Survival Analysis in N2 (+) Patients for Whom Surgical Resection Was Performed

Cerrahi Rezeksiyon Uygulanmış N2 (+) Hastalarda Sağkalım Analizi

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ABSTRACT

Objective: This study aimed to demonstrate survival assessment and determine survival of the number of metastatic stations which N2 lymph node station was involvement.

Material and Methods: Ninety six (10.6%) patients with N2 lymph node metastasis in 901 patients who had been operated for Non-Small Cell Lung Cancer (NSCLC) at hospital from January 2009 to October 2013, were included in the study. The patients were analized under two main headings. In the first title the survival analysis was performed depending on single station or multiple stations of lymph node involvement. In the second title patients were divided into 5 groups according to metastatic lymph node stations. Group 1 was composed of superior (No 2&4) stations metastases (20.8%), Group 2 was aorticopulmonary window (No 5&6) stations metastases(26%), Group 3 was central (No 7) station (13.5%), Group 4 was inferior (No 8&9) stations metastases(14.6%) and Group 5 was multiple station metastases were determined (25%).

Results: Average survival time was 33.3 months and the median survival time was 30.8 months. In patients with mediastinal lymph node metastasis, comparison of survival difference in single-multiple stations; median survival of 55.7 months in single station and median survival of 25.5 months in multiple stations has been found. Single station involvement was determined to caused statistically significant better survival ($p < 0.05$). Group 1&2 in comparison to 3&5 lead to better survival and statistical significance ($p < 0.05$) was observed.

Conclusion: Single station N2 involvement should be expected in better survival rates compared to the involvement of multiple stations. Due to decreased survival observed especially with the involvement of level 7 station. It has to be sampled in pre-peri operative period.

Key Words: Lung cancer surgery, Metastatic N2 lymph nodes, Survival

ÖZ

Amaç: Bu çalışma, operasyon sonrası metastatik olduğu saptanan N2 lenf nodu istasyonlarının sağkalım değerlendirmesini ve hangi N2 istasyon tutulumunun sağkalımının daha iyi olduğunun gösterilmesini amaçlamıştır.

Gereç ve Yöntemler: Hastanemizde Ocak 2009-Ekim 2013 tarihleri arasında küçük hücreli dışı primer akciğer kanseri nedeni ile opere edilen 901 hastadan N2 lenf nodu metastazı tespit edilmiş 96 (%10,6) hasta çalışmamıza dahil edildi. Hastalar iki ana başlık altında incelendi. İlk başlıkta, lenf nodu istasyonu tutulumunun tek istasyon ve multipl istasyon olmasına göre incelendi. İkinci başlıkta ise metastatik lenf nodu istasyonlarına göre 5 gruba ayrılarak tutulumların sağkalıma etkileri değerlendirildi. Grup 1'de süperior (No 2&4) istasyon metastazları(% 20,8), Grup 2'de aortikopulmoner pencere (No 5&6) metastazları(%26), Grup 3'te santral (No 7) istasyon metastazı(%13,5), Grup 4'de inferior (No 8&9) istasyon metastazları(%14,6) ve Grup 5'de multipl istasyon metastazları incelenmiştir (%25).

Bulgular: Ortalama sağkalım süresi 33,3 ay ve median sağkalım süresi 30,8 ay olarak bulundu. Mediastinal lenf nodlarında metastaz tespit edilen hastalarda, tek-multipl istasyon sağkalım farkı karşılaştırmasında tek istasyon tutulumunda 55,7 ay ortalama sağkalım ve multipl istasyon

tutulumunda ise 25,5 ay ortalama sağkalım olduğu tespit edildi. Tek istasyon tutulumunun istatistiksel olarak anlamlı (p<0,05) olarak daha iyi sağkalıma neden olduğu belirlendi. Grup 1 ve 2'nin Grup 3 ve 5 ile karşılaştırmasında istatistiksel olarak anlamlı (p<0,05) olduğu ve daha iyi sağkalıma neden olduğu görüldü.

Sonuç: Tek istasyon N2 tutulumunda multipl istasyon tutulumuna göre daha iyi sağkalım süreleri beklenmelidir. Özellikle 7 numaralı istasyon tutulumunda azalmış sağkalım görüldüğünden pre-peri operatif süreçte mutlaka örneklenmesi gerekmektedir.

Anahtar Sözcükler: Akciğer kanseri cerrahisi, N2 lenf nodu metastazı, Sağkalım

INTRODUCTION

The most significant prognostic factor in patients which are operated due to NSCLC, is those that undergo complete resection and without distant organ metastasis is mediastinal lymph node metastasis. Selection of cases with possibility for operation still remains a controversial issue. When published articles are reviewed, survival rates have extreme variability. The reason for this is variability is the selection criteria for the patients which are to be candidates for surgery and there are inadequacies in preoperative and/or postoperative stages of this disease. This study was conducted in order to evaluate how various factors effect survival in N2 (+) patients for whom surgical resection was performed. Moreover the focus was put on the effect of number and location of involvements when it came to survival.

MATERIAL and METHODS

Education Planning Board of our hospital (date/number: 11.05.2015/493). Our study was conducted in our hospital. There were 96 patients in which N2 lymph node metastases had been detected out of 901 patients which were operated on due to NSCLC between January 2009 and October 2013 in Departments of Chest Surgery. The data was reviewed retrospectively and included in our study. Duration for follow-up was determined to be 24-82 months. Patients' records were scanned from a databank of our hospital and the detailed information was obtained from these files.

