Radiologic Extranodal Extension of Metastatic Lymph Nodes in Patients With Non–Small Cell Lung Cancer: Prognostic Utility and Diagnostic Performance

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BACKGROUND. Pathologic extranodal extension (ENE) in metastatic lymph nodes (LNs) has been associated with unfavorable prognosis in patients with non–small cell lung cancer (NSCLC).

OBJECTIVE. The purpose of this article was to evaluate the prognostic utility of radiologic ENE and its diagnostic performance in predicting pathologic ENE in patients with NSCLC.

METHODS. This retrospective study included 382 patients (mean age, 67 ± 10 [SD] years; 297 men, 85 women) diagnosed with NSCLC and clinical N1 or N2 disease between January 2010 and December 2016. Two thoracic radiologists reviewed staging chest CT examinations to record subjective overall impression for radiologic ENE (no ENE, possible/probable ENE, or unambiguous ENE), reviewing 30 examinations in consensus and the remaining examinations independently. Kaplan-Meier survival analysis and multivariable Cox proportional hazards model were used to evaluate the utility of radiologic ENE in predicting overall survival (OS). Prognostic utility of radiologic ENE was also assessed in patients with clinical N2a disease. In patients who underwent surgery, sensitivity and specificity were determined of radiologic unambiguous ENE in predicting pathologic ENE.

RESULTS. The 5-year OS rates for no ENE, possible/probable ENE, and unambiguous ENE were 44.4%, 39.1%, and 20.9% for reader 1 and 45.7%, 36.6%, and 25.6% for reader 2, respectively. Unambiguous ENE was an independent prognostic factor for worse OS (reader 1: adjusted HR, 1.72, $p = .008$; reader 2: adjusted HR, 1.56, $p = .03$), whereas possible/probable ENE was not (reader 1: adjusted HR, 1.18, $p = .33$; reader 2: adjusted HR, 1.21, $p = .25$). In patients with clinical N2a disease, 5-year OS rate in patients with versus without unambiguous ENE for reader 1 was 22.2% versus 40.6% ($p = .59$) and for reader 2 was 27.6% versus 41.0% ($p = .49$). In 203 patients who underwent surgery (66 with pathologic ENE), sensitivity and specificity of radiologic unambiguous ENE for predicting pathologic ENE were 11% and 93% for reader 1 and 23% and 87% for reader 2.

CONCLUSION. Radiologic unambiguous ENE was an independent predictor of worse OS in patients with NSCLC. The finding had low sensitivity but high specificity for pathologic ENE.

CLINICAL IMPACT. Radiologic ENE may have a role in NSCLC staging workup and treatment selection.

In the 8th edition of the TNM classification of lung cancer, the N category is determined exclusively by the anatomic location of metastatic lymph nodes (LNs). However, this simple classification yields heterogeneous prognostic subgroups among patients within the same N category. Therefore, efforts have been made to incorporate the overall metastatic LN burden into lung cancer LN staging assessment. For this purpose, studies have proposed the use of various metrics, including the number, station, zone, and size of metastatic LNs, as well as the ratio of the number of metastatic LNs to the total number of removed nodes at surgery [1–3]. In addition, the International Association for the Study of Lung Cancer (IASLC) proposed further subdividing N1 and N2 disease on the basis of the presence of skip nodal metastases and the number of metastatic LN stations [4]. Although

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these efforts have been promising, opportunity for substantial improvement remains, because results to date either have been inconsistent or have indicated prognostic differences only between certain N subcategories [5–7].

Extranodal extension (ENE) of nodal metastasis is defined as the extension of metastatic cells beyond the capsule of the metastatic node. ENE has received increasing attention in oncology, now being recognized as a prognostic factor for several malignant tumors [8–10]. In addition, the 8th edition TNM staging system introduced the use of ENE in determining the N category for head and neck cancers and for vulvar cancer [11, 12]. After that change, the clinical N category of head and neck cancers now contains detailed subcategories based not only on the number and size of metastatic LNs but also on the clinical assessment of ENE. Specifically, patients with head and neck cancer may be judged as clinically positive for ENE on the basis of unambiguous findings of ENE on physical examination (e.g., fixation of the nodal mass in the neck or evidence of nerve dysfunction), supported by radiologic evidence of ENE (e.g., indistinct nodal margin or direct nodal invasion of surrounding structures) [11].

In 2018, the Staging and Prognostic Factors Committee of the IASLC highlighted the prognostic impact of ENE as a research goal in preparing the 9th edition of the N descriptor [13]. Several studies in patients with non–small cell lung cancer (NSCLC) have shown pathologic ENE in metastatic LNs to be associated with unfavorable prognosis [14–16]. If evidence of ENE on imaging studies were to predict pathologic ENE and likewise have prognostic impact, then radiologic ENE could play a role in determining treatment strategy. However, to our knowledge, the prognostic implications of radiologic ENE in the clinical staging of lung cancer and the diagnostic performance of radiologic ENE in predicting pathologic ENE have not been studied. Moreover, studies that have assessed the prognostic impact of ENE solely on the basis of pathologic assessment from surgical specimens are limited because up-front surgery is generally not performed in patients with clinical N2 disease if preoperative imaging shows evidence of ENE [17]; thus, studies including only patients who underwent up-front surgical resection would have captured a small fraction of all patients with ENE (i.e., primarily those patients without radiologic ENE). The aims of this study were to evaluate the prognostic utility of radiologic ENE and the diagnostic performance of radiologic ENE in predicting pathologic ENE in patients with NSCLC.

Highlights

Key Finding

- *Five-year OS rates for no, possible/probable, and unambiguous ENE on staging chest CT were 44.4%, 39.1%, and 20.9% for reader 1 and 45.7%, 36.6%, and 25.6% for reader 2, respectively. Unambiguous ENE independently predicted worse OS (reader 1: adjusted HR, 1.72, p = .008; reader 2: adjusted HR, 1.56, p = .03).*

Importance

- *Radiologic evidence of unambiguous ENE of LN metastases may have a role in the initial staging evaluation of patients diagnosed with non–small cell lung cancer.*

Methods

The institutional review board of the authors' institution approved this retrospective study and waived the requirement for informed consent.

Study Patients

The institution's clinical data warehouse, housed within the EMR, was searched for consecutive patients who underwent a staging workup, including chest CT, for histologically confirmed NSCLC that was initially diagnosed between January 2010 and December 2016 at Seoul National University Bundang Hospital (a tertiary care center). Patients were then excluded if they did not have clinical T (of any category), N1 or N2, and M0 disease, based on a review of the staging chest CT examinations and additional available staging-related imaging tests and pathology reports (as described later in the Methods). Additional patients were excluded if they had LN enlargement owing to concomitant lymphoma or previous malignancy with evidence of disease in the past 5 years (aside from inclusion of the latter patients in a sensitivity analysis, as explained later in the Methods). Of included patients, 242 were also included in a prior study that evaluated the prognostic performance of the clinical N descriptors proposed by the IASLC for lung cancer staging [18]; however, that prior study did not assess radiologic or pathologic ENE.

Baseline Characteristics

Two board-certified subspecialty-trained thoracic radiologists (S.J. and K.H.L. with 2 and 10 years of posttraining experience, respectively) in consensus determined patients' clinical T, N, and M categories according to the 8th edition of the TNM staging system, on the basis of a review that included assessment of the staging chest CT examinations and their associated clinical reports within the EMR. The clinical T category was classified as Tis or T1 (hereafter, Tis/T1), T2, T3, or T4. The clinical N category was classified on the basis of the IASLC system as N1a, N1b, N2a1, N2a2, or N2b. The clinical N category was determined on the basis of the results of all available staging tests, including imaging studies (e.g., chest CT and FDG PET/CT examinations), endobronchial ultrasound-guided transbronchial LN needle aspiration, and percutaneous cervical LN biopsy [19, 20]. For patients who did not undergo LN aspiration or biopsy, the clinical N category was determined on the basis of the results of imaging studies only (e.g., CT and FDG PET/CT). Contrast-enhanced CT, when available, was preferred over noncontrast CT for purposes of LN assessment. The two reviewers jointly measured LNs during this review. LNs were considered metastatic if having a short-axis diameter of at least 1.0 cm; however, peripheral LNs (i.e., LNs located at the lobar level or more distally) were considered metastatic if having a short-axis diameter of at least 0.8 cm, a location in the primary tumor's lymphatic drainage pathway, and either round morphology or contrast enhancement. The short-axis diameter of the largest metastatic LN was recorded. The M category was determined on the basis of the results of all available staging tests, including imaging studies (e.g., chest CT, brain MRI, and FDG PET/CT examinations) and pathology reports and was classified as M1 in the presence of clinical or microscopic evidence of distant metastasis and as M0 otherwise.

