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Missed intrapulmonary lymph node metastasis and survival after resection of non-small cell lung cancer

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Abstract

Background—Pathologic nodal stage is a key prognostic factor for patients with surgically resected lung cancer. We previously described the extent of missed intrapulmonary nodal metastasis in a cohort of patients treated at metropolitan Memphis, TN institutions. With long-term follow-up, we now quantify the survival impact of missed nodal metastasis.

Methods—We conducted a prospective cohort study to evaluate inadvertently discarded lymph nodes in re-dissected remnant lung resection specimens from lung cancer patients. Retrieved material was histologically examined and classified as lymph nodes with and without metastasis. Survival information was obtained from hospital cancer registries. We plotted survival distributions using the Kaplan Meier method and evaluated them with proportional hazards models controlling for significant demographic and clinical factors.

Results—The study included 110 patients who were 54% female and 69% Caucasian. Discarded lymph nodes with metastasis were found in 25 (23%) patients. Patients with missed lymph node metastasis had an increased risk of death with an unadjusted hazard ratio of 2.0 (p-value= 0.06) and an adjusted hazard ratio of 1.4 (p-value=0.45) compared with those without

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missed lymph node metastasis. Patients with >2 missed lymph nodes with metastasis had 4.8 (p-value=0.0005) times the hazard of death compared to patients without missed lymph node metastasis (adjusted hazard ratio =6.5, p-value=0.0001).

Conclusions—Metastasis to inadvertently discarded intrapulmonary lymph nodes from lung cancer resection specimens was associated with reduced survival. A more rigorous gross dissection protocol for lung cancer resection specimens may provide prognostically useful information.

Keywords

lymph nodes; metastases; lung cancer; quality improvement; survival

Lung cancer accounts for 27% of all US cancer deaths [1]. Most long-term survivors of lung cancer are patients with non-small cell lung cancer (NSCLC) who have undergone curative-intent surgical resection. However, most such patients die within five years of surgery [2]. The pathologic nodal stage is the most powerful prognostic factor in the curative-intent resection population, with 5-year survival rates of 56%, 38%, 22%, and 6% for patients with pathologic N0, N1, N2 and N3 respectively [3]. In acknowledgement of this, the Association of Directors of Anatomic and Surgical Pathology has recommended examination of all lymph nodes in lung resection specimens as standard pathology practice [4]. Unfortunately, this recommendation has not been widely implemented as standard practice [5, 6].

The gap in quality of pathologic (p) nodal staging is illustrated in the fact that 13% of all resections, and 18% of pathologic node-negative lung cancer resections in the US Surveillance, Epidemiology and End-Results (SEER) database have no lymph nodes examined (pNX) [6]. Furthermore, the median number of lymph nodes examined in pN0 resections is approximately 6, which is significantly lower than the median of 18–21 nodes associated with the best survival [7]. Failure to retrieve and examine intrapulmonary lymph nodes is a major contributor to the nodal staging quality gap. In a hypothesis-confirming experiment, we previously demonstrated that 60% of intrapulmonary lymph nodes were routinely discarded without examination, discarded lymph nodes were found in 90% of lobectomy specimens, and 29% of discarded lymph nodes had metastasis, including up to 12% of pN0 specimens [8].

However, our initial report did not include the survival impact of missed lymph node metastasis [9]. In the current report, we compared the survival of patients with and without discarded lymph node metastasis, to determine if missed lymph node metastasis has any prognostic value.

Material and Methods

We hypothesized that the low number of hilar and intrapulmonary (N1) lymph nodes routinely examined in lung resection specimens suggested that a significant number of lymph nodes were being discarded without examination, and further hypothesized that a clinically significant proportion of such discarded lymph nodes have metastasis. We have previously reported the details of the design and implementation of this study [8, 10].

Briefly, we collected consecutive lobectomy (or greater) lung cancer resection specimens, earmarked for permanent destruction after completion of routine pathology examination, in two hospital pathology departments in metropolitan Memphis, TN. Only specimens from patients who did not receive pre-operative chemotherapy or radiation therapy were examined. We applied a fastidious thin-section gross re-dissection protocol to retrieve all material that grossly appeared to be lymph nodes and processed all retrieved material for histologic examination by standard hemotoxylin and eosin-staining light microscopy. The histologic examination included only newly discovered lymph node material, and did not re-examine lymph nodes discovered by routine pathologic examination. We have previously provided details of the bench protocol for the fastidious re-dissection method [8, 10].

