. The aortocaval and left paraaortic regions contain the highest number of FDG-avid lymph nodes suggesting that larger margins around the aorta are appropriate. Our proposed contours may result in improved targeting of radiation treatment with decreased morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant support: Supported in part by the National Institutes of Health through M.D. Anderson's Support Grant, CA016672.

References

1. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of Radiation Therapy Oncology Group trial (RTOG) 90-01. *J Clin Oncol.* 2004; 22:872–880. [PubMed: 14990643]
2. Grigsby PW, Heydon K, Mutch DG, et al. Long-term follow-up of RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys.* 2001; 51:982–987. [PubMed: 11704321]
3. Small W Jr, Winter K, Levenback C, et al. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin chemotherapy for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of ARM 1 of RTOG 0116. *Int J Radiat Oncol Biol Phys.* 2007; 68:1081–1087. [PubMed: 17398031]
4. Benedetti-Panici P, Maneschi F, Scambia G, et al. Lymphatic spread of cervical cancer: an anatomical and pathological study based on 225 radical hysterectomies with systematic pelvic and aortic lymphadenectomy. *Gynecol Oncol.* 1996; 62:19–24. [PubMed: 8690286]
5. Marnitz S, Kohler C, Bongardt S, et al. Topographic distribution of sentinel lymph nodes in patients with cervical cancer. *Gynecol Oncol.* 2006; 103:35–44. [PubMed: 16600355]

6. Plentl AA, Friedman EA. Lymphatic system of the female genitalia. The morphologic basis of oncologic diagnosis and therapy. *Major Probl Obstet Gynecol.* 1971; 2:1–223. [PubMed: 5162136]
7. Choi HJ, Ju W, Myung SK, et al. Diagnostic performance of computer tomography, magnetic resonance imaging, and positron emission tomography or positron emission tomography/computer tomography for detection of metastatic lymph nodes in patients with cervical cancer: Meta-analysis. *Cancer Sci.* 2010; 101:1471–1479. [PubMed: 20298252]
8. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol.* 2001; 19:3745–3749. [PubMed: 11533097]
9. Narayan K, Hicks RJ, Jobling T, et al. A comparison of MRI and PET scanning in surgically staged loco-regionally advanced cervical cancer: potential impact on treatment. *Int J Gynecol Cancer.* 2001; 11:263–271. [PubMed: 11520363]
10. Reinhardt MJ, Ehrhrit-Braun C, Vogelgesang D, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. *Radiology.* 2001; 218:776–782. [PubMed: 11230656]
11. Ma SY, See LC, Lai CH, et al. Delayed (18)F-FDG PET for detection of paraaortic lymph node metastases in cervical cancer patients. *J Nucl Med.* 2003; 44:1775–1783. [PubMed: 14602859]
12. Roh JW, Seo SS, Lee S, et al. Role of positron emission tomography in pretreatment lymph node staging of uterine cervical cancer: a prospective surgicopathologic correlation study. *Eur J Cancer.* 2005; 41:2086–2092. [PubMed: 16125928]
13. Choi HJ, Roh JW, Seo SS, et al. Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. *Cancer.* 2006; 106:914–922. [PubMed: 16411226]
14. Loft A, Berthelsen AK, Roed H, et al. The diagnostic value of PET/CT scanning in patients with cervical cancer: a prospective study. *Gynecol Oncol.* 2007; 106:29–34. [PubMed: 17482666]
15. Wang H, Dong L, O'Daniel J, et al. Validation of an accelerated 'demons' algorithm for deformable image registration in radiation therapy. *Phys Med Biol.* 2005; 50:2887–2905. [PubMed: 15930609]
16. Paly J, Efsthathiou JA, Hedgire SS, Harisinghani M, Zietman AL, Beard C. Mapping Patterns of Nodal Metastases in Seminoma: Rethinking the Para-aortic Field. *Int J Radiat Oncol Biol Phys.* 2011; 81:S44–S45.
17. Frumovitz M, Ramirez PT, Macapinlac HA, et al. Anatomic Location of PET-positive aortocaval nodes in patients with locally advanced cervical cancer: implications for surgical staging. *Int J Gynecol Cancer.* 2012; 7:1203–1207. [PubMed: 22810967]

Figure 1.

Axial location of FDG-avid paraaortic lymph nodes in cervical cancer. Representative axial images (superior to inferior) depicting the location of 72 FDG-avid paraaortic lymph nodes. All lymph nodes from a single patient are contoured in the same color. Aorta demarcated as Ao, vena cava labeled VC.

Figure 2.

Lymph node location relative to the Aorta and IVC. AP and lateral views (a,b) and diagram (c), demonstrating that majority of paraaortic lymph nodes are to the left of the aorta or between the aorta and the IVC. Few lymph nodes are located to the right of the IVC and all are in the inferior portion of the retroperitoneum.

Figure 3.

(a) Volume probability map showing anatomic distribution of FDG-avid paraaortic lymph nodes at T12 –L5 vertebral bodies. A color gradient corresponding to the visible-light

spectrum is used to indicate the frequency of LN involvement. Red, highest frequency; yellow, moderate frequency; blue, low frequency. (b) Representative coronal and sagittal heatmap images. Sagittal and corresponding coronal sections of the volumetric probability map demonstrating the relative frequency of paraaortic lymph node involvement. Majority (37 lymph nodes) were to the left of midline, 34 lymph nodes were to the right of midline, and 1 lymph node was found at midline. Sagittal images demonstrate that the majority of lymph nodes (82%) were anterior to the vertebral body.

Figure 4.

Proposed contours for paraaortic lymph node targeting. Axial images with proposed contours (yellow) for targeting of clinically negative paraaortic lymph node region. Contours superior to the renal vessels (green) indicate extrapolated contours as there were no lymph nodes found at this level in our study. Contours provide larger margin to the left of the aorta which is at higher risk of lymph node positivity. All suspicious areas including grossly enlarged lymph nodes and surgical clips should be targeted in appropriate patients.

Table 1

The mean distance from lymph node center to the closest edge of various anatomic landmarks was determined as outlined in Supplemental Figure 1. FDG-avid PAN were generally found closer to the vena cava than the aorta and more often, to the right of midline.

Mean distance to LN center		SD
Aorta	8.3 mm	3.8 mm
IVC	5.6 mm	1.8 mm
Vertebral body		
Anterior	8.2 mm	7.1 mm
Posterior	4.6 mm	2.3 mm
Midline		
Left	19.1 mm	6.3 mm
Right	10.0 mm	5.7 mm