



Number of Lymph Nodes Harvested From a Mediastinal Lymphadenectomy

Results of the Randomized, Prospective American College of Surgeons Oncology Group Z0030 Trial

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Background: Lymph node status is a major determinant of stage and survival in patients with lung cancer; however, little information is available about the expected yield of a mediastinal lymphadenectomy.

Methods: The American College of Surgeons Oncology Group Z0030 prospective, randomized trial of mediastinal lymph node sampling vs complete mediastinal lymphadenectomy during pulmonary resection enrolled 1,111 patients from July 1999 to February 2004. Data from 524 patients who underwent complete mediastinal lymph node dissection were analyzed to determine the number of lymph nodes obtained.

Results: The median number of additional lymph nodes harvested from a mediastinal lymphadenectomy following systematic sampling was 18 with a range of one to 72 for right-sided tumors, and 18 with a range of four to 69 for left-sided tumors. The median number of N2 nodes harvested was 11 on the right and 12 on the left. A median of at least six nodes was harvested from at least three stations in 99% of patients, and 90% of patients had at least 10 nodes harvested from three stations. Overall, 21 patients (4%) were found to have occult N2 disease.

Conclusions: Although high variability exists in the actual number of lymph nodes obtained from various nodal stations, complete mediastinal lymphadenectomy removes one or more lymph nodes from all mediastinal stations. Adequate mediastinal lymphadenectomy should include stations 2R, 4R, 7, 8, and 9 for right-sided cancers and stations 4L, 5, 6, 7, 8, and 9 for left-sided cancers. Six or more nodes were resected in 99% of patients in this study.

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Abbreviations: ACOSOG = American College of Surgeons Oncology Group; MLND = mediastinal lymph node dissection; MLNS = mediastinal lymph node sampling; SVC = superior vena cava

The American College of Surgeons Oncology Group (ACOSOG) Z0030 study is a randomized, multi-institutional, prospective trial designed to determine whether long-term survival is affected by mediastinal lymph node dissection (MLND) vs lymph node sampling (MLNS) at the time of pulmonary resection for lung cancer. We enrolled 1,023 eligible and/or evaluable patients with stage T1 or T2, N0 or nonhilar N1 lung cancer to either MLNS (n = 498) or complete mediastinal lymphadenectomy (n = 525). After analysis, we concluded that a complete mediastinal lymphadenectomy adds little morbidity to a pulmonary

resection for lung cancer and found that the overall operative mortality for pulmonary resection was 1.4% (14/1,023).¹ The impact of MLND on long-term survival will be determined once long-term follow-up data of the study are mature.

Because lymph node status is a main determinate of stage, and thus prognosis, complete lymph node dissection has been recommended for all patients undergoing surgical resection of lung cancer. However, what constitutes a complete lymph node dissection is not defined, and different terminology is used to describe various techniques of surgical lymph node assessment.

The purpose of this analysis was to determine the expected yield of mediastinal lymphadenectomy following systematic MLNS in terms of the number of lymph nodes examined from each lymph node station, the frequency of obtaining at least one lymph node from a station, and the frequency of occult N2 disease, and to determine if surgical approach affected the yield of lymph node harvest when performing a lymph node dissection.

MATERIALS AND METHODS

Only eligible patients entered in the Z0030 trial who were randomized to complete lymph node dissection were analyzed for the purpose of this report (Fig 1). The protocol was approved by the central institutional review board and the institutional review board of each institution that enrolled patients. All patients signed informed consent. Eligibility requirements included patients older than 18 years of age with an Eastern Cooperative Oncology Group performance score lower than 3 and a clinically resectable T1 or T2 lung cancer with no evidence of distant metastatic disease. Prior to randomization, histologic or cytologic confirmation of non-small cell lung cancer (squamous cell carcinoma, large cell carcinoma, or adenocarcinoma, including bronchoalveolar carcinoma) was required. After confirming lymph node status as either N0 or nonhilar N1 based on preresection sampling of the mediastinal (N2 ± N3) and hilar (station 10) lymph nodes, patients were randomized intraoperatively to MLNS or to complete lymph node dissection at thoracotomy (or thoracoscopy). Patients randomized to sampling had no further lymph nodes removed other than those required by the protocol prior to randomization.