Information on age, sex, smoking status, and family history of lung cancer was obtained from the EMR. Treatment of lung cancer was classified as surgery without neoadjuvant chemotherapy, surgery with neoadjuvant chemotherapy, or nonsurgical management. The nodule type (subsolid vs solid) of the primary tumor and location (upper lobe, lower lobe, or both upper and lower lobes) of the primary tumor were recorded after review of the images from the staging chest CT examinations by the two previously noted radiologists (S.J. and K.H.L.) in consensus. Finally, the histologic subtype of lung cancer (adenocarcinoma, squamous cell carcinoma, or other) was recorded after review of pathologic reports.

Assessment of Radiologic Extranodal Extension

Six weeks after completion of the described steps, the previously noted two thoracic radiologists (S.J. and K.H.L.) performed an additional review of the staging chest CT in each patient, blinded to pathologic findings of ENE and to clinical outcomes. The examinations from the first 30 patients in the study sample (according to the date of staging chest CT, in chronologic order) were reviewed in consensus; the remaining examinations were reviewed independently. Figure 1 provides illustrations of the conceptual framework of ENE on which the selection of imaging features was based [21] (Fig. 1A: no ENE; Fig. 1B: microscopic ENE [breaching of LN capsule by tumor]; Fig. 1C: macroscopic ENE [grossly visible extranodal soft-tissue involvement]). The radiologists assessed the CT images for four possible findings of ENE (indistinct LN margin, coalescent LNs, direct invasion of adjacent structures, and central necrosis), each evaluated in a binary fashion. Figure 2 provides a representative example of each of the four findings, which in prior studies have shown varying degrees of association with pathologic ENE in head and neck cancer [22–24]. Indistinct margin was selected as a possible correlate of either microscopic or macroscopic ENE and was defined as a poorly defined or irregular nodal margin or infiltration of the fat plane around the LN. Coalescent LNs and direct invasion of adjacent structures were selected as possible correlates of macroscopic ENE; coalescent LNs were defined as juxtaposed LNs with no definable intervening fat plane, including a confluent mass of LNs that were indistinguishable from one other [24]. Although necrosis does not have a direct pathologic correlate relating to ENE, it was selected because of its previously observed strong association with pathologic ENE in head and neck cancer [23, 25]; necrosis was defined as central low attenuation within the LN, qualitatively similar to the attenuation of fluid. The four features were assessed on a patient level and considered positive if any intrathoracic LN showed the given feature. The radiologists also assessed overall confidence in the presence of ENE, scored on a subjective 3-point scale on the basis of gestalt impression at the patient level: no evidence of ENE, possible or probable ENE (hereafter, possible/probable ENE), and unambiguous ENE. Figure 3 provides a representative example of each of these three tiers.

Assessment of Pathologic Extranodal Extension

In patients who underwent surgery, the pathologic reports were reviewed to record the presence of pathologic ENE; the pathologic slides were not reviewed for this purpose. During the study period, attending pathologists at the study institution routinely commented on the presence of pathologic ENE within the reports as part of the standard of care. The pathologists defined pathologic ENE as the extension of tumor cells beyond the capsule of a metastatic LN and into perinodal tissue. The pathology reports did not differentiate ENE involving LNs in the primary lung specimen versus in separately submitted LNs. No attempt was made to correlate the specific location of LNs between radiologic and pathologic assessments. In addition, in patients who underwent surgery, the pathologic T category and pathologic N category were recorded based on the pathologic reports.

Overall Survival

A database of the Ministry of the Interior and Safety, Republic of Korea, was reviewed to determine information regarding survival status and date of death for each patient. Overall survival (OS) was determined for each patient, defined as the interval from the date of staging CT to the date of death from any cause. The time of censoring was the earliest of the date of death, the last follow-up date, or February 17, 2022 (reflecting the date of final database review).

Statistical Analysis

The study's primary outcome was OS. Secondary outcomes were interreader agreement for radiologic ENE and the diagnostic performance of radiologic ENE in predicting pathologic ENE.

Survival curves and 5-year OS rates were derived and compared using the Kaplan-Meier method and log-rank test. Univariable Cox regression analysis was performed using clinical and radiologic variables, including age, sex, smoking history, family history, primary tumor nodule type, primary tumor lobar location, tumor histology (classified as adenocarcinoma vs other), clinical T category, clinical N category, LN size (classified as < 2.0 cm vs ≥ 2.0 cm), and radiologic ENE. Variables with p values less than .10 in the univariable analysis were entered into the multivariable analyses. Multivariable Cox proportional hazards models were constructed to estimate the multivariable-adjusted HRs and 95% CIs of radiologic ENE. The assumption of proportionality was checked by visually inspecting Schoenfeld residual plots. The prognostic significance of radiologic ENE was analyzed separately for each reader.

Two sensitivity analyses were performed. The first sensitivity analysis assessed clinical N category as a three-tiered classification (N1, N2a, N2b), reflecting a prior study that showed significant differences in survival between these three groups [18]. The second sensitivity analysis included patients with a history of malignancy and evidence of disease within the prior 5 years who otherwise were excluded from the study. The Kaplan-Meier method was also used to assess the association of survival rates with pathologic ENE in the subset of patients who underwent surgery (adjusting for pathologic T and N categories rather than clinical T and N categories). An exploratory analysis was also performed using the previously noted three-tiered classification of nodal disease, with further stratification of clinical N2a disease (i.e., a single N2 metastatic LN) by the presence versus absence of radiologic unambiguous ENE; this analysis used the Holm method to adjust for multiple comparisons [26].

Interreader agreement between the two readers was evaluated on the basis of Cohen kappa coefficients for the four binary fea-

tures and weighted kappa coefficients for radiologic ENE. Kappa coefficients were classified as follows: 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect [27]. Agreement was also calculated for the four binary features and three-tiered radiologic ENE using percentage agreements.

For each reader, the sensitivity, specificity, PPV, NPV, and accuracy of CT findings were calculated in patients who underwent surgery, using as reference standard pathologic ENE as documented in the pathologic reports. These performance measures were assessed for each of the four binary CT features, for possible/probable ENE or unambiguous ENE, and for unambiguous ENE. These assessments were also performed in patients who underwent surgery without neoadjuvant chemotherapy. The sensitivity, specificity, PPV, and NPV of the four binary CT findings were also assessed, stratified by histologic type.

In both the survival and diagnostic performance assessments, the analysis for each reader used the results of the consensus assessments for the first 30 patients and the results of the given reader's independent assessments for the remaining patients. The assessment of interreader agreement was performed only in the patients evaluated independently by the two readers (e.g., excluding the initial 30 patients used in the consensus reading). A p value less than .05 was considered to be statistically significant. All statistical analyses were performed using R software, version 4.1.2.

Results

Patient Characteristics

The initial search identified 3252 patients who underwent staging workup for histologically confirmed NSCLC during the study period. Of these patients, 2851 were excluded because they did not have clinical T (of any category), N1 or N2, and M0 disease based on the two radiologists' review of all available staging-related imaging tests and pathology reports. Of the remaining 401 patients, one was excluded owing to lymphoma as cause of LN enlargement, and 18 were excluded owing to previous malignancy with evidence of disease in the past 5 years. Thus, the final study sample included 382 patients (mean age, 67 ± 10 [SD] years; 297 men, 85 women). Figure 4 shows the flow of patient selection.

