The Impact of N2 Lymph Node Positivity on Survival Rates Among Patients Undergoing Surgery for Non-Small Cell Lung Cancer

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Abstract

Aim: Our study aims to identify patients diagnosed with non-small cell lung cancer who have undergone lung resection and have ipsilateral mediastinal metastatic lymph nodes (N2). We intend to categorize them into surprise N2 and potentially resectable N2 groups based on clinical approach and investigate the impact of these groups on survival outcomes.

Methods: Between January 2011 and December 2017, a retrospective cohort study was conducted on 953 patients who underwent lung resection for non-small cell lung cancer (NSCLC) at our hospital. Patients were categorized into three groups: patients without initial clinical N2 involvement but with postoperative pathological N2 involvement (group 1), patients with initial clinical N2 involvement who underwent immediate surgery (group 2), and patients with initial clinical N2 involvement who demonstrated stable pathological N2 involvement or partial regression after receiving neoadjuvant chemotherapy or chemoradiotherapy and subsequently underwent surgery (group 3).

Results: A total of 71 patients (7.45% of the cohort) with postoperative pN2 were included in this study. Among these 71 patients, 41 (57.74%) did not have initial cN2 involvement and were categorized as postoperative pN2 (group 1). Twenty patients (28.16%) with a single cN2 were considered as carefully selected patients and underwent surgery (group 2). Ten patients (14.08%) were selected patients who received neoadjuvant treatment and subsequently had a single N2 involvement, and they underwent anatomical resection (group 3). Statistical analysis revealed no significant differences in survival between the three groups (p=0.882).

Conclusions: No consensus currently exists regarding the role of surgery in the management of patients with NSCLC and mediastinal lymph node metastases. Existing evidence suggests that studies encompassing larger patient cohorts are necessary to comprehensively investigate the subgroups of patients with N2 disease.

Keywords: *Non-small cell lung cancer, N2, mediastinal lymph node, surprise N2, skip N2*

1. Introduction

Cancer remains a significant global and national public health concern, ranking second after cardiovascular diseases as the leading cause of death [1, 2]. Lung cancer, specifically, accounts for approximately 12.9% of all cancer cases, with an estimated 1.8 million new cases reported annually[3]. Unfortunately, only a small percentage (15-20%) of Non-Small Cell Lung Cancer (NSCLC) patients are diagnosed at an early stage (Stage IA, IB, IIA, IIB) and qualify for surgical intervention, while a larger proportion (30%) present with locally advanced disease (Stage 3A and 3B)[3]. In Turkey, the distribution of lung cancer cases is as follows: 18% present with localized disease, 30% with regional spread, and 52% with distant metastasis[4]. When considering clinical staging, the 5-year survival rates for NSCLC patients were reported as follows: 82% for Stage IA, 66% for Stage IB, 52% for Stage IIA, 47% for Stage IIB, 47% for Stage IIIA, 36% for Stage IIIB, and 19% for Stage IV[5]. Lung cancer treatment options include surgical treatment, chemotherapy, radiotherapy and immunotherapy. Despite advances in chemotherapy and radiotherapy, the best treatment option in early-stage lung cancer is still surgical treatment[6].

In numerous studies examining Non-Small Cell Lung Cancer (NSCLC), it has been consistently identified that N2 positivity represents a significant negative prognostic factor[7, 8, 9]. Consequently, one of the primary strategies for improving survival rates in NSCLC is to employ the most suitable treatment for mediastinal lymph node metastasis. Among physicians specializing in lung cancer treatment,

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the management of N2 positivity remains a topic of considerable debate and controversy.

In cases of locally advanced lung cancer with ipsilateral mediastinal metastatic lymph nodes, the current recommended treatment approach involves definitive chemotherapy (CT) or concurrent chemoradiotherapy (CRT). However, there is limited research available on the role of surgery in stage 3 patients with positive N2 lymph nodes.

