



Size and histologic characteristics of lymph node material retrieved from tissue discarded after routine pathologic examination of lung cancer resection specimens^{☆,☆☆}



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ABSTRACT

Redissection of discarded lung resection specimens after routine pathology examination reveals missed lymph node metastasis. We sought to determine if size can be used to grossly select lymph nodes for microscopic examination. This is a prospective cohort study of lymph nodes retrieved from discarded lung resection specimens. The association between size and histologic characteristics of retrieved material was compared by the Wilcoxon-Mann-Whitney test. We retrieved 1094 grossly "lymph node-like" tissue from 112 remnant lung resection specimens, of which 345 (32%) proved not to be lymph nodes and 71 (9%) of 749 lymph nodes had metastasis. Metastasis was present in discarded nodes in 26 (23%) of 112 patients. The non-lymph node tissue was significantly smaller than lymph nodes ($P < .0001$); lymph nodes with metastases were significantly larger than those without metastases ($P < .0001$). However, there was significant size overlap between the 3 types of grossly lymph node-like tissue. Thirty-two percent of nodes with metastasis were less than 1 cm; 15% of patients had at least 1 lymph node less than 1 cm with metastasis. The size difference between lymph nodes with and without metastasis is clinically unhelpful because of broad overlap. Size is insufficiently discriminatory and cannot be relied on to select materials for histologic examination. A third of grossly retrieved material was non-lymph node tissue. This probably occurs during routine pathologic examination and likely contributes to the low N1 lymph node count.

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1. Introduction

Long-term survival after resection for non-small cell lung cancer (NSCLC) most closely correlates with the presence, extent, and number of lymph node metastasis [1–4]. However, current pathologic nodal staging is insufficiently discriminatory of long-term lung cancer mortality risk. Forty-four percent of patients with resected pathologic N0 (pN0) NSCLC die within 5 years [1]. There is a direct correlation

between the number of lymph nodes examined and survival in patients with pN0, despite similar stage [5–8]. In those with known lymph node metastasis, the number and ratio of lymph nodes with metastasis is also of prognostic value [2–4,9–11]. The thoroughness of pathologic nodal examination is, therefore, of paramount importance in the resection population, irrespective of nodal stage. This includes the thoroughness of examination of hilar/intrapulmonary (N1) lymph nodes. The Association of Directors of Anatomic and Surgical Pathology recommends that all lymph nodes within a lung resection specimen should be examined [12].

Opportunity exists to improve the quality of nodal examination of lung resection specimens. In the United States, 18% of patients with "node-negative" NSCLC resections actually have no lymph nodes examined. These patients have a 5-year survival curve similar to patients with pN1 [13]. Only a median of 3 to 5 lymph nodes are examined in patients with resected pN0 NSCLC, significantly lower

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than the optimal number associated with the highest long-term survival, estimated to be between 11 and 21 nodes [5–8].

The opportunity for quality improvement includes the intraoperative collection of hilar and mediastinal lymph nodes, to which pathologists have no direct access [14,15]. However, a thorough retrieval and examination of intrapulmonary lymph nodes can partially off-set the problem of incomplete intraoperative nodal mapping because of strong correlation between intrapulmonary lymph node metastasis and the likelihood of mediastinal lymph node metastasis [2–4]. Moreover, thorough examination of the resection specimen poses no additional risk to the patient.

Current pathology practice focuses the search for intrapulmonary lymph nodes mostly to the hilum of the resection specimen [16,17]. Lymph nodes are grossly identified by visual (anthracotic appearance), textural, and size characteristics. Because of the general belief that big lymph nodes are more likely to contain metastasis, large nodes are more likely to be retrieved for histologic examination. This principle is similar to radiologic nodal staging, which primarily uses size criteria. However, computed tomographic prediction of lymph node metastasis is insensitive, nonspecific, and unreliable [18].

We previously demonstrated a high proportion of unexamined intrapulmonary lymph nodes in discarded lung resection specimens, some of which harbored metastasis [19]. In the current report, we evaluated the correlation between the size and histologic characteristics of the material retrieved from discarded lung resection specimens, which, but for our redissertation protocol, would have been permanently lost to examination.