All surgeons participating in the trial were general thoracic surgeons and diplomats of the American Board of Thoracic Surgery or the equivalent. Patients were enrolled in the trial by 102 different surgeons from 63 institutions. The enrolling surgeon was required to read a detailed description of the technique of MLND, watch a video that demonstrated the technique of a complete MLND, and certify that he or she would perform the MLND as demonstrated.

Complete MLND for tumors on the right involved removing all tissue from an area bounded caudally by the origin of the right upper lobe bronchus, superiorly by the innominate artery, anteriorly by the superior vena cava (SVC), and posteriorly by the trachea. All tissue was removed from this area and, at the completion of the dissection, the trachea, vagus nerve, and SVC were visible.

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A complete list of study participants is located in e-Appendix 1.

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Lymph nodes in the prevascular area, adjacent to the SVC, were removed, as were lymph nodes in the retrotracheal area.

Complete MLND for tumors on the left involved removing all tissue from the area between the phrenic nerve anteriorly and the vagus nerve posteriorly. Superiorly, all tissue was removed to the apex of the triangle between the two nerves. The caudal boundary was the left main stem bronchus. At the completion of the dissection, the aortopulmonary window was free of lymph tissue and the recurrent nerve was preserved.

Regardless of the side on which the tumor was located, all subcarinal, inferior pulmonary ligament, periesophageal, lobar, and intralobar lymph nodes were resected. Complete subcarinal lymph node dissection included removing all tissue caudal to the carina and both left and right mainstem bronchi. All lymph nodes adjacent to the inferior pulmonary ligament and the caudal half of the esophagus were also removed. When the dissection was complete, both mainstem bronchi, the posterior pericardium, and the esophagus were free of all lymph tissue. During resection of the lung, all lobar and interlobar lymph nodes were resected.

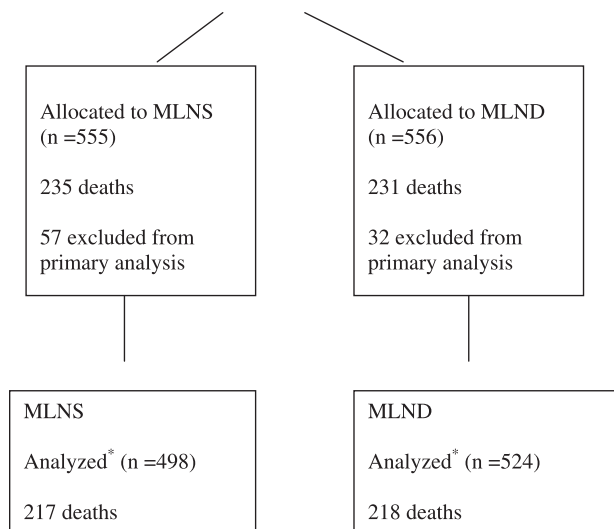
Information on the number of lymph nodes examined from each station was collected beginning in January 2002. For patients enrolled between 1999 and 2002, two authors (M. S. A. and G. E. D.) reviewed operative and pathology reports to determine the number of lymph nodes obtained from each station. The ATS lymph node map was used for documentation. For consistency, nonspecific terms used in pathology reports were standardized: multiple was translated into four lymph nodes, aggregate into three, several into three, fragment into three, and numerous into five. Concordance between the two reviews was within one lymph node 90% of the time.

Lymph node data were summarized using mean ± SD, median, and range. The two-sample rank sum test was used to compare lymph node data between groups. Regression analyses were used to assess the association of select variables with the number of lymph nodes resected. In all cases, *P* values < .05 were considered statistically significant.

RESULTS

Five hundred twenty-four patients were in the complete lymphadenectomy group: 271 men, with a median age of 67.4 years (range 37-87 years). Histology of resected tumors and stage are shown in Tables 1 and 2, respectively. The tumor was located in the right lung in 317 patients and in the left in 207 patients.

The median number of lymph nodes dissected was the same for both right-sided and left-sided cancers: 18 with a range of one to 72 for right-sided tumors and 18 with a range of four to 69 for left-sided tumors (*P* = .93). All patients had at least one lymph node removed in addition to those removed for preresection sampling (at mediastinoscopy and/or thoracotomy or video-assisted thoracic surgery). The median number of lymph nodes resected from N1 stations 10 to 14 was similar between right-sided and left-sided cancers (five vs six, *P* = .134). The largest numbers of lymph nodes were resected from stations 7 and 4R, with a median of three and four nodes, respectively (Tables 3, 4). Almost all patients (517 or 98.7%) had at least six lymph nodes examined and 470 (89.7%) had at least 10 lymph nodes examined. Lymph nodes were



* Note: intent to treat analyses were also performed.