Patients' baseline characteristics are summarized in Table 1. The clinical T category at the time of NSCLC diagnosis was Tis/T1 disease in 69 (18%), T2 disease in 133 (35%), T3 disease in 100 (26%), and T4 disease in 80 (21%) patients. The clinical N category was N1a in 118 (31%), N1b in 37 (10%), N2a1 in 63 (16%), N2a2 in 88 (23%), and N2b in 76 (20%) patients. The median size of the largest metastatic LN was 1.4 cm (IQR, 1.0–1.9 cm); the size was smaller than 2.0 cm in 295 (77%) and at least 2.0 cm in 87 (23%) patients. The histologic type of lung cancer was adenocarcinoma in 174 (46%), squamous cell carcinoma in 172 (45%), and other types in 36 (9%) patients. Death from any cause occurred in 263 (69%) patients at a median follow-up of 1107 days (IQR, 447–2442 days) after diagnosis.

Association of Radiologic Extranodal Extension With Overall Survival

Figure 5 shows the Kaplan-Meier survival curves, stratified by radiologic ENE. OS was significantly associated with radiologic ENE for both readers (both $p < .001$). The 5-year OS rates in patients with no ENE, possible/probable ENE, and unambiguous ENE, were, for reader 1, 44.4% (95% CI, 38.3–51.4%), 39.1% (95% CI, 30.3–50.5%), and 20.9% (95% CI, 13.1–33.3%), respectively, and for reader 2, 45.7% (95% CI, 39.5–53.0%), 36.6% (95% CI, 27.5–48.7%), and 25.6% (95% CI, 18.0–36.4%), respectively.

Table 2 shows the results of the univariable and multivariable Cox regression analyses for predicting OS. The univariable analyses showed associations with OS for all covariates except for family history. Using the no-ENE category as a reference group, the HRs of the possible/probable ENE group were 1.31 (95% CI, 0.97–1.75; $p = .07$) for reader 1 and 1.35 (95% CI, 0.99–1.83; $p = .06$) for reader 2. The HRs of the unambiguous ENE group were 2.01 (95% CI, 1.47–2.74; $p < .001$) for reader 1 and 1.78 (95% CI, 1.33–2.38; $p < .001$) for reader 2.

In the multivariable Cox regression analyses, unambiguous ENE was an independent prognostic factor for worse OS. Unambiguous ENE was associated with an adjusted HR of 1.72 (95% CI, 1.15–2.58; $p = .008$) for reader 1 and 1.56 (95% CI, 1.06–2.31; $p = .03$) for reader 2. Possible/probable ENE was not an independent prognostic factor (adjusted HRs, 1.18 [95% CI, 0.85–1.65; $p = .33$] for reader 1 and 1.21 [95% CI, 0.87–1.68; $p = .25$] for reader 2). The two sensitivity analyses yielded similar results as the primary analysis (Tables S1 and S2, available in the online supplement).

The 5-year OS was 61.5% (95% CI, 53.0–71.3%) in patients without pathologic ENE versus 52.3% (95% CI, 39.4–69.3%) in patients with pathologic ENE ($p = .50$) (Fig. S1, available in the online supplement).

Exploratory Analysis With Stratification of Clinical N2a Disease by Radiologic Unambiguous Extranodal Extension

Figure S2 (available in the online supplement) shows the results of the exploratory analysis that incorporated stratification of clinical N2a disease by radiologic unambiguous ENE. In patients with clinical N2a disease and unambiguous radiologic ENE, the 5-year OS rate was 22.2% and 27.6% for readers 1 and 2, respectively; in comparison, the 5-year OS rate was 21.1% in patients with clinical N2b disease (regardless of radiologic ENE). Among patients with clinical N2a disease, the 5-year OS rate was lower in those with unambiguous radiologic ENE (reader 1: 22.2% [95% CI, 9.4–52.7%], 18 patients; reader 2: 27.6% [95% CI, 15.3–49.7%], 29 patients) than in those without unambiguous radiologic ENE (reader 1: 40.6% [95% CI, 33.1–49.9%], 133 patients; reader 2: 41.0% [95% CI, 33.1–50.7%], 122 patients); however, the Kaplan-Meier survival curves did not show a statistically significant difference between these groups (Holm-adjusted $p = .59$ and .49 for readers 1 and 2, respectively).

Reader Agreement in Assessing Radiologic Extranodal Extension

Table 3 summarizes findings regarding interreader agreement. For radiologic ENE assessment, the interreader agreement was substantial (κ, 0.72; 95% CI, 0.68–0.76) and the proportion of agreement was 75.9% (267/352). The interreader agreement was substantial for LN margin (κ, 0.70; 95% CI, 0.62–0.77) and LN necrosis (κ, 0.65; 95% CI, 0.57–0.72) and moderate for coalescent LNs (κ, 0.54; 95% CI, 0.37–0.70) and direct invasion of adjacent structures (κ, 0.60; 95% CI, 0.50–0.71). Table S3 (available in the online supplement) presents a cross-tabulation of the two readers' three-tiered assessments of overall impression for radiologic ENE.

TABLE 1: Patient and Tumor Characteristics

Characteristic	Total (*n* = 382)	Overall Impression for Radiologic ENE							
		Reader 1				Reader 2			
		None (*n* = 223)	Possible/Probable (*n* = 92)	Unambiguous (*n* = 67)	*p*	None (*n* = 210)	Possible/Probable (*n* = 82)	Unambiguous (*n* = 90)	*p*
Age (y), mean ± SD	67 ± 10	68 ± 10	66 ± 9	66 ± 10	.14	68 ± 10	66 ± 8	66 ± 10	.20
Sex					.002				.001
Male	297 (78)	159 (71)	80 (87)	58 (87)		149 (71)	68 (83)	80 (89)	
Female	85 (22)	64 (29)	12 (13)	9 (13)		61 (29)	14 (17)	10 (11)	
Smoking status					.001				< .001
Never	75 (20)	58 (26)	11 (12)	6 (9)		55 (26)	14 (17)	6 (7)	
Former or current	307 (80)	165 (74)	81 (88)	61 (91)		155 (74)	68 (83)	84 (93)	
Family history of lung cancer					.47				.07
Absent	348 (91)	206 (92)	81 (88)	61 (91)		197 (94)	70 (85)	81 (90)	
Present	34 (9)	17 (8)	11 (12)	6 (9)		13 (6)	12 (15)	9 (10)	
Nodule type of primary tumor					.03				.02
Solid	372 (97)	213 (96)	92 (100)	67 (100)		200 (95)	82 (100)	90 (100)	
Subsolid	10 (3)	10 (4)	0 (0)	0 (0)		10 (5)	0 (0)	0 (0)	
Location of primary tumor					.31				.68
Upper lobe[a]	201 (53)	113 (51)	47 (51)	41 (61)		104 (50)	45 (55)	52 (58)	
Lower lobe	160 (42)	100 (45)	37 (40)	23 (34)		95 (45)	32 (39)	33 (37)	
Both upper and lower lobes	21 (5)	10 (4)	8 (9)	3 (5)		11 (5)	5 (6)	5 (6)	
Histology					< .001				< .001
Adenocarcinoma	174 (46)	131 (59)	30 (33)	13 (19)		125 (60)	31 (38)	18 (20)	
Squamous cell carcinoma	172 (45)	75 (34)	52 (57)	45 (67)		71 (34)	41 (50)	60 (67)	
Other	36 (9)	17 (8)	10 (11)	9 (13)		14 (7)	10 (12)	12 (13)	
Clinical T category[b]					< .001				< .001
Tis/T1	69 (18)	51 (23)	14 (15)	4 (6)		50 (24)	12 (15)	7 (8)	
T2	133 (35)	90 (40)	34 (37)	9 (13)		80 (38)	33 (40)	20 (22)	
T3	100 (26)	50 (22)	24 (26)	26 (39)		45 (21)	22 (27)	33 (37)	
T4	80 (21)	32 (14)	20 (22)	28 (42)		35 (17)	15 (18)	30 (33)	