With the passage of time, we have now retrieved survival information from the participating institutions' tumor registries, which are obtained through state vital records. We measured survival time from the date of surgery to the date of death or last follow-up. Patients currently alive were censored on March 31, 2015. The median duration of follow up for the study cohort was 44 months (range: 0 – 62 months). This study was approved by the Institutional Review Boards at each participating institution, with a waiver of informed consent.

Data and Statistical Analysis

Lymph node metastasis was evaluated per patient as 'any additional lymph nodes with metastasis found' ('yes' or 'no'), and as the total number of additional lymph nodes with metastasis found (0, 1–2, >2). Sex, race (African-American or Caucasian), pathologic N-category (pN 0, 1 or 2), pathologic T-category (pT1/T2/Tx or pT3/T4), resection margin status (positive or negative), age, %DLC0, %FEV1, type of procedure, and Charlson comorbidity score were evaluated as potential confounders in the multiple variable analyses. The best multiple variable model (parsimonious model) was determined using a step-wise procedure based on confounding variables that impact the hazard ratio estimate by more than 10%. To evaluate the sensitivity of the model selection, full models adjusting for all potential confounders are reported in the Appendix.

Survival distributions were estimated and plotted using the Kaplan-Meier method and compared with the logrank test. Three-year survival estimates are presented with 95% confidence intervals. Multiple variable models were evaluated using cox proportional hazards models, and crude and adjusted hazard ratios are presented with 95% confidence intervals. All analyses were conducted in SAS Version 9.4 (Cary, NC).

Results

Clinical and demographic characteristics

The 110 patients available for this analysis were 54% female and 69% Caucasian. A lobectomy or bilobectomy was performed in 91% of patients, with the remaining 9% undergoing pneumonectomy. Sixty-nine percent of patients had private insurance, 24% had

Set MMC box: The Appendix can be viewed in the online version of this article [INSERT article doi] on http://www.annalsthoracicsurgery.org.

Medicaid or Medicare, and 7% were uninsured. A preoperative CT scan was performed in 99% of patients and 79% had preoperative PET scans. Forty-four percent of patients had T1 disease, while 35% were T2, 16% were T3, 4% were T4, and 1% were TX. Additional demographic and clinical information is reported overall and according to status of discovery of discarded lymph nodes with metastasis (Table 1).

Discovery of missed lymph node metastasis

After routine pathology examination, 69%, 16% and 15% of patients were pN0, pN1, and pN2 respectively. After re-dissection of the discarded lung resection specimens, additional lymph nodes with metastasis were found in 25 (23%) patients. Of these 25 patients, 6 were pN0 after routine pathology examination, 12 were pN1, and 7 were pN2. Eleven of the 25 patients had >2 additional lymph nodes discovered with metastasis, 3 were pN0 after routine pathology examination, 4 were pN1, and 4 were pN2. Including information from the discarded lymph nodes, the number of patients with pN0 decreased from 77 (70%) to 71 (65%), and the pN1 population increased from 18 (16%) to 24 (22%) (Table 1).

Missed lymph node metastasis and survival

Patients with at least one missed lymph node with metastasis had decreased survival estimates when evaluated crudely (Fig 1), and after stratification for pathologic N-category and T-category (Table 2), with a strong trend towards statistical significance. The hazard of death in patients with missed lymph node metastasis was 2.0 times (95% CI: 1.0, 4.1) the hazard in those without missed lymph node metastasis (p-value= 0.0633).

After evaluating sex, race, pathologic N-category, pathologic T-category, margin status, age, %DLC0, %FEV1, type of procedure, and Charlson comorbidity score as potential confounding variables, age, procedure, and pathologic N-category were retained in the final adjusted model. After controlling for confounding, we still observed decreased survival times in patients with missed lymph node metastasis (hazard ratio = 1.4 (95% CI: 0.6, 3.7); p-value=0.45).

We further evaluated patients based on the number of missed intrapulmonary lymph node metastasis (0, 1–2, or >2) found on re-dissection, both overall and by stage (Table 2, Figure 2). Patients with >2 discarded intrapulmonary lymph nodes with metastasis had 4.8 times (95% CI: 2.1, 10.9) the hazard of death compared with those without missed lymph node metastasis, (unadjusted p-value=0.0005). This result was consistent after evaluating potential confounding, with the final model controlling for age, procedure, and pathologic N-category (adjusted hazard ratio =6.5 (95% CI: 2.3, 18.2), p-value=0.0001).

