

## Appendix D: Use of Lymph Node Size Criteria in Imaging

The use of size criteria for determining lymph node disease with anatomic imaging was established in the medical literature in the 1990s. There is a large body of literature on the use of size criteria in diagnostic imaging for the differentiation of metastatic from non-metastatic lymph nodes and the recommendations are consistent across different primary tumor types in different anatomic regions. Size criteria are the widely accepted standard for the differentiation of metastatic lymph nodes from benign or hyperplastic nodes. The most common established criterion for abnormality being a lymph node that is greater than 1 cm.

Following are excerpts from articles establishing the current use of size criteria for differentiating metastatic from non-metastatic lymph nodes. This is only a brief review of the existing literature. The article excerpts are presented in general and for various anatomic regions. They are listed in reverse chronological order in each category. Copies of the articles referenced here were provided in the May 24, 2004 submission.

### *General Articles*

“In many types of cancer, nodal disease is an independent adverse prognostic factor. However, measurement of the nodes is the only widely accepted method of assessing nodal involvement by means of imaging.” (New Horizons in Oncologic Imaging, D. Koh, NEJM, June, 2003)

“On cross sectional imaging, size (>1 cm) remains the primary criterion for predicting nodal metastasis using any modality, although it is well known that size is not an ideal indicator of disease: Benign nodes may be enlarged, and sub-centimeter nodes may contain metastatic tumor.” (Imaging in Oncology from the University of Texas M.D. Anderson Cancer Center, R. Iyer, American Journal of Radiology, July, 2002)

“All current cross sectional imaging techniques (US, CT, and MRI) have an established low sensitivity (50-70%) in detecting nodal metastases, primarily because detection relies on insensitive size criteria. The disadvantages of size discrimination become evident, for example, in patients with colon cancer, where 65% of lymph node metastases measured less than 5 mm, 22% between 5-10 mm and only 13% were larger than 10 mm.” (Detection of Lymph Node Metastases by Contrast-Enhanced MRI in an Experimental Model, P. Wunderbaldinger, Magnetic Resonance in Medicine, 2002)

“Ultrasound and CT have a common limitation, the criterion for abnormality being based on lymph node size”.....”Likewise, the current MR imaging diagnosis of nodal involvement is also based on size criteria, since T1 and T2 relaxation times of normal, metastatic, lymphomatous, and hyperplastic lymph nodes show a considerable overlap.” (Ultrasmall Superparamagnetic Iron Oxide: An Intravenous Contrast Agent for Assessing Lymph Nodes with MR Imaging, R. Weissleder, Radiology, May 1990)

*Cervical Cancer/Pelvic Lymph Nodes*

“Although there have been several MR imaging studies in which different relaxation times or special contrast media enhancement was used to differentiate metastatic from hyperplastic nodes, the only CT and MR imaging criterion that is generally accepted in the evaluation of pelvic node metastases is the size of the node. Size criteria of 1 – 2 cm have been reported in the literature. In the past decade, a 1 cm diameter has become the preferred criterion as either the maximum or minimum transverse diameter.” (Metastatic Lymph Nodes in Patients with Cervical Cancer: Detection with MR Imaging and FDG PET, M. Reinhart, Radiology March 2001)

“The detection of nodal metastases with CT scan is based on size criteria, with a nodal size of 1.0 cm often used as the upper limit of normal.” .....”Magnetic resonance imaging, similar to CT scan, identifies metastatic lymph nodes based on size criteria.” (Lymph Node Size Does Not Correlate with the Presence of Prostate Cancer Metastasis, R. Tiguert, Urology, 1999)

“Lymph node evaluation should be based on the size and location of the lymph nodes; thus, MRI has the same accuracy as CT.” .....”The size criteria for positive lymph nodes is still under debate: as a result the reported accuracy varies. However, Kim et al reported high accuracy with use of their new criteria and that minimal axial diameter greater than 1 cm is a sign of lymph node metastasis.” (Review: Cervical Cancer, K. Togashi, Journal of Magnetic Resonance Imaging, March/April 1998)