(Table 1 continues on next page)

TABLE 1: Patient and Tumor Characteristics (continued)

Characteristic	Total (*n* = 382)	Overall Impression for Radiologic ENE							
		Reader 1				Reader 2			
		None (*n* = 223)	Possible/Probable (*n* = 92)	Unambiguous (*n* = 67)	*p*	None (*n* = 210)	Possible/Probable (*n* = 82)	Unambiguous (*n* = 90)	*p*
Clinical N category[b,c]					< .001				< .001
N1a	118 (31)	82 (37)	23 (25)	13 (19)		82 (39)	18 (22)	18 (20)	
N1b	37 (10)	21 (9)	7 (8)	9 (13)		17 (8)	6 (7)	14 (16)	
N2a1	63 (16)	47 (21)	12 (13)	4 (6)		43 (21)	15 (18)	5 (6)	
N2a2	88 (23)	41 (18)	33 (36)	14 (21)		40 (19)	24 (29)	24 (27)	
N2b	76 (20)	32 (14)	17 (19)	27 (40)		28 (13)	19 (23)	29 (32)	
Lymph node size					< .001				< .001
< 2.0 cm	295 (77)	213 (96)	60 (65)	22 (33)		197 (94)	58 (71)	22 (24)	
≥ 2.0 cm	87 (23)	10 (4)	32 (35)	45 (67)		13 (6)	24 (29)	68 (76)	
Treatment					< .001				< .001
Surgery without neoadjuvant therapy	156 (41)	116 (52)	31 (34)	9 (13)		109 (52)	28 (34)	19 (21)	
Surgery after neoadjuvant therapy	50 (13)	27 (12)	14 (15)	9 (13)		24 (11)	11 (13)	15 (17)	
Nonsurgical treatment	176 (46)	80 (36)	47 (51)	49 (73)		77 (37)	43 (52)	56 (62)	
Death					.008				.03
No	119 (31)	81 (36)	27 (29)	11 (16)		77 (37)	22 (27)	20 (22)	
Yes	263 (69)	142 (64)	65 (71)	56 (84)		133 (63)	60 (73)	70 (78)	

Note—Unless otherwise specified, data are numbers of patients, with percentages in parentheses. The percentages may not sum to 100% owing to rounding. ENE = extranodal extension.
[a]Right middle lobe was considered as upper lobe location.
[b]Clinical T and N categories were based on the 8th edition of the TNM staging system for lung cancer of the AJCC.
[c]Clinical N categories were subdivided according to the proposal by the International Association for the Study of Lung Cancer.

Diagnostic Performance of Radiologic Extranodal Extension in Predicting Pathologic Extranodal Extension

Of 206 patients who underwent surgery, information on pathologic ENE was available for 203 patients; 66 (33%) of these patients had pathologic ENE. Table 4 summarizes the diagnostic performance of CT findings for predicting pathologic ENE. The four binary CT findings showed sensitivity ranging from 6% to 46% and specificity ranging from 66% to 99% for reader 1 and sensitivity ranging from 9% to 36% and specificity ranging from 73% to 98% for reader 2. Specificity was highest for direct invasion and coalescent LNs (range across both readers, 85–99%). Accuracy was relatively low for necrosis (reader 1: 59%; reader 2: 60%) in comparison with the other CT findings (reader 1: 66–69%; reader 2: 62–69%). Table S4 (available in the online supplement) summarizes diagnostic performance of the four binary features, stratified by lung cancer histologic subtype.

In terms of overall impression, radiologic possible/probable ENE or unambiguous radiologic ENE showed sensitivity and specificity of 44% and 76%, respectively, for reader 1 and 55% and 75%, respectively, for reader 2. Radiologic unambiguous ENE showed sensitivity and specificity of 11% and 93%, respectively, for reader 1 and 23% and 87%, respectively, for reader 2.

Table 4 also shows diagnostic performance of radiologic ENE among 153 patients who underwent up-front surgery without neoadjuvant therapy. A total of 44 (29%) of these patients had ENE on pathologic assessment. Sensitivity, specificity, PPV, and NPV were similar in these patients as in all patients who underwent surgery.

Discussion

In this retrospective study, we evaluated the prognostic implications of radiologic ENE on staging chest CT in patients with NSCLC. The 5-year OS rate was significantly associated with radiologic ENE, being progressively worse in patients with, in order, no ENE, possible/probable ENE, and unambiguous ENE. In addition, for both readers, unambiguous ENE was an independent

TABLE 2: Univariable and Multivariable Cox Regression Analyses of Overall Survival in Patients With Non–Small Cell Lung Cancer

Characteristic	Univariable Analysis		Multivariable Analysis			
			Reader 1		Reader 2	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age > 60 y	1.84 (1.35–2.50)	< .001	1.99 (1.44–2.76)	< .001	2.01 (1.45–2.79)	< .001
Female sex	0.73 (0.54–0.98)	.04	1.46 (0.87–2.45)	.15	1.38 (0.81–2.36)	.24
Former or current smoker	1.58 (1.14–2.18)	.006	2.27 (1.30–3.95)	.004	2.08 (1.17–3.70)	.01
Family history of lung cancer	0.90 (0.58–1.40)	.65	NA	NA	NA	NA
Subsolid nodule (reference: solid nodule)	0.29 (0.09–0.90)	.03	0.45 (0.14–1.45)	.18	0.45 (0.14–1.46)	.18
Location (reference: upper lobe[a])						
Lower lobe	1.37 (1.07–1.76)	.01	1.50 (1.15–1.95)	.003	1.52 (1.17–1.98)	.002
Both upper and lower lobes	1.10 (0.64–1.88)	.73	1.27 (0.73–2.20)	.40	1.23 (0.71–2.13)	.47
Adenocarcinoma (reference: other histologic types)	0.68 (0.54–0.87)	.002	1.05 (0.78–1.42)	.75	1.05 (0.77–1.42)	.76
Clinical T category[b] (reference: Tis/T1)						
T2	1.71 (1.15–2.53)	.008	1.52 (1.01–2.29)	.045	1.48 (0.98–2.24)	.06
T3	2.51 (1.67–3.76)	< .001	1.98 (1.29–3.03)	.002	2.00 (1.31–3.07)	.001
T4	2.60 (1.72–3.95)	< .001	1.89 (1.22–2.93)	.005	1.97 (1.27–3.04)	.002
Clinical N category[b,c] (reference: N1a)						
N1b	1.51 (0.96–2.36)	.07	1.07 (0.67–1.70)	.78	1.02 (0.64–1.63)	.93
N2a1	1.68 (1.16–2.44)	.007	1.62 (1.11–2.36)	.01	1.54 (1.05–2.26)	.03
N2a2	1.49 (1.05–2.12)	.03	1.51 (1.04–2.18)	.03	1.49 (1.03–2.14)	.03
N2b	2.66 (1.87–3.76)	< .001	2.57 (1.76–3.77)	< .001	2.49 (1.70–3.65)	< .001
LN size ≥ 2.0 cm	1.46 (1.10–1.93)	.009	0.78 (0.53–1.15)	.22	0.78 (0.53–1.16)	.22
Overall impression for radiologic ENE (reference: no ENE)						
Reader 1						
Possible/probable ENE	1.31 (0.97–1.75)	.07	1.18 (0.85–1.65)	.33	NA	NA
Unambiguous ENE	2.01 (1.47–2.74)	< .001	1.72 (1.15–2.58)	.008	NA	NA
Reader 2						
Possible/probable ENE	1.35 (0.99–1.83)	.06	NA	NA	1.21 (0.87–1.68)	.25
Unambiguous ENE	1.78 (1.33–2.38)	< .001	NA	NA	1.56 (1.06–2.31)	.03

Note—NA = not applicable, LN = lymph node, ENE = extranodal extension.
[a]Right middle lobe was considered as upper lobe location.
[b]Clinical T and N categories were based on the 8th edition of the TNM stage system for lung cancer of the AJCC.
[c]Clinical N categories were subdivided according to the proposal by International Association for the Study of Lung Cancer.