Comment

We have previously demonstrated that current routine gross dissection of lung cancer resection specimens discards the majority of intrapulmonary lymph nodes, a significant minority of which have metastasis on H&E microscopy [8, 10]. After a median of 44 months' follow-up, we now show that missed lymph node metastasis has prognostic implications, irrespective of patients' stage. This finding provides one plausible explanation for the oft-described association between the number of lymph nodes examined and survival

in patients with pathologic node-negative lung cancer [11–13], and affirms the connection between the number of lymph nodes with metastasis and survival in patients with node-positive disease [14–20]. It also provides one potential explanation for the dismal survival of patients who have no lymph nodes examined (pNX) [5, 6].

The Tumor, Node, Metastasis staging system is our most powerful prognostic tool in lung cancer. However, there are ongoing attempts to enhance its value [21, 22]. There is also an ongoing debate about the relative prognostic value of the number of lymph nodes involved with metastasis [19, 23]. Several investigators have proposed the number of lymph nodes involved as a more powerful prognostic factor than the location of lymph node metastasis, which is currently the basis of the pathologic nodal staging system [14, 16, 19]. Some have shown a link between the number of lymph nodes involved and the anatomic dispersal of nodal metastasis, suggesting that patients with more N1 nodal metastasis are more likely to have mediastinal nodal involvement [14, 16]. It is true that pathologists have no direct access to hilar and mediastinal lymph nodes, retrieval of which is heavily dependent on surgical practice, which is also highly variable [24, 25]. However, the volume-outcome relationship is maintained, even in clinical trials with very rigorous surgical hilar and mediastinal lymph node dissection, but no tight control of pathology examination practice [26].

Patients with nodal metastasis generally benefit from post-operative adjuvant chemotherapy, which significantly decreases their hazard for death or disease recurrence [27–29]. There is also ongoing interest in developing more effective post-operative adjuvant therapies. Obviously such studies benefit significantly from accurate categorization of patients into post-operative risk subsets. Mis-categorization of pathologic N-stage inhibits the successful testing of such novel adjuvant treatments, increases the effect-size needed for such novel treatments to be demonstrably effective, increases the probability of false negative results in clinical trials, and raises the sample size needed for adequate statistical power in clinical trials of such adjuvant therapies.

Our hypothesis-testing study is limited by a relatively small sample size and relatively short duration of follow up (3 years, rather than the customary 5 years), which restricted our statistical power in certain analyses. Therefore, the strong trends towards survival impact demonstrable in this limited study suggests that the negative survival impact of missed lymph node metastasis is probably even greater than we report. Another limitation is our evaluation of specimens from only 2 pathology groups in a single city. Therefore these findings might not reflect practice in other parts of the US. However, we have shown from analysis of the SEER database that the Memphis experience with the nodal staging quality gap accurately reflects US national practice [5–7, 30, 31]. Comparison of the lymph node staging quality gap from analyses of US national databases vs. the Memphis Metropolitan Area Quality of Surgical Resection cohort illustrates this fact. The rate of resections without lymph node examination is 13% in SEER [6] vs. 12% in the Memphis cohort [5]; resections without mediastinal lymph node examination in a 2001 American College of Surgeons patient care survey was 42% [32] vs. 42% in the Memphis cohort [30]; the median total number of lymph nodes examined in pN0 resections was 6 in a SEER analysis [7] vs. 5 in the Memphis cohort [5].

It is possible that this quality gap in gross retrieval and examination of intrapulmonary lymph nodes is limited to the types of community-based pathology practices included in our study. Much better results are probably achieved within academic institutions. However, one of the institutions included in our study is a teaching institution with a pathology residency training program. Moreover, the fact remains that 80% of surgical lung cancer care in the US occurs in community hospitals, similar to those included in our study [32]. Besides, there is also evidence of heterogeneity in quality of lung cancer care in academic centers. For example, Little et al found only slight improvement in nodal staging quality in academic centers compared to non-academic centers [32].