In our study, we conducted a comparative evaluation of survival outcomes and prognostic factors within two distinct groups of NSCLC patients who underwent anatomical resection. The first group consisted of "surprise N2" cases, where no metastatic N2 disease was initially detected during the preoperative evaluation, but metastasis was later identified during postoperative pathologic evaluation. The second group comprised "probable resectable N2" cases, characterized by the presence of metastatic N2 disease detected during the preoperative evaluation.

2. Materials and methods

2.1 Patient Selection:

This retrospective study reviewed patients who were admitted to the Çukurova University Department of Thoracic Surgery between January 2011 and December 2017. The inclusion criteria were patients who underwent anatomical lung resection and mediastinal lymph node dissection for non-small cell lung cancer (NSCLC) and were found to have N2 lymph node metastasis (pN2) during postoperative pathologic evaluation. However, patients who were clinically diagnosed with N2 lymph node metastasis in preoperative evaluation (cN2), showed complete regression in clinical and radiologic evaluation after neoadjuvant treatment, or had no N2 lymph node metastasis in postoperative pathologic evaluation (N0) were excluded from the study.

2.2 Study Design:

We divided the patients into three groups: patients who did not have cN2 but had pN2 postoperatively (group 1), patients who had cN2 and were primarily operated (group 2), and patients who had cN2 and had stable pN2 or partial regression after neoadjuvant CT or CRT treatment and underwent surgery (group 3).

The study involved examining the data and archive files of the patients. Through this analysis, several factors were determined, including the demographic characteristics of the patients, histological type and location of the tumor, date of diagnosis, invasive mediastinal intervention, clinical and pathological TNM stages according to the 8th TNM staging system, treatment applied, and overall survival values.

2.3. Statistical Analysis:

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences Version 22.0; SPSS Inc. Chicago, IL, USA) software. Descriptive statistics were utilized to present the variables: parametric data were expressed as mean ± standard error, categorical data as frequency and percentage, and survival levels as median. To explore the relationship between parametric data and categori¬cal variables, independent t-test and one-way analysis of variance (ANOVA) tests were employed. Chi-square Fisher's Exact test was used to examine the relationship between categorical variables. The log-rank analysis was employed to assess the impact of various parameters on survival. Parameters with p-values of ≤0.10 in the log-rank analyses were included in the multivariate analyses. Model fit and the assumption of proportionality of periodic risk were evaluated using residual analyses, including Schoenfeld and Martingale methods. Any p-value below 5% was considered statistically significant, indicating a type 1 error level.

3. Results

Between January 2011 and December 2017, a retrospective review was conducted on 953 patients who underwent lung resection for NSCLC at our hospital. The study included 71 patients (7.45%) with postoperative pN2. Of these patients, the mean age was 58.83±1.07 years, with 63 (88.73%) being male and 8 (11.27%) being female. The most common histopathologic diagnosis was adenocarcinoma (n=36, 50.70%), followed by squamous cell carcinoma (n=28, 39.43%), pleomorphic carcinoma (n=3, 4.22%), adenosquamous carcinoma (n=1, 1.40%), large cell carcinoma (n=1, 1.40%), carcinosarcoma (n=1, 1.40%), and combined large cell - squamous cell carcinoma (n=1, 1.40%). In terms of tumor localization, 24 (33.80%) were located in the right upper lobe, 22 (30.98%) in the left upper lobe, 14 (19.71%) in the right lower lobe, 7 (9.85%) in the left lower lobe, 2 (2.81%) in the right middle lobe, 1 (1.40%) in the right hilar, and 1 (1.40%) in the left hilar.

3.1. Evaluation of groups

Forty-one (57.74%) of 71 patients in our study had no cN2 and were evaluated as pN2 postoperatively (group 1). Twenty (28.16%) patients with a single cN2 were evaluated as selected patients in good condition and underwent surgery (group 2). 10 (14.08%) patients were selected patients who received neoadjuvant treatment and then had a single N2 and anatomical resection was performed (Group 3).