TABLE 3: Interreader Agreement in Assessing Radiologic ENE

Characteristic	Kappa (95% CI)	Proportion of Agreement[a]
Indistinct margin	0.70 (0.62–0.77)	85.5 (301/352)
Coalescent lymph nodes	0.54 (0.37–0.70)	93.2 (328/352)
Direct invasion of adjacent structures	0.60 (0.50–0.71)	87.5 (308/352)
Necrosis	0.65 (0.57–0.72)	83.0 (292/352)
Overall impression for radiologic ENE	0.72 (0.68–0.76)	75.9 (267/352)

Note—Interreader agreement was calculated among patients evaluated independently by the two readers, therefore excluding the 30 patients who were used in the initial consensus reading. Agreement between two readers was assessed by weighted kappa coefficient for overall impression for radiologic extranodal extension (ENE) and by Cohen kappa coefficient for the other features.
[a]Expressed as percentage, with numerator and denominator in parentheses.

poor prognostic predictor of OS in multivariable analysis incorporating a range of clinical variables. Interreader agreement was moderate or substantial for four binary CT features that were evaluated as potential predictors of ENE and substantial for overall impression of radiologic ENE. Unambiguous radiologic ENE had low sensitivity (9–23%) but high specificity (87–96%) for predicting pathologic ENE.

The findings support the use of radiologic ENE in prognostic assessment in patients with NSCLC. Although radiologic ENE is an imperfect predictor of pathologic ENE, radiologic ENE can be applied in patients who are not candidates for surgery. Radiologic unambiguous ENE but not radiologic possible/probable ENE was an independent poor prognostic factor. This result is consistent with the current clinical staging guideline for head and neck cancers, in which only unambiguous ENE is considered to represent clinical ENE [28, 29]. Previous studies of pathologic ENE in head and neck cancers also support the present findings in that only macroscopic ENE is associated with poor outcomes, whereas microscopic ENE has a similar prognosis as no ENE [21, 30]. In the current study, the CT features with highest specificity were those selected to correlate with macroscopic ENE (coalescent LNs and direct invasion of adjacent structures). Given these considerations, we believe that only radiologic unambiguous ENE should be considered to represent clinical ENE in lung cancer staging.

In patients with NSCLC and clinical N2 disease, surgery may be deferred in those with unambiguous radiologic ENE, in whom the disease may be deemed unresectable [17]. Although debate continues regarding the role of surgery in patients with N2 disease, international guidelines [31, 32] suggest that surgical resection may be appropriate in the subset of patients with N2a disease (i.e., single-station N2 disease). Radiologic ENE could potentially be used to help refine prognosis assessments and surgical decision-making in patients with clinical N2a disease. The exploratory analysis in patients with clinical N2a disease showed a nonsignificant difference in the 5-year OS rate between those with and without radiologic unambiguous ENE. Identification of radiologic ENE may also be important in patients with clinical N1 disease in that pathologic ENE results in reclassification of such patients from R0 to R1 status (in terms of presence of residual tumor) [33]. Thus, patients with clinical N1 disease and radiologic unambiguous ENE may be selected to undergo neoadjuvant chemotherapy or to undergo surgery with planned postoperative adjuvant therapy given anticipated R1 resection.

The interreader agreement for assessment of radiologic ENE, when considering binary features and overall impression, was

TABLE 4: Diagnostic Performance of CT Findings in Predicting Pathologic ENE

Reader, Patient Group, Feature	Sensitivity	Specificity	PPV	NPV	Accuracy
Reader 1					
Patients who underwent surgery					
Indistinct margin	46 (30/66) [33–58]	79 (108/137) [72–86]	51 (30/59) [38–64]	75 (108/144) [68–82]	68 (138/203) [61–74]
Coalescent LNs	6 (4/66) [0–12]	99 (135/137) [97–100]	67 (4/6) [29–100]	69 (135/197) [62–75]	69 (139/203) [62–75]
Direct invasion	11 (7/66) [3–18]	92 (126/137) [87–97]	39 (7/18) [16–61]	68 (126/185) [61–75]	66 (133/203) [59–72]
Necrosis	44 (29/66) [32–56]	66 (90/137) [58–74]	38 (29/76) [27–49]	71 (90/127) [63–79]	59 (119/203) [52–65]
Overall impression: possible/probable or unambiguous ENE[a]	44 (29/66) [32–56]	76 (104/137) [69–83]	47 (29/62) [34–59]	74 (104/141) [67–81]	66 (133/203) [59–72]
Overall impression: unambiguous ENE	11 (7/66) [3–18]	93 (127/137) [88–97]	41 (7/17) [18–65]	68 (127/186) [62–75]	66 (134/203) [59–72]
Patients who underwent surgery without neoadjuvant chemotherapy					
Indistinct margin	41 (18/44) [26–55]	83 (90/109) [75–90]	49 (18/37) [33–65]	78 (90/116) [70–85]	71 (108/153) [63–78]
Coalescent LNs	2 (1/44) [0–7]	99 (108/109) [97–100]	50 (1/2) [0–100]	72 (108/151) [64–79]	71 (109/153) [63–78]
Direct invasion	7 (3/44) [0–14]	96 (105/109) [93–100]	43 (3/7) [6–78]	72 (105/146) [65–79]	71 (108/153) [63–78]
Necrosis	43 (19/44) [29–58]	73 (79/109) [64–81]	39 (19/49) [25–52]	76 (79/104) [68–84]	64 (98/153) [56–72]
Overall impression: possible/probable or unambiguous ENE[a]	41 (18/44) [26–55]	81 (88/109) [73–88]	46 (18/39) [31–62]	77 (88/114) [70–85]	69 (106/153) [61–76]
Overall impression: unambiguous ENE	9 (4/44) [1–18]	96 (105/109) [93–100]	50 (4/8) [15–85]	72 (105/145) [65–80]	71 (109/153) [63–78]

(Table 4 continues on next page)

TABLE 4: Diagnostic Performance of CT Findings in Predicting Pathologic ENE (continued)

Reader, Patient Group, Feature	Sensitivity	Specificity	PPV	NPV	Accuracy
Reader 2					
Patients who underwent surgery					
Indistinct margin	36 (24/66) [25–48]	75 (102/137) [67–82]	41 (24/59) [28–53]	71 (102/144) [63–78]	62 (126/203) [55–69]
Coalescent LNs	9 (6/66) [2–16]	98 (134/137) [95–100]	67 (6/9) [36–98]	69 (134/194) [63–76]	69 (140/203) [62–75]
Direct invasion	26 (17/66) [15–36]	85 (117/137) [80–91]	46 (17/37) [30–62]	71 (117/166) [64–77]	66 (134/203) [59–72]
Necrosis	33 (22/66) [22–45]	73 (100/137) [66–80]	37 (22/59) [25–50]	69 (100/144) [62–77]	60 (122/203) [53–67]
Overall impression: possible/probable or unambiguous ENE[a]	55 (36/66) [43–67]	75 (102/137) [67–82]	51 (36/71) [39–62]	77 (102/132) [70–84]	68 (138/203) [61–74]
Overall impression: unambiguous ENE	23 (15/66) [13–33]	87 (119/137) [81–93]	46 (15/33) [29–62]	70 (119/170) [63–77]	66 (134/203) [59–72]
Patients who underwent surgery without neoadjuvant chemotherapy					
Indistinct margin	32 (14/44) [18–46]	78 (85/109) [70–86]	37 (14/38) [22–52]	74 (85/115) [66–82]	65 (99/153) [57–72]
Coalescent LNs	5 (2/44) [0–11]	98 (107/109) [96–100]	50 (2/4) [1–99]	72 (107/149) [65–79]	71 (109/153) [63–78]
Direct invasion	23 (10/44) [10–35]	90 (98/109) [84–96]	48 (10/21) [26–69]	74 (98/132) [67–82]	71 (108/153) [63–78]
Necrosis	34 (15/44) [20–48]	77 (84/109) [69–85]	38 (15/40) [23–53]	74 (84/113) [66–82]	65 (99/153) [57–72]
Overall impression: possible/probable or unambiguous ENE[a]	52 (23/44) [38–67]	80 (87/109) [72–87]	51 (23/45) [37–66]	81 (87/108) [73–88]	72 (110/153) [64–79]
Overall impression: unambiguous ENE	18 (8/44) [7–30]	91 (99/109) [85–96]	44 (8/18) [22–67]	73 (99/135) [66–81]	70 (107/153) [62–77]