Furthermore, analysis of the landmark American College of Surgeons Oncology Group Z0030 trial, which involved predominantly academic centers in North America shows that the distribution of N1 lymph node counts is similarly weighted towards the low end, with a median of 5 nodes examined [26], identical to results in our cohort [8]. By comparison, a median of 11 N1 lymph nodes are examined when the discarded intrapulmonary lymph nodes are included in our cohort [8]. Finally, variation in the thoroughness of pathologic N1 nodal examination is a plausible hypothesis to explain the striking geographic differences in pN0 survival rates in Asian patients in the International Association for the Study of Lung Cancer database (5-year survival 79%), compared to patients from Australia, Europe and North/South America, with respective 5-year survival rates of 58%, 54%, and 67% [33].

Accurate pathologic nodal staging requires improvement in surgical processes to retrieve and accurately label the anatomic provenance of hilar and mediastinal nodes, and concurrent improvement in gross retrieval of intrapulmonary lymph nodes. Current recommendations, such as those of the Association of Directors of Anatomic and Surgical Pathology, require examination of all lymph nodes present in a resection specimen [4]. Two widely used manuals of gross dissection describe methods to achieve this, but may need to be modified in view of these findings, and reports of improved intrapulmonary lymph node yield from a novel gross dissection protocol [34–36]. The stage-migration possible with the combination of corrective interventions to improve surgical and pathology processes has also been reported, including the impact on post-operative adjuvant therapy eligibility rates [37]. If validated in prospective studies involving more heterogeneous practice settings, wide dissemination and implementation of such improved processes as the standard of care for curative-intent lung cancer resection may provide a practical means of improving lung cancer survival at the broad population level. Scientifically rigorous large-scale studies to definitively establish the population-level impact of these quality improvement projects are both ongoing, and in gestation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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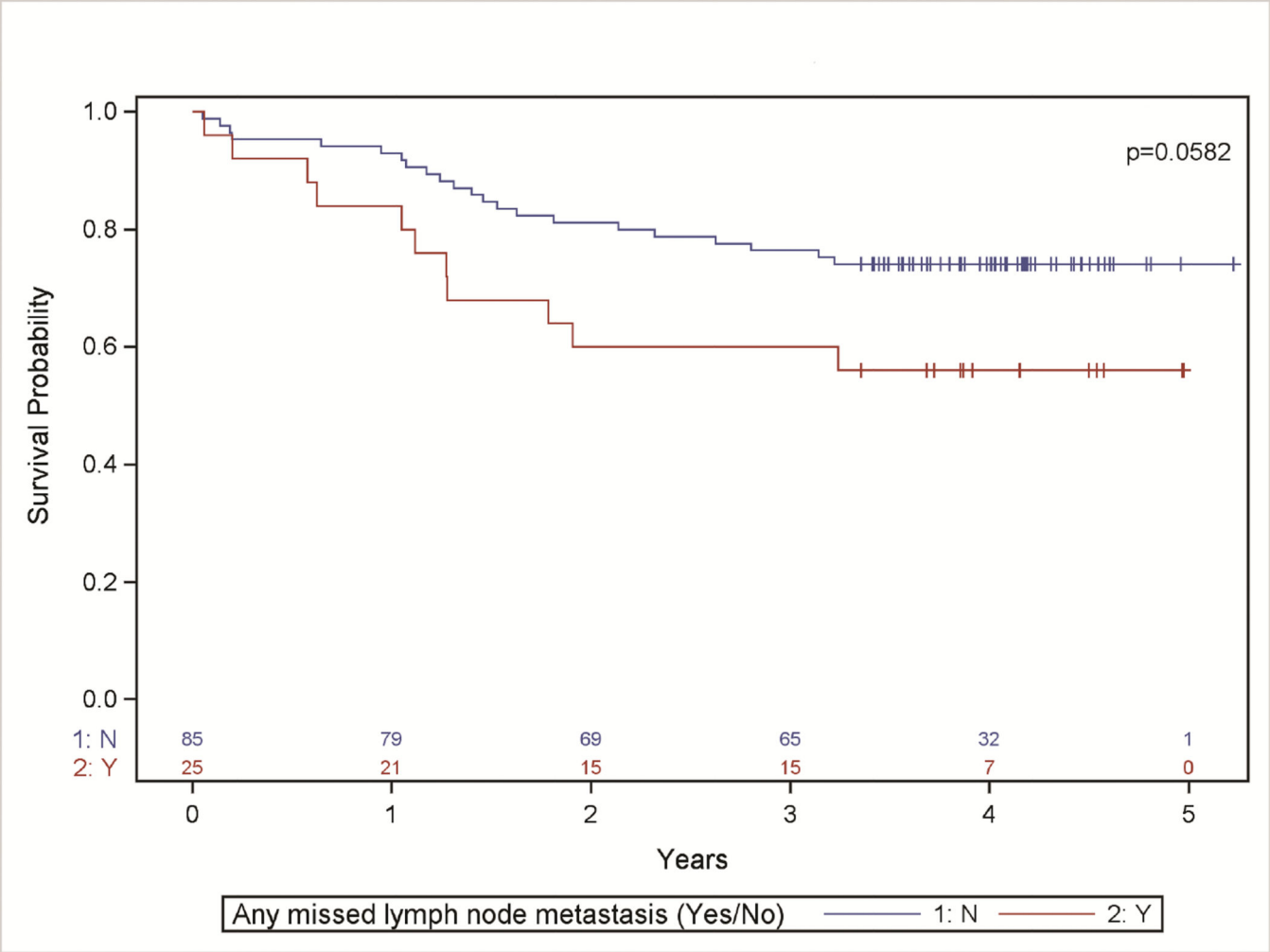