3.1.1 Group 1 - "Surprise N2" (n=41)

In this group, 35 patients (85.36%) were male, while 6 patients (14.64%) were female, with a mean age of 59.07±1.32 years. Histopathologic evaluation revealed that 19 cases (46.34%) were diagnosed as adenocarcinoma, 18 cases (43.90%) as squamous cell carcinoma, and 4 cases (9.75%) as other types. The localization of the masses was as follows: 16 cases (39.02%) in the right upper lobe (RUL), 10 cases (24.39%) in the right lower lobe (RLL), 10 cases (24.39%) in the left upper lobe (LUL), 3 cases (7.31%) in the left lower lobe (LLL), 1 case in the right central region, and 1 case in the left central region. Among the 41 patients, 34 (82.93%) underwent lobectomy, while 7 (17.07%) underwent pneumonectomy. Single-station pathologic N2 lymph node involvement was detected in 34 (82.91%) cases, while multiple pathologic N2 lymph node involvement was observed in 7 (17.07%) cases. The postoperative pathologic evaluation showed N2 lymph node metastasis in 42 (22.70%) out of 185 lymph nodes examined. The most common metastases to N2 lymph node stations were observed in station 4 (n=15, 35.71%) and station 7 (n=11, 26.19%). Skip N2 lymph node metastasis was present in 22 (53.65%) patients. Among the patients, 22 (53.7%) were classified as Stage 3A, while 19 (46.3%) were classified as Stage 3B. Lymphovascular invasion was detected in 31 (75.70%) patients, while visceral pleural invasion was observed in 2 (4.87%) patients. The median survival of the patients was 33.53 months (95% CI 20.136-46.930), and 26 (63.41%) of the patients had deceased during the study period (Table 1, 2).

3.1.2. Group 2 - Known N2 "selected patients" (n=20)

In this group, there were 18 (90%) male and 2 (10%) female patients with a mean age of 58.25±2.31 years. The median survival was calculated as 22.70 months (min: 1, max: 92). In this group, adenocarcinoma (n=9, 45%) and squamous cell carcinoma (n=8, 40%) were the most common tumor types observed.

Table 1
Descriptive statistics of variables

		Group 1 (n=41)	Group 2 (n=20)	Group 3 (n=10)	Total (n=71)	p
Age (mean ± SE)		59.07±1.32	58.25±2.31	59 ±3.07	58.83±1.07	0.946
Gender	•Male n(%)	35, 85.36%	18(90%)	10(100%)	63 (88.73%)	0.592
	•Female n(%)	6, 14.64%	2 (10%)	0(0%)	8(11.27%)	
Histopathology n(%)	•Adenocarsinoma	19(46.34%)	9 (45%)	8(80%)	36(50.70%)	0.390
	•squamous cell carcinoma	18(43.90%)	8(40%)	2 (20%)	28(39.43%)	
	•Others	4(9.75%)	3(15%)	0(0%)	7(9.85%)	
Tumor size (cm)		5.017(±0.351)	5.015(±0.389)	4.010(±0.571)	4.66(±0.344)	0.369
Localization of tumour n(%)	•RUL	16 (39.02%)	4(20%)	4(40%)	24(33.80%)	0.533
	•RML	0 (0%)	1(5%)	1(10%)	2 (2.81%)	
	•RLL	10 (24.39%)	4(20%)	0(0%)	14 (19.71%)	
	•LUL	10 (24.39%)	8(40%)	4(40%)	22 (30.98%)	
	•LLL	3 (7.31%)	3(15%)	1(10%)	7 (9.85%)	
	•Right hilar	1 (2.43%)	0	0(0%)	1(1.40%)	
	•Left hilar	1 (2.43%)	0	0(0%)	1(1.40%)	
Operation n(%)	•Lobectomy	34 (82.93%)	17(85%)	7 (70%)	58(81.69)	0.569
	•Pneumonectomy	7(17.07%)	3(15%)	3(30%)	13(18.30%)	
Lymph node: N2 met./ total(%)		42/185(22.20%)	28/70(40%)	14/92(15.21%)	84/347(24.20)	0.001
N2 lymph node metastasis n(%)	•single station	34(82.91%)	14(70%)	7(70%)	55(77.46%)	0.433*
	•multiple station	7(17.07%)	6(30%)	3(30%)	16(22.53%)	
Pathologic Stage	•3A	22(53.7%)	9(45.0%)	7(70.0%)	38(53.52%)	0.444
	•3B	19(46.3%)	11(55.5%)	3(30.0%)	33(46.47%)	
Skip N2 metastasis n(%)		22(53.65%)	6(30%)	6(60%)	34(47.88%)	0.157
Lymphovascular invasion n(%)		31(75.70%)	18(90%)	9(%90)	58(81.69%)	0.176
Visceral pleura invasion n(%)		2(4.87%)	3(15%)	1(10%)	6(8.45%)	0.326*
Excitus n(%)		26(63.41%)	11 (55%)	7(70%)	44(61.97%)	0.785