FIGURE 1. Consort diagram. Note that intent-to-treat analyses were also performed. MLND = mediastinal lymph node dissection; MLNS = mediastinal lymph node sampling.

harvested from at least three stations in 521 patients (99.4%). Combining these data, 516 (98.5%) had at least six lymph nodes examined from three lymph node stations and 469 (89.5%) had at least 10 lymph nodes examined from three stations.

In terms of individual stations for the 317 right-sided cancers, the median yield from station 2R was two lymph nodes; for station 4R it was four; station 7, three; station 8, one; station 9, one; and station 10R, one (Table 3). For the 207 left-sided cancers, the median yield from station 2L was one; for station 4L it was two; station 5, two; station 6, two; station 7, three; station 8, one; station 9, one; and station 10L, two (Table 5).

Twenty-one patients (4%) had occult N2 disease identified by mediastinal lymphadenectomy that was not found by the rigorous prerandomization systematic sampling used in this protocol. Overall, 63 patients had N1 disease, and 21 patients had N2 disease. However, of the 21 patients with N2 disease, only 11 had positive N1 nodes. Patients with positive station 2 nodes also had positive nodes in station 4 (Table 5). The reasons for designation of stage IIIA/B (non-N2) in the MLND arm included another cancer in the same lobe, tumor < 2 cm from carina, involvement of the phrenic nerve, and tracheal involvement.

Table 1—Histology of Resected Tumors

Histology	No. (%)
Squamous cell	141 (27.1)
Adenocarcinoma	227 (43.6)
Large cell	22 (4.2)
Bronchoalveolar	32 (6.1)
Other	99 (19.0)

Table 2—Tumor Stage

Pathologic Stage	No. (%)
IA	211 (40.4)
IB	213 (40.8)
IIA	24 (4.6)
IIB	41 (7.9)
IIIA	22 (4.2)
IIIB	11 (2.1)

Most patients were resected using an open thoracotomy, but 29 were resected using video-assisted thoracic surgery. There was no significant difference between the two approaches with respect to the number of lymph nodes dissected (Table 6). There was no association between tumor histology, patient age, and gender and the number of nodes harvested, but increasing N stage was associated with increased lymph node harvest (N0, 19.2 ± 10.1 ; N1, 22.8 ± 10.9 ; N2, 24.5 ± 10.8 ; $P = .043$).

DISCUSSION

It is well established that adequate lymph node assessment is important in the staging of non-small cell lung cancer.^{2,3} Despite this, in a recent pattern of care study, only 57.3% of patients had mediastinal lymph nodes removed at the time of pulmonary resection.⁴ In the ACOSOG Z0030 study, which was conducted by both community and academic thoracic surgeons, 99% of patients had at least six nodes removed, and a median of 18 lymph nodes were examined with MLND. Overall, two-thirds of the lymph nodes examined were N2 lymph nodes. Although the overall lymph node harvest was variable in our study, all patients had at least one node assessed in addition to those sampled prior to resection and > 90% had at least two N2 stations (right, 4R/7; left, 5/7) and one N1 (station 10) examined. In terms of individual lymph node stations, the number of nodes found and removed was also variable, depending on the station. Occasionally, few or even no nodes were found in some stations, such as stations 8 and 9, despite exploration of these stations as documented by the operating surgeon. Station 4L is often not routinely dissected for left-sided tumors and was not part of the mandatory dissection in the study protocol, hence the lower yield for this station in our results.