2. Materials and methods

With the permission of the institutional review boards of the hospital systems from which the lung resection specimens were obtained, we tested the hypothesis that low N1 lymph node counts suggest incomplete retrieval of intrapulmonary lymph nodes during the routine pathology examination by redisserting discarded remnant lobar or greater lung cancer resection specimens. We have previously described our protocol [19]. Briefly, we subjected remnant lung resection specimens to a thin (3–5 mm) section redissertation protocol designed to extract all material that grossly appeared to be lymph nodes, irrespective of their size.

We measured the largest diameter of all specimens and placed each in a separate cassette for processing for histology. A single hematoxylin and eosin-stained slide was made from each specimen, for examination by a pathologist who determined if the specimen was a lymph node and if each lymph node had metastasis. We identified lymph nodes histologically by the combination of their rounded contour, the presence of a capsule, subcapsular sinus, and lymphoid follicles. Nests of cancer cells without all of these criteria were identified as satellite metastatic nodules and were not counted as lymph node metastasis. The presence of metastasis was identified solely by hematoxylin and eosin staining [19].

Specimen sizes were compared by histologic characteristics using the Wilcoxon-Mann-Whitney test. Associations between categorical variables were compared using the χ^2 test. We set a $P < .05$ as the level for rejection of the null hypothesis.

3. Results

3.1. Tumor characteristic

We retrieved 1094 grossly lymph node-like materials from 112 lung resection specimens. Most cases (56%) were adenocarcinomas, 80% were T1 or T2 tumors, and 70% were said to be pN0 after routine pathology examination (Table 1).

Table 1
Clinical characteristics and findings on histologic examination

Characteristic	n (%)	
Histology		
Adenocarcinoma	63 (56)	
Squamous	32 (29)	
Large cell	2 (2)	
Other	15 (13)	
T-category		
1	49 (44)	
2	40 (36)	
3	18 (16)	
4	4 (4)	
X	1 (1)	
N-category (after routine examination)		
0	78 (70)	
1	18 (16)	
2	16 (14)	
No. of lymph nodes after routine examination	Mean (SD)	Median (range)
From N1 stations	4.96 (3.51)	4 (0–18)
From N2 stations	5.23 (4.14)	4 (0–19)
Total	10.18 (5.87)	10 (1–30)
No. of additional material found on redissertation		
All (irrespective of histology)	9.79 (7.35)	8 (1–51)
Lymph nodes	6.73 (6.53)	5 (0–46)
Lymph nodes with metastasis	0.62 (1.61)	0 (0–12)

3.2. Histologic characteristics of retrieved grossly lymph node-like material

Of the 1094 materials retrieved, 345 (32%) were histologically determined not to be lymph nodes (including 11 satellite metastatic nodules); 749 (68%) were lymph nodes. Of the 749 lymph nodes, 71 (9%) had metastasis (Table 2). Lymph nodes were found in 101 (90%) of 112 lung resection specimens, and lymph node metastasis was found in 26 specimens (23%). Of the 26 resections with lymph node metastasis, 7 (27%) were found in patients identified as pN0 after the routine pathology examination.

3.3. Size and histologic characteristics

The most common size of retrieved material was in the 0.5 to 0.9 cm range (45% of all specimens), but 19% of all materials were greater than or equal to 1 cm (Table 2). Twenty-two percent of all retrieved materials greater than or equal to 1 cm were lymph nodes with missed metastasis, and 26% of all retrieved lymph nodes greater than or equal to 1 cm had missed metastasis. Approximately half of all retrieved materials less than 0.5 cm turned out not to be lymph nodes (Table 2).

The median size of retrieved non-lymph node tissue was 4 mm, significantly less than the 7-mm median size of lymph nodes ($P < .0001$). However, there was considerable overlap in the size range between the materials that were lymph nodes and non-lymph node

Table 2
Size (in centimeters) distribution and histologic characteristics of retrieved lymph node-like materials

Specimen histology	Retrieved material, n (%)			
	<0.5	0.5–0.9	1.0–1.4	>1.5
All specimens	390 (36) ^a	488 (45) ^a	157 (14) ^a	59 (5) ^a
Non-lymph node	199 (51) ^b	112 (23) ^b	24 (15) ^b	10 (17) ^b
Lymph node	191 (49) ^b	376 (77) ^b	133 (85) ^b	49 (83) ^b
Without metastasis	188 (48) ^b	356 (73) ^b	111 (71) ^b	23 (39) ^b
With metastasis	3 (2) ^b	20 (4) ^b	22 (14) ^b	26 (44) ^b

^a Percentage of all retrieved materials.