**Fischer Exact test, SE: Standart error, n:number, RUL: right upper lobe, RML: Right middle lobe, RLL: right lower lobe, LUL: left upper lobe, LLL left lower lobe.*

Tumor localization was found to be in LUL in 8 cases (40%), RUL in 4 cases (20%), RLL in 4 cases (20%), LLL in 3 cases (15%), and RML in one case (5%). Lobectomy was performed in 17 (85%) patients, and pneumonectomy was performed in 3 (15%) patients. Among the patients, 9 (45%) were diagnosed with Stage 3A disease, while 11 (55%) were diagnosed with Stage 3B disease. Postoperative pathologic evaluation revealed single-station N2 lymph node metastasis in 14 (70%) and multiple-station N2 lymph node metastasis in 6 (30%) patients. Lymphovascular invasion was present in 18 (90%) of the 20 patients, while 3 (15%) patients showed visceral pleural invasion. A total of 70 lymph node samplings were performed in this group, and N2 station metastasis was detected in 28 (40%) of them. Skip N2 lymph node metastasis was observed in 6 (30%) patients. The median survival of this patient group was 25.967 months (95% CI: 11.220-40.713). At the end of the study, 11 (55%) patients had deceased.

3.1.3. Group 3 - "Persistent N2" "selected patients after neoadjuvant therapy"(n=10)

The mean age of the patients in this group was 59 ± 3.07 years, and all patients were male. Adenocarcinoma was the observed pathology in 8 (80%) patients, while squamous cell carcinoma was present in 2 (20%) patients. Among the patients, 4 (40%) had tumors located in the RUL, 4 (40%) in the LUL, 1 (10%) in the RML, and 1 (10%) in the LLL. Lobectomy was performed in 7 (70%) patients, while pneumonectomy was carried out in 3 (30%) patients. Based on the diagnoses, 7 (70%) patients were classified as Stage 3A, and 3 (30%) patients were classified as Stage 3B. In the postoperative pathologic evaluation, a single N2 metastasis was found in 7 (70%) patients, and multiple N2 station metastases were observed in 3 (30%) patients. Lymphovascular invasion was detected in 9 (90%) patients, and visceral pleural invasion was observed in 1 (10%) patient. N2 station metastasis was identified in 14 (15.21%) out of 92 lymph node samplings. Skip N2 lymph node metastasis was present in 6 (60%) patients. The median survival was calculated as 27.767

Table 2
Evaluation of the efficacy of parameters on survival

		n	Survival		p
			Median (month)	95% Confidence interval	
Groups	•Group 1	41	33.533	20.136-46.930	0.882
	•Group 2	20	25.967	11.220-40.713	
	•Group 3	10	27.767	0.00-60.590	
Gender	•Male	63	26.133	15.345-36.922	0.008
	•Female	8	48.183	26.849-69.442	
Histopathologic Type	•Adenocarsinoma	36	33.900	16.168-51.632	0.240
	•Squamous Cell Carsinoma	28	18.167	4.444-31.890	
	•Others	7	39.300	5.701-72.899	
Operasyon Type	•lobectomy	58	33.700	24.100-43.300	0.254
	•pneumonectomy	13	16.633	1.734-31.533	
Pathologic Stage	•3A	38	39.000	25.695-52.305	0.337
	•3B	33	20.133	8.053-32.213	
Lymphovascular invasion	•yes	57	33.533	21.333-45.737	0.800
	•no	13	33.900	11.328-56.472	
Visceral pleura invasion	•yes	6	11.700	0.000-29.656	0.100
	•no	65	33.700	23.587-43.813	

months (95% CI: 0.00-60.590). At the time the study was terminated, 7 (70%) of the patients had exited (Table 1, 2).