Figure 1. Survival distribution stratified by discovery of any missed lymph node metastasis (Yes/No)

Kaplan-Meier Survival Analysis comparing patients with and without the discovery of missed lymph nodes with metastasis (Yes or No) (p-value=0.0582). After controlling for age, procedure, and pathologic N-category, patients with missed lymph node metastasis had 1.4 times the hazard of death compared to those with no missed lymph node metastasis (p-value=0.45).

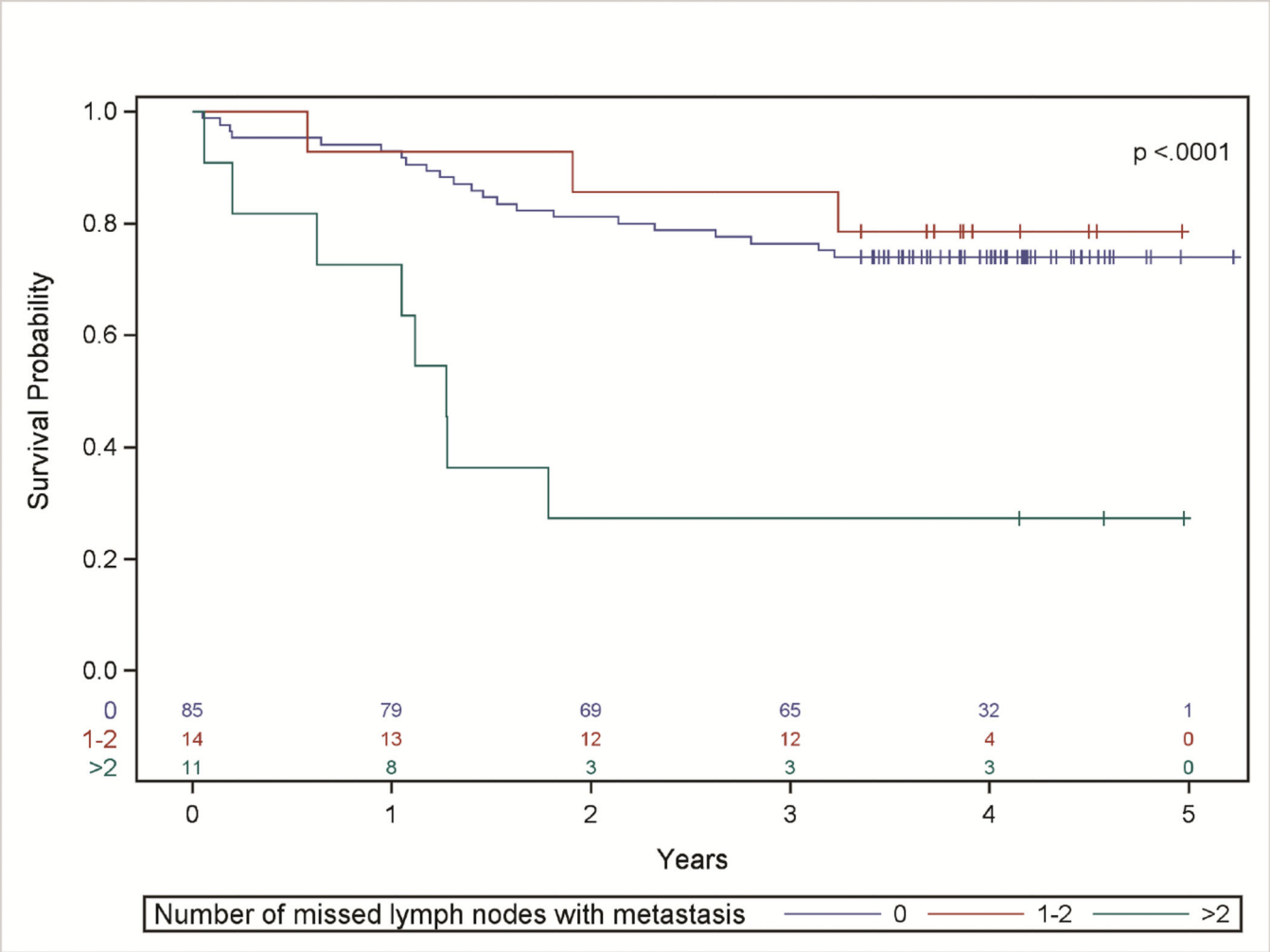

Figure 2. Survival distribution stratified by number of missed lymph nodes with metastasis

Kaplan-Meier Survival Analysis of Patients Categorized by Number of Discovered Missed Lymph Nodes with Metastasis (p-value < 0.0001). After controlling for age, procedure, and pathologic N-category, patients with >2 missed lymph nodes with metastasis had 6.5 times the hazard of death compared to those with no missed lymph node metastasis (p-value= 0.0001).

Table 1

Demographic and Clinical Variables of Patients Categorized by Discovery of Missed Lymph Node Metastasis

Variable	Lymph Node Metastasis No N (%)	Lymph Node Metastasis Yes N (%)	Total
Female	46 (54)	13 (52)	59
Male	39 (46)	12 (48)	51
African-American	23 (27)	11 (44)	34
Caucasian	62 (73)	14 (56)	76
Commercial	60 (71)	16 (64)	76
Medicaid	9 (11)	1 (4)	10
Medicare	12 (14)	4 (16)	16
None	4 (5)	4 (16)	8