Note—Data are expressed as percentage with numerator and denominator in parentheses and 95% CI in brackets. ENE = extranodal extension, LN = lymph node.
[a]Overall impression was evaluated by considering both possible/probable ENE and unambiguous ENE to be positive ENE.

moderate to substantial. Previous studies investigating radiologic ENE in head and neck cancers found wide interreader agreement across features (κ, 0.18–0.86) [22, 23, 25, 34]. Diagnostic performance of radiologic ENE for predicting pathologic ENE was also suboptimal. Therefore, more reliable diagnostic CT criteria for ENE should be established and radiologists should be trained in the application of such criteria. In particular, the sensitivity of the various features and of overall impression was low. In comparison with cervical and axillary LNs, evaluation of the margins of mediastinal LNs is difficult given the scarcity of surrounding fat and adjacent bronchovascular structures. In addition, necrosis showed relatively low accuracy compared with the other binary findings; this finding was selected as a potential CT feature of ENE on the basis of its association with pathologic ENE in head and neck cancers, rather than on the basis of an anticipated direct correlation with ENE. Despite these various concerns, overall impression for radiologic ENE had high specificity for pathologic ENE; the high specificity is important for radiologic ENE to maintain prognostic impact during staging and risk stratification.

There were limitations to this study. First, generalizability remains uncertain, given the study's retrospective single-institution design. Second, the study sample had a strong male predominance, also introducing bias. Third, only two fellowship-trained thoracic radiologists participated in the image assessment. Further research should study interreader agreement among readers with greater variation in background and experience and assess intrareader agreement. Fourth, the evaluation of intrathoracic LN metastasis may have been confounded by the high prevalence of *Mycobacterium tuberculosis* in the Republic of Korea. Fifth, the association of radiologic ENE with pathologic ENE was evaluated on a per-patient basis, not on a per-station basis. Finally, ENE involving LNs within the main lung specimen and involving separately submitted LNs were both counted as pathologic ENE.

In conclusion, radiologic unambiguous ENE was an independent predictor of worse OS in patients with NSCLC in multivariable analysis including numerous clinical prognostic factors. Radiologists' overall impression for ENE showed substantial interreader agreement and low sensitivity but high specificity for pathologic ENE. Although the findings require validation in further studies, the results support the use of radiologic ENE in staging workup and treatment selection in patients with NSCLC and clinical N1 or N2 disease.

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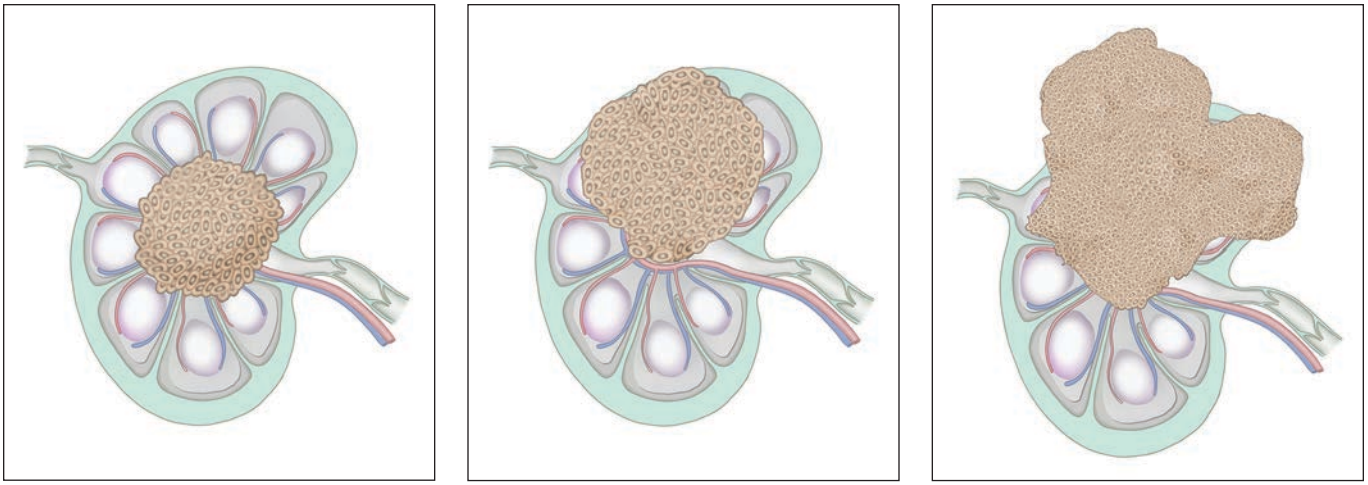


Fig. 1—Conceptual framework for extranodal extension (ENE) of metastatic lymph nodes in non–small cell lung cancer.
A, Illustration shows no ENE.
B, Illustration shows microscopic ENE.
C, Illustration shows macroscopic ENE.

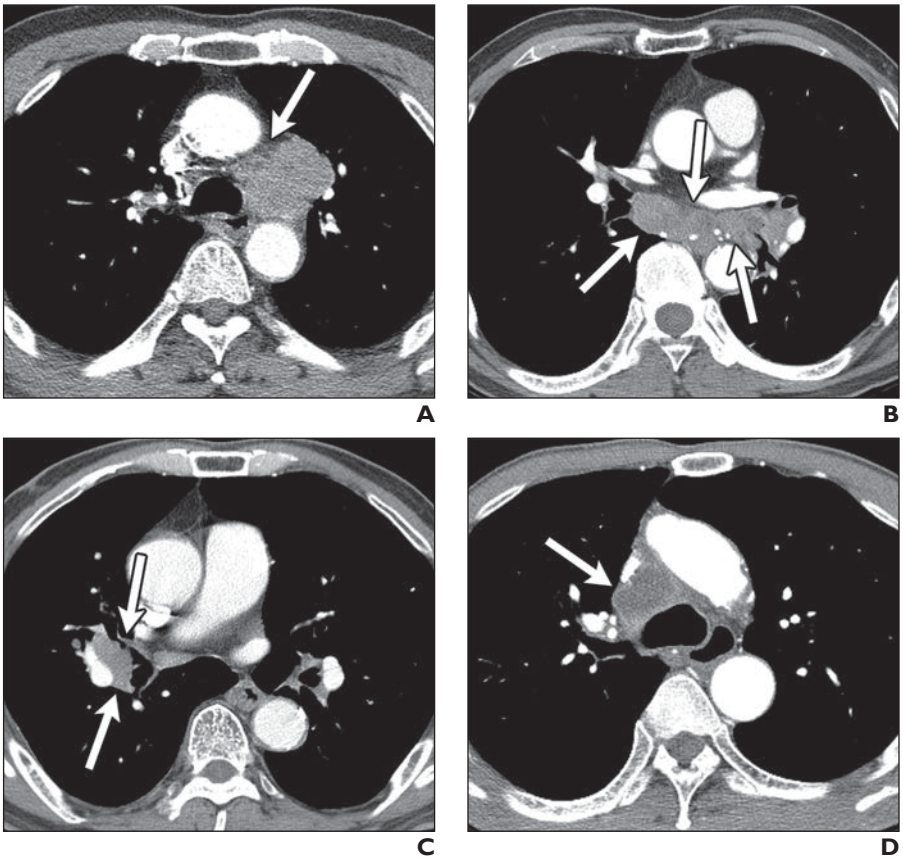


Fig. 2—Axial images from contrast-enhanced staging chest CT examinations in four patients with non–small cell lung cancer show representative examples of binary features assessed as possible predictors of extranodal extension.
A, 76-year-old patient. CT scan shows indistinct margin (*arrow*) of metastatic lymph node.
B, 65-year-old patient. CT scan shows coalescent lymph nodes (*arrows*).
C, 70-year-old patient. CT scan shows direct invasion of metastatic lymph node into adjacent structure (tracheobronchial tree) (*arrows*).
D, 73-year-old patient. CT scan shows central necrosis (*arrow*) of metastatic lymph node.