3.2. Statistical comparison of descriptive values of the groups

There were no statistically significant differences between the groups in terms of patient demographic information such as age and gender (p=0.946, 0.592, respectively). Additionally, no statistically significant differences were observed between the groups regarding histopathological type, size, location, pathological stage, lymphovascular invasion rate, visceral pleural invasion rate, and the type of operation performed (p=0.390, 0.369, 0.533, 0.444, 0.176, 0.326, 0.569, respectively). Similarly, there were no statistically significant differences between the groups in terms of single or multiple N2 lymph node metastases and skip metastasis rate (p=0.433, 0.157, respectively). Furthermore, there was no statistically significant difference between the groups in terms of the rate of mortality (p=0.785, respectively). However, when analyzing the ratio of N2 lymph node metastasis to the total sampled lymph node metastasis, it was found that group 2 had a significantly higher rate than the other groups (p=0.001) (Table 1).

3.3. Survival Analysis

There was no statistically significant difference in survival between the groups (p=0.882). The survival time for male patients was 26.133 months (95% CI=15.345-36.922), while for female patients, it was 48.183 months (95% CI=26.849-69.442). A gender-related survival evaluation revealed a significantly longer survival time in female patients (p=0.008). When evaluating the histopathologic types, the median survival was 33.9 months (95% CI=16.168-51.632) for adenocarcinoma, 18.167 months (95% CI=4.444-31.890) for squamous cell carcinoma, and 39.3 months (95% CI=5.701-72.899) for other types. However, the histopathologic types did not have a significant statistical effect on survival (p=0.240). Median survival was 33.7 months (95% CI=24.100-43.300) for lobectomy and 16.633 months (95% CI=1.734-31.533) for pneumonectomy, and the type of operation performed did not show a statistically significant difference (p=0.254). Postoperative pathologic cancer staging indicated a median survival of 39 months (95% CI=25.695-52.305) for stage 3A patients and 20.133 months (95% CI=8.053-32.213) for stage 3B patients. However, cancer staging did not show a significant statistical difference in survival (p=0.337). The median survival for patients with lymphovascular invasion was 33.533 months (95% CI=21.333-45.737), compared to 33.9 months (95% CI=11.328-56.472) for patients without lymphovascular invasion, indicating that the presence or absence of lymphovascular invasion had no effect on survival (p=0.800). Among the 6 patients with visceral pleural invasion, the median survival was 11.7 months (95% CI=0.000-29.656), while for the 65 patients without invasion, it was 33.7 months (95% CI=23.587-43.813). The invasion of the visceral pleura did not affect survival (p=0.100) (Table 2).

4. Discussions

N2 positivity in patients can vary from single station microscopic N2 involvement to multi-station bulky N2 positivity, and even to skip N2 involvement. Considering the clinical information of the patients, subgroups such as possible resectable N2 and surprise N2 may arise. Consequently, approaching the patient solely as an N2 positive patient in treatment decisions can be a controversial matter.

According to recent studies, the incidence of surprise N2 positivity in patients who undergo surgery following a comprehensive preoperative evaluation is around 10%[11, 12]. In our study, surprise N2 involvement was identified in 4.3% of the total cohort (n=953) who underwent resection for NSCLC, with a total of 41 cases.