“It is generally accepted that enlarged pelvic lymph nodes greater than 1.0 cm in diameter are an indication of metastatic disease but that normal sized pelvic lymph nodes may be identified with newer imaging modalities which contain metastases.” .....”The only CT or MRI criterion that is generally accepted in the evaluation of pelvic lymph nodes is the size of the node. Earlier in the literature, the size criterion for pelvic lymph node metastasis varied between 1.0 cm and 2.0 cm in diameter, but recently 1.0 cm has become accepted” (Small Pelvic Lymph Node Metastases: Evaluation with MR Imaging, C. Roy, Clinical Radiology, 1997)

“For both CT and MR imaging a guideline of 1 cm in short axis nodal diameter has been recommended for diagnosis of lymph node metastasis. It needs to be acknowledged that CT and MR imaging will fail to detect metastases in normal size lymph nodes.” (Radiological Evaluation of Lymph Node Metastases in Patients with Cervical Cancer, J. Scheidler, Journal of the American Medical Association, October 1997)

“It is generally agreed that CT or MR imaging criteria other than nodal size are not valuable in helping differentiate metastatic lymph nodes from benign hyperplastic nodes. It has been reported that the shape of the lymph node is not a valuable criterion for assessment of lymph node metastases in the neck; however, to our knowledge there have been no previous reports to define the validity of the criteria other than nodal size in the detection of metastatic pelvic lymph nodes in patients with cervical carcinoma.” (Uterine Cervical Carcinoma: Evaluation of Pelvic Lymph Node Metastasis with MR Imaging, S. H. Kim, Radiology March 1994)

*Neck Metastases*

“Nodal size cutoff points of 1.0 –1.5 are frequently used in clinical practice.” (Comparison of CT and MR Imaging in Staging of Neck Metastases, H. Curtin, Radiology, April 1998)

“Size has been a widely used criterion to determine the presence of nodal metastases. Because size data are a continuum, the relative sensitivity and specificity of any size criteria can be adjusted by changes in the threshold, depending on a clinical setting. More recently, size criteria have been reassessed with extensive pathologic analysis of more than 2,700 lymph nodes. This study suggested that the minimum short axial diameter of 11 mm for the jugulodigastric nodes and 10 mm for all other nodes more accurately reflects the presence of metastases” (Imaging of Nodal Metastases in the Head and Neck, Y. Anzai, Journal of Magnetic Resonance Imaging, September/October 1997)

*Mediastinal Lymph Nodes*

“Currently, lymph node size is the sole criterion used to distinguish normal from abnormal nodes. Lymph node size is an imperfect measure of nodal status, since normal sized nodes can harbor metastatic disease and enlarged nodes may be tumor free.” (Mediastinal Lymph Nodes: Relaxation Time/Pathologic Correlation and Implications in Staging of Lung Cancer with MR Imaging, Glazer, Radiology, August 1998)

***The Establishment of the 1 cm Size Cutoff***

In addition to the above referenced studies, the following page shows a partial review of published imaging studies evaluating size criteria to define abnormal lymph nodes and summary results. The table shows the author and article title, the patient population, the imaging modalities used, the size criteria evaluated and the resultant sensitivity and specificity.

This is only a brief review of the literature intended to demonstrate that size criteria have been evaluated across a wide variety of imaging modalities and in different carcinomas in different anatomic regions. The 1 cm size criterion has been well established over the last decade and is the standard in current clinical practice. It is the only objective criteria for image analysis that can be used in a blinded reading for this indication which is why it was used in the Phase III blind read. The Medical Imaging Guidance Document recommends objective endpoints over subjective assessments for demonstration of efficacy.

In addition to the literature supporting the use of size there is extensive literature demonstrating the trade off in sensitivity and specificity using size criteria. Use of a size criterion smaller than 1 cm increases sensitivity at the expense of specificity and vice versa for a larger size criterion as can be seen by the literature reviewed in the table below. Copies of these references were provided in the May 24, 2004 submission.