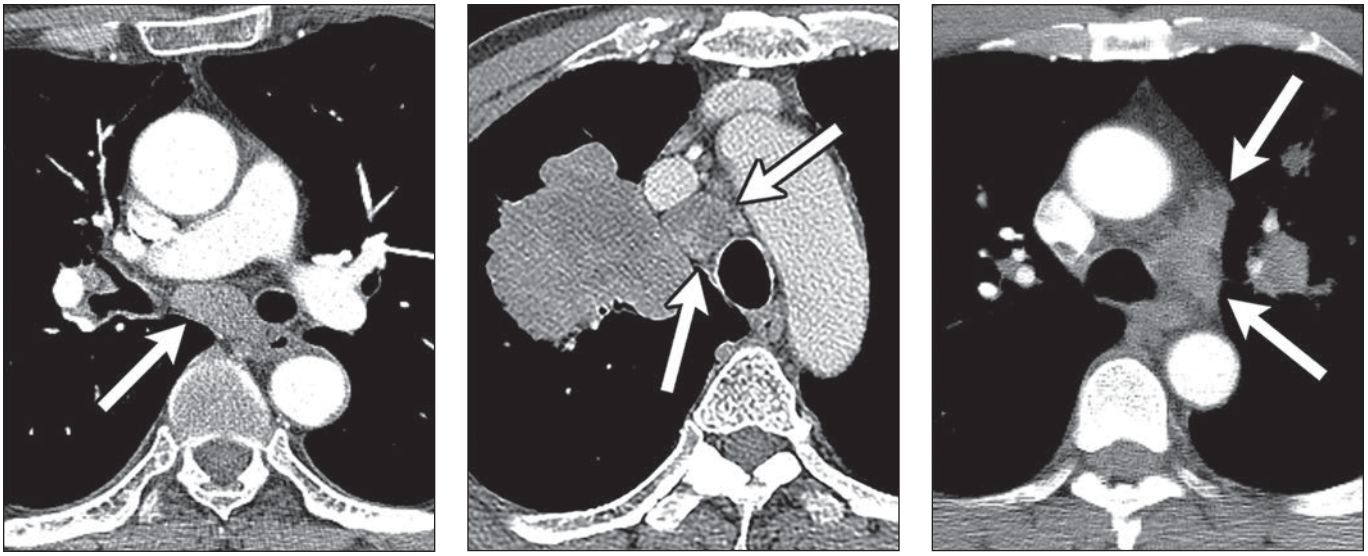


Fig. 3—Axial images from contrast-enhanced staging chest CT examinations in three patients with non–small cell lung cancer show representative examples of overall impression for radiologic extranodal extension (ENE).
A, 71-year-old patient. Lymph node (LN) (*arrow*) was assessed by both readers as showing no radiologic ENE.
B, 64-year-old patient. LN (*arrows*) was assessed by both readers as showing possible/probable ENE.
C, 58-year-old patient. LN (*arrows*) was assessed by both readers as showing unambiguous ENE.

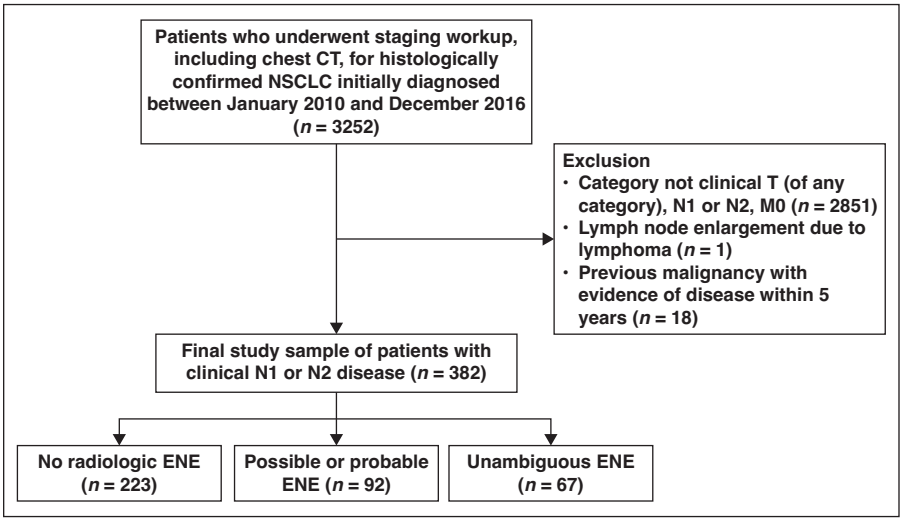
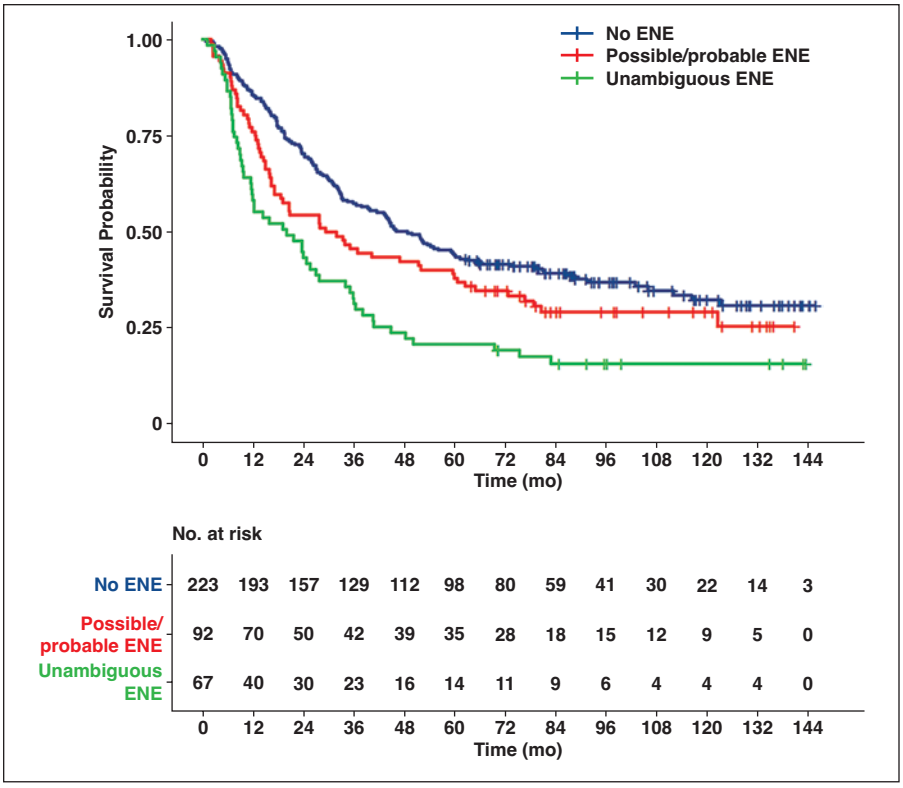
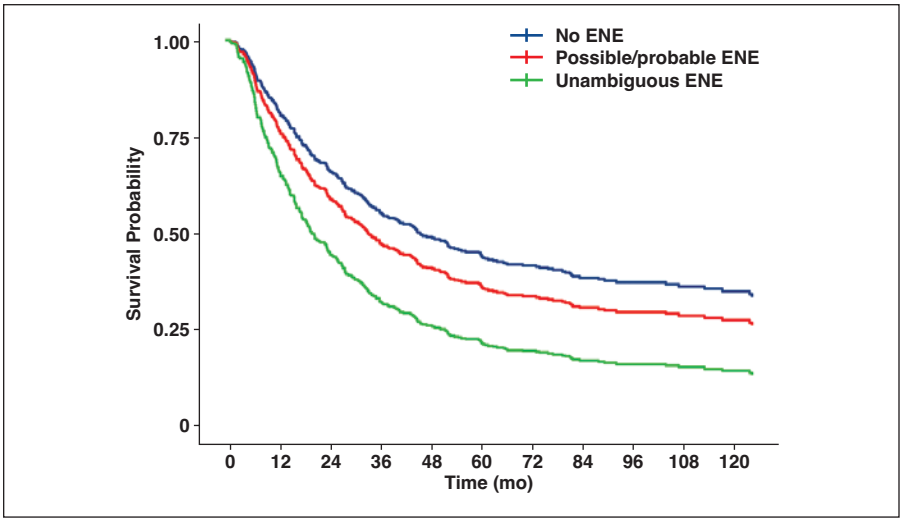