The current NCCN guidelines categorize definitive concurrent chemoradiotherapy (CRT) as a 'category 1' treatment approach for

stage IIIA (N2 positive) disease. Additionally, surgery after indication chemoradiotherapy is also recommended as an alternative treatment option[13]. In cases where discrete (non-infiltrative) N2 involvement is detected prior to surgery, the ACCP guidelines suggest performing surgery after definitive CRT or neoadjuvant therapy, rather than opting for surgery alone or radiotherapy alone (grade 1A)[14]. However, despite undergoing invasive mediastinal procedures, there is still a possibility of encountering intraoperative N2 metastasis. In such instances, it is recommended to proceed with the planned resection if complete removal of the primary tumor and mediastinal lymph nodes can be achieved[14]. Detterbeck's research demonstrated that there is no significant difference in quality of life and mortality between patients who undergo thoracotomy without lung resection and those who undergo lung resection. He suggests that it is more beneficial to proceed with resection in patients who are found to have intraoperative N2 involvement, even in the absence of preoperative clinical suspicion[15]. In studies focusing on patients with surprise N2 positivity detected during surgery, the 5-year survival rate was reported to be around 20-25%[16, 17]. In your study, the median survival of patients who received adjuvant chemotherapy (n=41), which was categorized as surprise N2 involvement, was 33.5 months, consistent with findings reported in the literature.

In the existing literature, varying rates of morbidity and mortality have been reported among stage 3 (N2 positive) patients based on the specific type of surgical resection. The randomized phase 3 trial conducted by North American Intergroup (INT0139) failed to demonstrate any survival advantage associated with surgical treatment following concurrent neoadjuvant chemoradiotherapy (CRT), when compared to definitive CRT alone. The authors of this study attribute this finding to the higher occurrence of pneumonectomy cases within the surgical group. They additionally discovered elevated rates of postoperative morbidity and mortality among patients who underwent pneumonectomy following neoadjuvant CRT, as opposed to those who underwent lobectomy. Conversely, in the same study, a survival advantage was observed among patients who underwent lobectomy after neoadjuvant CRT, when compared to the group of patients who solely received definitive CRT[18]. In our study, 81.6% (n=58) of patients underwent lobectomy, while 18.3% (n=13) underwent pneumonectomy. The median survival times recorded were 33.7 months and 16.6 months, respectively, and no statistically significant difference in survival outcomes was observed between these two resection types.

Goldstraw et al. conducted a study on non-small cell lung cancer (NSCLC) and determined the median survival for Stage IIIA and IIIB as 41.9 and 22.0 months, respectively, based on clinical staging in the lung cancer staging project of the International Association for the Study of Lung Cancer (IASLC)[5]. In our study, we observed median survival values of 39.0 and 20.1 months for Stage IIIA and IIIB, respectively. When comparing the survival times between these stages, no significant difference in survival was found (p-value: 0.337).

Even if a statistically significant difference exists in the survival times of men and women, it may not hold clinical significance due to a significant disparity in the ratio of male and female individuals.

5. Conclusions

The current updated treatment of stage 3 (N2 positive) non-small cell lung cancer (NSCLC) has not yet achieved the desired survival outcomes. In cases of multiple N2 metastases, it is essential to perform a comprehensive preoperative evaluation of mediastinal lymph nodes as surgical intervention does not contribute to improved survival. However, experienced centers with a multidisciplinary treatment approach may be able to perform surgical treatment with acceptable mortality and morbidity rates. In patients with clinical suspicion of N2 positivity, particularly those with centrally located tumors, N1 metastases, absence of pathologically-sized lymph nodes in the mediastinum on thoracic CT but increased metabolic activity on PET CT, an invasive mediastinal procedure should be considered. Despite a complete invasive mediastinal procedure, intraoperative N2 positivity remains highly probable. It is crucial to define the large and heterogeneous subgroups of N2 positive patients accurately.

Therefore, further investigation is warranted on the role of surgical treatment in N2 positive NSCLC.

Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by Çukurova University Faculty of Medicine Ethics Committee. (2018-- 80) Thesis number: 234238-2018
https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=UPP_Zu9isEmWGFXFCBYascen54xi2SCrQsuqpgVznbC9U9D9PToCDnw-s-B8Ueu5

Conflict of interest statement

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Author contributions

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