Bi-lobectomy	8 (9)	2 (8)	10
Lobectomy	74 (87)	16 (64)	90
Pneumonectomy	3 (4)	7 (28)	10
N0	70 (82)	6 (24)	76
N1	6 (7)	12 (48)	18
N2	9 (11)	7 (28)	16
T1	45 (52)	3 (12)	48
T2	28 (33)	11 (44)	39
T3	10 (12)	8 (32)	18
T4	2 (2)	2 (8)	4
Tx	0 (0)	1 (4)	1
Margin Negative	82 (96)	22 (88)	104
Margin Positive	3 (4)	3 (12)	6
	Mean (SD)	**Mean (SD)**	

Variable	Lymph Node Metastasis		Total
	No	Yes	
	N (%)	N (%)	
Age	66.3 (12.3)	64.4 (9.9)	65.8 (11.8)
Charlson Score	1.8 (1.6)	1.8 (1.7)	1.8 (1.6)
Tumor Size (cm)	3.2 (1.7)	5.0 (2.1)	3.6 (2.0)

Table 2

Kaplan Meier Survival Estimates of Patients Categorized by Discovery of Missed Lymph Node Metastasis, T-Stage, and N-Stage.

	3-Year Overall Survival (95% Confidence Interval)			
	Missed Lymph Node Metastasis?			
	No	Yes		P-Value
Overall	76% (67%, 85%)	60% (41%, 78%)		0.0582
T1/T2	77% (66%, 86%)	67% (42%, 87%)		0.30
T3/T4	75% (48%, 94%)	50% (21%, 79%)		0.14
N0	79% (68%, 87%)	83% (46%, 100%)		0.70
N1	67% (28%, 95%)	58% (31%, 83%)		0.72
N2	67% (35%, 92%)	43% (11%, 78%)		0.10
	Number of missed lymph node metastasis			
	0	1–2	>2	P-Value
Overall	76% (67%, 85%)	86% (63%, 98%)	27% (6%, 56%)	<0.0001
T1/T2	77% (66%, 86%)	82% (55%, 98%)	25% (0%, 72%)	0.0426
T3/T4	75% (48%, 94%)	100% (NA)	29% (4%, 65%)	0.0125
N0	79% (68%, 87%)	100% (NA)	67% (14%, 100%)	0.60
N1	67% (28%, 95%)	75% (42%, 97%)	25% (0%, 72%)	0.13
N2	67% (35%, 92%)	100% (NA)	0% (NA)	0.0006