Fig. 4—Flow diagram shows patient selection. The excluded previous malignancies with evidence of disease within 5 years were included in one of two sensitivity analyses of Cox regression analysis of overall survival. NSCLC = non–small cell lung cancer, ENE = extranodal extension.



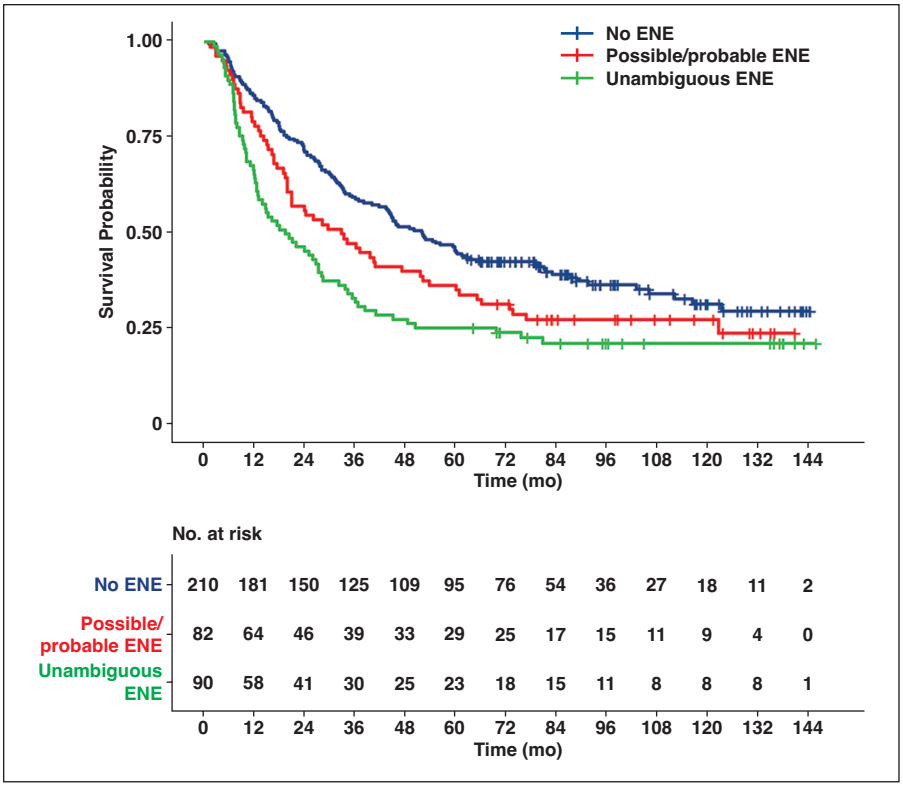
A



B

Fig. 5—Kaplan-Meier curves for overall survival stratified by radiologic extranodal extension (ENE). Covariates for adjustment included age, sex, smoking history, primary tumor nodule type, primary tumor lobar location, tumor histology, clinical T category, clinical N category, and lymph node size.
A and **B,** Graphs show unadjusted (**A**) and adjusted (**B**) survival curves for reader 1.

(Fig. 5 continues on next page)



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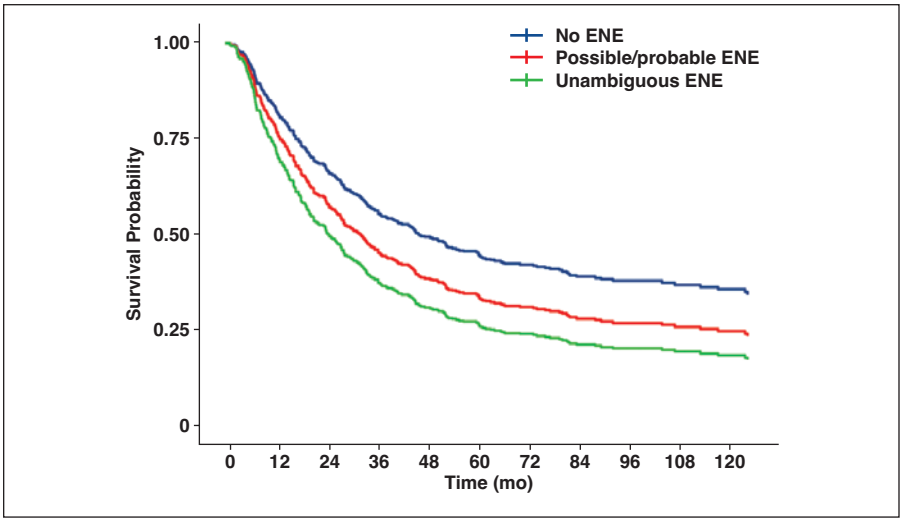

D

Fig. 5 (continued)—Kaplan-Meier curves for overall survival stratified by radiologic extranodal extension (ENE). Covariates for adjustment included age, sex, smoking history, primary tumor nodule type, primary tumor lobar location, tumor histology, clinical T category, clinical N category, and lymph node size.
C and **D,** Graphs show unadjusted (**C**) and adjusted (**D**) survival curves for reader 2.

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Editorial Comment: Prognostic Implications of CT-Defined Extranodal Extension of Metastatic Lymph Nodes in Patients With Non–Small Cell Lung Cancer

A major component in the lung cancer TNM staging system is the status of lymph node (LN) involvement, and accurate LN assessment is crucial in patient management. The N component is currently stratified into categories of N0 to N3 solely on the basis of the anatomic stations with metastatic LN involvement. Options for revising the N classification include counting LNs, LN stations, or LN zones, as well as detecting extranodal extension (ENE) [1].

For metastatic LNs, ENE is defined as extension of metastatic cells beyond the LN capsule into perinodal tissue. ENE has been incorporated into N category determination for head and neck cancers and for vulvar cancer. In a meta-analysis of pathologic ENE in patients with non–small cell lung cancer (NSCLC), ENE was associated with poor prognosis in terms of disease recurrence and all-cause mortality [2].

This retrospective study of 382 patients with NSCLC investigated prognostic implications of CT-based ENE and the diagnostic performance of CT-based ENE in predicting pathologic ENE. Indistinct LN margin, coalescent LNs, direct invasion of adjacent structures, and central necrosis were found to be possible CT findings of ENE. These findings were adopted from previously explored CT findings of ENE in head and neck cancer [3]. Two chest radiologists also classified CT examinations for overall confidence in presence of ENE on a patient level as no ENE, possible or probable ENE, and unambiguous ENE. For both readers, 5-year overall survival rates were significantly different among these three tiers. Unambiguous ENE independently predicted worse overall survival and was highly specific in predicting pathologic ENE.

This is the first study, to my knowledge, to evaluate the impact of CT-based ENE in predicting prognosis and pathologic ENE. Although identifying ENE on CT is challenging, this study opens a new window into CT-based evaluation for ENE of metastatic LNs in NSCLC.

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