^b Percentage of all retrieved materials of that size.

Table 3

Histology	n (%)	Mean (SD)	Range	Median (IQR)
Non-lymph node	345 (32)	0.48 (0.36)	0.09–2.0	0.4 (0.2–0.6)
Lymph node				
All	749 (68)	0.75 (0.45)	0.1–2.7	0.7 (0.4–0.9)
No metastasis	678 (91) ^a	0.69 (0.39)	0.1–2.7	0.6 (0.4–0.8)
With metastasis	71 (9) ^a	1.32 (0.62)	0.1–2.7	1.2 (0.8–1.7)

All size units in centimeters. Abbreviation: IQR, interquartile range.

^a Percentage of all lymph node material.

tissue (Table 3; Fig. 1). Similarly, although lymph nodes with metastasis were significantly larger than those without metastases ($P < .0001$), there was significant overlap in the range of sizes (Table 3; Fig. 1).

3.4. Patient-level impact

The most common size range of retrieved lymph nodes was 5 to 9 mm, found in 79% of patients (Table 4). In the whole cohort of 112 patients, 3% had at least 1 lymph node less than 5 mm, which harbored metastasis, and 13% had at least 1 lymph node with metastasis each in the 5 to 9 mm, 10 to 15 mm, and greater than 15 mm range (Table 4). Grossly lymph node-like material was retrieved in all 112 remnant lung specimens, at least 1 of which was histologically confirmed to be a lymph node in 90% of specimens. At least 1 lymph node with metastasis was identified in 23% of all patients (Table 5; Fig. 2).

4. Discussion

The importance of accurate pathologic nodal staging of resected NSCLC is reflected in the Association of Directors of Anatomic Pathology recommendation for examination of all lymph nodes in the resection specimen [12]. Despite this, the N1 lymph node yield from lung resection specimens is low, even when surgeons specifically dissect stations 10 (hilar), 11 (interlobar), and 12 (lobar) lymph nodes [20,21]. There is no universally accepted minimum number of lymph nodes mandated for examination in lung cancer. For example, the International Association for the Study of Lung Cancer Staging Handbook recommends a minimum of 6 total lymph nodes, 3 from N1 stations, and 3 from N2 stations [22]. However, analyses of large US databases suggest that examination of more than 10 lymph nodes, possibly as many as 18 to 21, is associated with maximal survival of

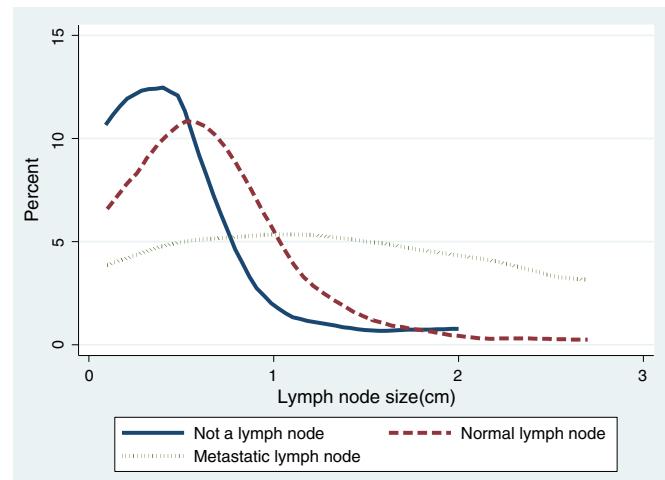


Fig. 1. Size distribution of 3 different histologic types of "grossly lymph node-like" tissue retrieved from discarded lung resection specimens.

Table 4

Frequency of finding lymph node material of various sizes (in centimeters)

Histologic variable	No. of patients affected (%)			
	<0.5	0.5–0.9	1.0–1.5	>1.5
At least 1 grossly lymph node-like material	100 (89%)	97 (87%)	62 (55%)	24 (21%)
At least 1 lymph node	74 (66%)	88 (79%)	57 (51%)	22 (20%)
At least 1 lymph node with metastasis	3 (3%)	15 (13%)	14 (13%)	15 (13%)

patients with pNO [5–8]. Even in groups of patients with known nodal metastasis, the number (and ratio) of lymph nodes with metastasis is also of prognostic value [2–4,9–11].