It has been recommended that the minimum requirements for accurate nodal staging include the removal of at least six lymph nodes from hilar and mediastinal stations, at least one of which must be subcarinal.^{5,6} Gajra et al⁷ also reported that assessment of six nodes provided accurate staging. However, others recommend examination of a minimum of 10 lymph nodes and at least three lymph node stations.^{8,9} These

Table 3—Lymph Nodes Examined for Right-Sided Cancers

Station	No. Patients (%)	No. Lymph Nodes			Histologically Positive (%)
		Mean (SD)	Median	Range	
All lymph nodes	317 (100)	19.9 (11.1)	18.0	1-72	...
N2 stations ^a	317 (100)	13.6 (8.4)	11.0	1-49	...
N1 stations ^b	311 (98)	6.4 (5.0)	5.0	1-37	...
Right-sided cancers: N2 stations					
2R	276 (87)	3.1 (2.7)	2.0	1-17	1 (0.3)
4R	305 (96)	5.1 (4.3)	4.0	1-24	5 (1.6)
7	310 (98)	4.5 (3.6)	3.0	1-24	4 (1.3)
8	154 (49)	1.4 (1.0)	1.0	1-6	2 (0.6)
9	204 (64)	1.4 (0.8)	1.0	1-6	1 (0.3)
Right-sided cancers: N1 stations					
10R	303 (95)	2.3 (2.1)	1.0	1-14	7 (2.2)
11R	246 (77)	2.8 (3.0)	2.0	1-28	17 (5.4)
12R	154 (48)	3.5 (3.4)	3.0	1-28	10 (3.2)
13R	32 (10)	2.6 (2.0)	2.0	1-8	1 (0.3)
14R	7 (2)	2.1 (1.3)	2.0	1-4	0

^aN2 stations: 2R, 4R, 7, 8, and 9.

^bN1 stations: 10R, 11R, 12R, 13R, and 14R.

recommendations are derived either from consensus conferences or by retrospective analysis of staging accuracy based on lymph nodes harvested. Given this standard, clearly the majority of patients in the ACOSOG Z0030 study had sufficient nodes examined for staging accuracy. The ACOSOG Z0030 study provides prospective data as to what can be expected in terms of adequate lymph node harvest in the conduct of pulmonary resection for non-small cell lung cancer. For those treating non-small cell lung cancer, these data provide a benchmark for determining whether an adequate lymph node assessment has been performed.

Although MLNS and MLND appear to be comparable in terms of staging accuracy, nonsystematic sampling is less reliable. MLND is reported to be more accurate in determining multilevel N2 disease and skip metastases.¹⁰⁻¹⁴ Because two to five lymph nodes were resected from each N2 station in the majority of patients in our study, it is likely that occult N2 disease would be discovered if present and, despite rigorous systematic sampling prior to randomization, 21 patients were found to have occult N2 disease with MLND.

Based on our median lymph node harvest of 18 nodes with two-thirds being N2 nodes, the ACOSOG Z0030

Table 4—Lymph Nodes Examined for Left-Sided Cancers

Station	No. Patients (%)	No. Lymph Nodes			Histologically Positive (%)
		Mean (SD)	Median	Range	
All lymph nodes	207 (100)	19.1 (8.9)	18.0	4-69	...
N2 stations ^a	207 (100)	12.7 (7.1)	12.0	3-52	...
N1 stations ^b	200 (97)	6.6 (4.1)	6.0	1-22	...
Left-sided cancers: N2 stations					
2L	19 (9)	2.0 (1.5)	1.0	1-6	0
4L	102 (49)	2.7 (3.6)	2.0	1-33	0
5	203 (98)	3.0 (2.4)	2.0	1-18	3 (1.5)
6	177 (86)	2.5 (1.7)	2.0	1-11	2 (1.0)
7	200 (97)	4.2 (3.7)	3.0	1-25	3 (1.5)
8	90 (43)	1.4 (0.9)	1.0	1-7	0
9	166 (80)	1.8 (1.2)	1.0	1-8	1 (0.5)
Left-sided cancers: N1 stations					
10L	186 (90)	2.5 (2.2)	2.0	1-12	3 (1.5)
11L	151 (73)	3.0 (2.6)	2.0	1-17	13 (6.3)
12L	101 (49)	3.0 (2.2)	3.0	1-13	14 (6.9)
13L	28 (14)	3.5 (3.0)	2.0	1-12	5 (2.5)
14L	5 (2)	2.0 (1.7)	1.0	1-5	1 (0.5)

^aN2 stations: 2L, 4L, 5, 6, 7, 8, and 9.

^bN1 stations: 10L, 11L, 12L, 13L, and 14L.