**Literature Review of Lymph Node Imaging**

Article	Patients	Imaging Modality	Abnormal Criteria	Results
Reinhart et al Metastatic Lymph Nodes in Patients with Cervical Cancer: Detection with MR Imaging and FDG PET	Cervical cancer	MR FDG-PET	>1 cm uptake	Sensitivity 73%, Specificity 83%, Sensitivity 91%, Specificity 100%
Kemp et al PET, CT and MRI with Combidex for Mediastinal Staging in Non-small Lung Cell Lung Carcinoma	NSCLC	FDG-PET CT MR-C	uptake >1 cm SI change	Sensitivity 70%, Specificity 86%, Accuracy 84% Sensitivity 65%, Specificity 79%, Accuracy 76% Sensitivity 86%, Specificity 82%, Accuracy 83%
Hoffman et al Functional Magnetic Resonance Imaging using iron oxide Particles in Characterizing Head and Neck Adenopathy	Head & Neck	MR-C MR	SI change >1 cm	Sensitivity 95%, Specificity 99% Size alone Sensitivity 67%, Specificity 11%
Staples et al Mediastinal Nodes in Bronchogenic Carcinoma: Comparison between CT and Mediastinoscopy	Bronchogenic cancer	CT	>5mm >10 mm >15mm >10mm (short axis) mediastinoscopy	Sensitivity 95%, Specificity 23%, Accuracy 50% Sensitivity 79%, Specificity 65%, Accuracy 72% Sensitivity 61%, Specificity 93%, Accuracy 81% Sensitivity 61%, Specificity 93%, Accuracy 91%
Van Den Brekel, et al Cervical Lymph Node Metastasis: Assessment of Radiological Criteria	Cervical nodes	CT	>6 mm >8 mm >9 mm >10 mm >11 mm >12 mm	Sensitivity 79%, Specificity 100%, Accuracy 91% Sensitivity 69%, Specificity 92% Sensitivity 54%, Specificity 97% Sensitivity 48%, Specificity 99% Sensitivity 42%, Specificity 99% Sensitivity 29%, Specificity 100% Sensitivity 26%, Specificity 100%
Curtin, et al Comparison of CT and MR Imaging in Staging of Neck Metastases	Head & Neck	CT MR	5 mm 10 mm 15 mm 5 mm 10 mm 15 mm	Sensitivity 98%, Specificity 13% Sensitivity 88%, Specificity 39% Sensitivity 56%, Specificity 84% Sensitivity 92%, Specificity 20% Sensitivity 81%, Specificity 48% Sensitivity 51%, Specificity 86%

**Literature Review of Lymph Node Imaging (continued)**

Article	Patients	Imaging Modality	Abnormal Criteria	Results
McLoud, et al Bronchogenic Carcinoma: Analysis of Staging in the Mediastinum with CT by Correlative Lymph Node Mapping and Sampling	Bronchogenic cancer	CT	>1 cm	Sensitivity 64%, Specificity 62%
Kim, et al Uterine Cervical Carcinoma: Evaluation of Pelvic Lymph Node metastasis with MR Imaging	Uterine cervical cancer	MR	>1 cm	Sensitivity 62%, Specificity 98%, Accuracy 93%
Sohn, et al Comparing MR Imaging and CT in the Staging of Gastric Carcinoma	Gastric cancer	CT MR	>8 mm	Accuracy 55% Accuracy 59%
Roy et al Small Pelvic Lymph Node Metastases: Evaluation with MR Imaging	Pelvic cancer	MR	>0.5 cm >1 cm	Sensitivity 75%, Specificity 91%, Accuracy 85% Sensitivity 65%, Specificity 96%, Accuracy 88%
Forstner et al Ovarian Cancer: Staging with CT and MR imaging	Ovarian cancer	CT MR	>1 cm	Sensitivity 50%, Specificity 92%, Accuracy 88% Sensitivity 83%, Specificity 95%, Accuracy 94%
Hilton et al CT Detection of Retroperitoneal Lymph Node Metastases in Patients with Clinical Stage I Testicular Nonseminomatous Germ Cell Cancer: Assessment of Size and Distribution Criteria	Testicular cancer	CT	≥4 mm ≥6 mm ≥8 mm ≥10 mm	Sensitivity 93%, Specificity 58% Sensitivity 67%, Specificity 83% Sensitivity 47%, Specificity 100% Sensitivity 37%, Specificity 100%
Jager et al Pelvic Adenopathy in Prostatic and Urinary Bladder Carcinoma: MR Imaging with a Three Dimensional T1 Weighted Magnetization Prepared Rapid Gradient Echo Sequence	Prostate/ bladder cancer	MR	> 10 mm or > 8 mm with w/l index >0.8	Sensitivity 75%, Specificity 98%, Accuracy 90%