We found a large number of unexamined lymph nodes in our cohort, 9% of which had metastasis. Ninety percent of the cohort had 1 or more unexamined lymph nodes, and 23% had at least 1 unexamined lymph node with metastasis. We also found that one-third of all grossly identified lymph node specimens turned out not to be lymph nodes on microscopic examination. Although the non-lymph node specimens were significantly smaller than the lymph node specimens, the breadth of overlap means that size is relatively unreliable in distinguishing between lymph node and non-lymph node materials. We found the same difficulty in using size to distinguish between lymph nodes with and without metastasis.

Patients with intrapulmonary lymph node metastasis have a significantly worse survival than those with pathologic node-negative NSCLC, although their survival is better than that of patients with hilar zone metastasis [23]. This suggests the need for histologic examination of all materials that might be lymph nodes, irrespective of their size and location. However, this counsel of perfection raises a frustrating problem because almost half of the retrieved materials less than 0.5 cm were not lymph nodes and only 3% were lymph nodes with metastasis. The quest for optimal thoroughness of examination is, therefore, associated with diminishing returns as smaller materials are retrieved.

Our findings are similar to those of Prenzel et al [24], who, in their examination of 256 lung resection specimens, found a direct correlation between lymph node size and lymph node metastasis but also found that 44% of lymph nodes with metastasis were less than 10 mm in diameter and that 18% of patients with pathologic N2 disease had no lymph nodes greater than 10 mm in diameter. In our series, 23 (32%) of 71 lymph nodes with metastasis were less than 10 mm in diameter (Table 2). Similar findings have also been reported in colon cancer [25]. The difference between these reports and ours is that we have examined lymph nodes retrieved after redissecting the discarded remains of previously examined lung resection specimens. The information from these lymph nodes would have been permanently lost to postoperative prognostication and clinical decision making. Our findings further reinforce the unreliability of size in identifying the status of lymph nodes and suggest a need to modify the current approach to gross retrieval of intrapulmonary lymph nodes (stations 11–14).

More speculatively, we hypothesize from our finding of a high percentage of non-lymph node material that a significant proportion of the material obtained during routine gross dissection of lung

Table 5

Cumulative frequency distribution of patients with lymph node material of various sizes (in centimeters)

Histologic variable	Cumulative no. of patients affected, n (%)			
	<0.5	0–0.9	0–1.5	All sizes
At least 1 lymph node material	100 (89%)	111 (99%)	112 (100%)	112 (100%)
At least 1 lymph node	74 (66%)	96 (86%)	100 (89%)	101 (90%)
At least 1 lymph node with metastasis	3 (3%)	17 (15%)	24 (21%)	26 (23%)

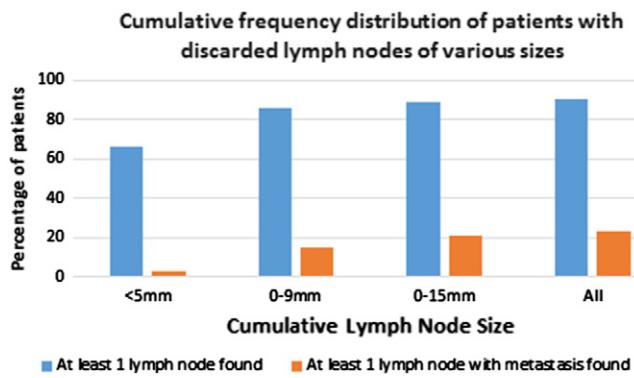


Fig. 2. Cumulative frequency of patients with discarded lymph nodes of various sizes.

resection specimens may also turn out not to be lymph nodes. This may partially explain the low overall lymph node counts in routine pathologic examination of lung resection specimens. By extension, we also speculate that this may explain the baffling finding of Little et al [14] that 52% of mediastinoscopy procedures performed in a cross-sectional sample of US lung resections in the National Cancer Data Base did not provide any lymph node material for examination. It is plausible that a significant proportion of the submitted specimens were found on microscopy to be non-lymph node tissue.

We recommend modification of the current protocol for gross dissection of lung cancer resection specimens to improve the examination of intrapulmonary lymph nodes. The improved protocol must avoid bias against the collection of small specimens [26]. Although thorough examination may seem labor intensive and time consuming, implementation is feasible even in clinically busy pathology departments because the time required diminishes with experience [19]. We are now testing a modified gross dissection protocol that can be used on fresh lung resection specimens and that yields significantly more intrapulmonary lymph nodes than the traditional method of gross dissection.

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