Table 5—N2 Patients

Patient	Stage	T Stage	N Stage	Histology	Location	Positive Stations
1	IIIA	T2	N2	Squamous	LUL	5
2	IIIA	T2	N2	Adenocarcinoma	LLL	9
3	IIIA	T2	N2	Adenocarcinoma	LUL	5, 11L
4	IIIA	T2	N2	Squamous	LUL	7
5	IIIA	T2	N2	Bronchoalveolar	LLL	7, 12L
6	IIIA	T2	N2	Other NSCLC ^a	LUL, LLL	11L ^b
7	IIIA	T1	N2	Adenocarcinoma	LUL	6, 12L
8	IIIA	T1	N2	Adenocarcinoma	LLL	6, 7, 11L
9	IIIA	T1	N2	Other NSCLC ^a	LUL	5, 12L
10	IIIA	T2	N2	Adenocarcinoma	RLL	7, 11R
11	IIIB	T4	N2	Adenocarcinoma	RUL	2R, 4R
12	IIIA	T3	N2	Adenocarcinoma	RLL	4R
13	IIIA	T2	N2	Adenocarcinoma	RUL	4R
14	IIIA	T2	N2	Other NSCLC ^a	RLL	11R ^b
15	IIIA	T2	N2	Other NSCLC ^a	RLL	7
16	IIIA	T2	N2	Squamous	RLL	7, 11R
17	IIIA	T2	N2	Adenocarcinoma	RLL	8,9
18	IIIA	T1	N2	Adenocarcinoma	RUL	4R, 10R
19	IIIB	T4	N2	Squamous	RHIL	^b
20	IIIA	T2	N2	Squamous	RUL	4R, 10R
21	IIIA	T2	N2	Other NSCLC ^a	RLL	^b

LLL = left lower lobe; LUL = left upper lobe; NSCLC = non-small cell lung cancer; RLL = right lower lobe; RUL = right upper lobe.

^aOther NSCLC not otherwise specified.

^bPositive N2 nodes not specified.

study group recommends that the number of lymph nodes resected during MLND be ≥ 12 , with nodes removed from stations 2R, 4R, 7, 8, 9, and 10R on the right, and stations 4L, 5, 6, 7, 8, 9, and 10L on the left.

Whether MLND offers any therapeutic benefit remains to be determined. Reports in the literature suggest that MLND offers some survival advantage, but this is largely related to stage migration. Several authors report improved survival with harvest of > 10 lymph nodes, but that removal of > 16 nodes did not confer any further improvement in survival.^{8,9} In a population-based study of 16,800 patients, multivariate analysis showed maximum survival for all-cause mortality (hazard ratio, 0.78; 95% CI, 0.68-0.90) and lung-cancer-specific mortality (hazard ratio, 0.74; 95% CI, 0.62- 0.89) in patients who had resection of 13 to 16 lymph nodes.¹⁵ Similar results were reported by Ou and Zell¹⁶ and Varlotto et al.¹⁷ Mature results of the ACOSOG Z0030 trial will provide level 1 evidence addressing the question of survival benefit.

Table 6—Thoracotomy vs VATS

Approach	No. Patients	No. Lymph Nodes		
		Mean (SD)	Median	Range
Thoracotomy	488	20.3 (10.7)	19.0	1-83
VATS	29	17.6 (8.6)	15.0	5-48

P = .17 (two-sample rank sum test). Note that intent-to-treat analyses were also performed. VATS = video-assisted thoracic surgery.

CONCLUSIONS

The ACOSOG Z0030 study demonstrates that MLND can be performed reliably and safely by thoracic surgeons in both community and academic settings. A minimum of six lymph nodes were resected in 99% and > 10 lymph nodes in 90% of patients. Overall, a median of 18 lymph nodes were resected per patient. In the majority of patients, dissection of N2 stations provided a median of one to four lymph nodes per station. The ACOSOG Z0030 study provides a benchmark for assessment of the adequacy of lymph node harvest in the conduct of pulmonary resection for non-small cell lung cancer. This study demonstrates that the minimum requirements for lymph node staging can be provided in both community and academic centers and should be expected for optimum care of the patient with resectable non-small cell lung cancer.

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Dr Landreneau: contributed to data collection and review and approval of the manuscript.

Dr Putnam: contributed to acquisition of data, review of data, and approval of the manuscript.

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Additional information: The e-Appendix can be found in the Online Supplement at <http://chestjournal.chestpubs.org/content/139/5/1124/suppl/DC1>.

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