Lung Cancer (2008) **61**, 177–185

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journal homepage: www.elsevier.com/locate/lungcan

Recommendations for optimal use of imaging studies to clinically stage mediastinal lymph nodes in non-small-cell lung cancer patients

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Received 15 May 2007; received in revised form 27 November 2007; accepted 16 December 2007

KEYWORDS
Non-small-cell lung cancer;
Lymph nodes;
Staging;
Mediastinum;
Computed tomography;
Positron emission tomography

Summary Appropriate clinical staging of mediastinal lymph nodes in non-small-cell lung cancer (NSCLC) patients has important therapeutic and prognostic implications. Because of the wide variations in practice patterns among community and academic physicians, we reviewed the literature so that we could provide evidence-based recommendations on the use of imaging studies in the pretreatment clinical staging of NSCLC patients. We concluded that the most sensitive and accurate method of noninvasive mediastinal nodal staging is a positron emission tomography/computed tomography fusion scan; we believe this tool should be a component of clinical staging of all NSCLC patients. Given insufficient sensitivity with currently available imaging studies, mediastinal nodal staging should also include histologic evaluation.

1. Introduction

Accurate mediastinal lymph node (MLN) staging in non-small-cell lung cancer (NSCLC) patients has important therapeutic and prognostic implications [1,2]. Though imaging studies play an important role in the clinical staging of the mediastinum, their use varies widely among community and academic physicians [3–6].

Chest roentograms and computed tomography (CT) scans are widely used for clinical MLN staging in NSCLC patients [3–6]. However, positron emission tomography (PET), which offers superior sensitivity and specificity as compared to CT, is used infrequently (0–26.4%) for clinical staging of NSCLC patients [4–7]. Sporadic use of PET may be due, in part, to its lack of widespread availability at the time the just-referenced surveys were conducted. However, its sporadic use may also be due to a lack of physician education with regard to the evidence favoring PET. Given the implications of inaccurate clinical staging, we reviewed the literature so that we could provide evidence-based recommendations on the optimal use of imaging studies for clinical MLN staging.

2. Methods

For our literature search, we used the PubMed database (www.pubmed.gov) of the National Library of Medicine and the National Institutes of Health. To identify relevant stud-

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doi:10.1016/j.lungcan.2007.12.019

Table 1 Statistical formulae definitions

Descriptor	Formula
Sensitivity	$\frac{\text{true positives}}{\text{true positives}+\text{false negatives}}$
Specificity	$\frac{\text{true negatives}}{\text{true negatives}+\text{false positives}}$
Negative predictive value	$\frac{\text{true negatives}}{\text{true negatives}+\text{false negatives}}$
Positive predictive value	$\frac{\text{true positives}}{\text{true positives}+\text{false positives}}$
Accuracy	$\frac{\text{true negatives}+\text{true positives}}{\text{true positives}+\text{false positives}+\text{true negatives}+\text{false negatives}}$

ies, we utilized the following keywords and medical subject headings: non-small-cell lung cancer, lymph node, mediastinum, evaluation, staging, imaging, chest roentogram, X-ray, magnetic resonance imaging (MRI), CT, and PET. We excluded case reports and articles focusing on disease other than NSCLC.

In order to adequately compare imaging modalities in terms of their clinical efficacy, we utilized five biostatistical descriptors: sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy. The formulae for calculating these descriptors are detailed in Table 1. Sensitivity, or the rate of true positives, describes how effective a screening test is. Specificity, or the rate of true negatives, describes the adequacy of a confirmatory test. The NPV and the PPV allow one to ascertain how a negative or positive test, respectively, correlates with the actual, true result. Finally, the accuracy describes how well a test identifies true-positive and true-negative results.

2.1. Clinical staging of MLNs: radiographic techniques

In the initial evaluation of lung cancer, posterior—anterior and lateral chest roentograms are valuable. However, because of their poor sensitivity (less than 50%) [8], chest roentograms are an inadequate method to screen for NSCLC MLN metastasis, in the absence of obvious, bulky mediastinal adenopathy [9,10]. Unless the patient is not a candidate for surgery or for definitive chemoradiation therapy, additional imaging studies are required.

2.2. CT

Because of its relatively widespread availability and its superior sensitivity, specificity and diagnostic accuracy, as compared with plain films (Tables 2 and 3), CT is the most widely used imaging modality for MLN staging for NSCLC patients in the United States [4]. Despite its advantages as compared with chest roentograms, CT relies on an inaccurate (<70%) method to differentiate benign from malignant MLNs: the size of the LN. The criterion of 1 cm is generally used to differentiate potentially malignant MLNs (more than 1 cm in diameter) from benign MLNs (less than 1 cm in diameter). Using this paradigm, the false-positive rate of CT in the diagnosis of MLN metastasis is 10—20% [11]; this rate is even higher in patients with central T3 lesions, central adenocarcinomas, or left upper lobe lesions [12]. More importantly, the false-negative rate is more than 10% [11]. If CT alone was used to screen for MLN metastasis, patients with false-negative results would be denied optimal treatment for their cancer.

In an observational study in which NSCLC patients underwent CT and subsequently thoracotomy for tumor resection and pathologic staging, MLN size was poorly correlated with the presence of malignancy. MLNs harboring malignant disease were not significantly different in size than those containing benign disease. MLNs less than 1 cm in diameter contained malignant pathology 15% of the time, while MLNs larger than 1 cm were not infrequently (43%) associated with benign disease processes [13]. Because of the limitations of CT in staging MLNs, functional imaging has emerged as a valuable adjunct.

2.3. PET and PET/CT

In January of 1998 the Centers for Medicare and Medicaid Services (CMS) approved the use and reimbursement of ^{18}FDG-PET for the initial staging of NSCLC. In July 2001, this coverage was extended to diagnosis, staging, and restaging [14]. In addition, the NCCN advocates that PET imaging plays a role in the staging and diagnostic management of every stage of NSCLC disease [15]. While the anecdotal experience at tertiary and quaternary treatment centers is that a large percentage majority of patients receive ^{18}FDG-PET or PET/CT fusion scans, the data available describing community clinical practice reveal lower utilization rates (0—26.4%) [4—7].

Table 2 Radiographic modalities for mediastinal lymph node staging [8,16—23,38,40—43,45,47]

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)
Chest roentogram	45	78	78	45	68
CT	19—84	49—99	70—84	31—62	56—94
FDG-PET	50—96	77—97	45—91	44—80	45—96
Choline-PET	100	97			96
FDG-PET and CT	81	94			88
FDG-PET/CT fusion	60—94	85—94	43—60	56—99	78—96
MRI	64—71	48—91			61—83

CT: computed tomography, FDG: fluorodeoxyglucose, PET: positron emission tomography, MRI: magnetic resonance imaging, NPV: negative predictive value, PPV: positive predictive value.