Of 96 patients included in the study; 75 were male and 21 were female. Mean age of patients on the date of operation was 57.3, while it varied between 21 and 79. The operation was performed via thoracotomy incision. In fact, number of patients with metastatic lymph node station (N2) was excluded. The 11 patients that were excluded from the study were due to following criteria: Patients died within first 30 postoperative days (n: 2), patients with pathological N2 involvement before the operation (n:2), patients with positive surgical margin (R1 or R2) and with narrow surgical margin (closer than 5 mm) (n:7) were excluded from the study.

During the postoperative survival analyses of patients; the effects of age, gender, site of operation, type of operation, status of receiving neoadjuvant or adjuvant chemotherapy or radiotherapy, cell type, metastatic mediastinal lymph node (N2) stations and number of stations on survival were evaluated.

N2 station involvements of patients were evaluated by using N factor in 7th TNM staging and histopathological typing was also performed in accordance with World Health Organization classification.

Statistics

The patients survival durations and other examined data was transferred to digital medium by using Microsoft Excel 2010 program. In addition all the data was entered into SPSS (Statistical Package for Social Sciences) 22 for Windows. Frequencies and the mean data concerning the factors which influence survival were calculated using this program.

Factors influencing survival were statistically analyzed via Kaplan- Meier Method. Also statistical comparisons of survival differences among groups were calculated using Log rank test and Chi-square test. Statistical outcomes were considered to be statistically significant within confidence interval of 95% and significance level of $p<0.05$.

RESULTS

There was a total of 96 patients, of which 75 were male (78.1%) and 21 were female (21.9%), that were included in the study. In 96 (10.6%) of 901 patients which were operated due to NSCLC, metastatic N2 disease was determined. The mean age of patients that had N2 was 57.3 years (21-79). Findings concerning ages, genders, stations and number of stations with N2 involvement, pathological types, resection types and personal data is given in Table I.

The examination of patients was done by dividing them into 5 groups according to which station was involved in the operation. The stations were based on the metastatic mediastinal lymph node stations, and the following outcomes were achieved: It was observed that Group 1 was composed of patients in which superior (stations No 2 and 4) mediastinal lymph node metastases were found (20.8 % , n:20), Group 2 was composed of patients in which aorticopulmonary window (stations No 5 and 6) lymph node metastases was determined (26%, n:25), Group 3 was composed of patients where central (station No 7) mediastinal lymph node metastasis was determined (13.5 %, n:13), Group 4 was composed of patients where inferior

(stations No 8 and 9) mediastinal lymph node metastases was determined (14.6 %, n:14) and Group 5 was composed of patients where multiple mediastinal lymph node station metastases were determined (25 % , n: 24).

The 77.1% (n:74) of the patients received postoperative adjuvant chemotherapy. Remaining patients (22.9 %, n:22) were comprised of patients which refused the treatment, since they could not tolerated the chemotherapy or doctors did not consider the need for it. For the group that received adjuvant chemotherapy, survival analysis was performed. Also 33.3% (n:32) of the chemotherapy patients received postoperative adjuvant radiotherapy. No statistically significant difference was found between adjuvant chemotherapy and adjuvant radiotherapy treatment groups in survival analysis performed via Kaplan-Meier method (P = 0.829, P = 0.673).

Patients follow-up occurred during the periods of 24 to 82 months. In addition, 1, 2, 3, 4 and 5 - year survival rates of patients where mediastinal lymph node metastases was found happen to be 85.6 %, 67 %, 41.2 %, 22.6 % and 12.3 %, respectively. When survival analysis was done using the Kaplan – Meier method, the mean survival duration was determined to be 33.3 (1.4 - 82.3 months) months and median survival duration was determined to be 30,8 months.

Whereas in 54 (56.3%) of 96 cases included in the study death was observed during the follow-up period, 42 patients were still alive during the follow-up period.

Mean survival was determined to be 45.5 months (median 35.9 months) for males, whereas mean survival was determined to be 39.9 months (median 37.9 months) in females. When survival analysis is done via Kaplan-Meier Method regarding effect of gender on survival, no statistically significant difference was determined (P = 0.958).

Table I: Characteristic features of cases with metastatic N2 station.

Variable	Number of patients	%	Mean and age interval
Age			
< 60	56	62.2	57.3 and 21-79
> 60	40	37.8	
Gender			
Male	75	78.1	
Female	21	21.9	
pN2			
Superior (2 or 4)	20	20.8	
Aorticopulmonary (5 or 6)	25	26	
Central (7)	13	13.5	
Inferior (8 or 9)	14	14.6	
Multiple	24	25	
pN2			
Single	63	65.6	
Multiple	33	34.4	
Pathology			
SCC	37	38.5	
Adenocarcinoma	49	51	
Adenosquamous carcinoma	6	6.3	
Other	4	4.2	
Resection			
Upper lobectomy	46	47.9	
Middle lobectomy	6	6.3	
Lower lobectomy	25	26	
Bilobectomi Superior	1	1	
Bilobectomi Inferior	7	7.3	
Pneumonectomy	11	11.5	
Operation side			
Right	54	56.3	
Left	42	43.8	

When patients were evaluated by being divided into two groups ones under age of 60 and ones over 60; mean survival was determined to be 47.9 months (median 42.4) in the group under 60, whereas mean survival was determined to be 38.4 months (median 28.8 months) in the group at the age of 60 and over. Although survival duration of the group under 60 was longer, no statistically significant difference was determined in survival analysis performed using Kaplan-Meier method (P = 0.078).

Additionally, an analysis was done of how the site of operation effected the survival; mean survival was observed to be 44.7 months (median 35.9 months) when the operation was performed through right hemithorax and mean survival was observed to be 46.1 months (median 35.9 months) the operation through left hemithorax, however, no statistically significant difference was determined between the two (P = 0.970).

When a closer look is taken at the right hemithorax (56.3%, n:54) some conclusion were drawn. Analysis concerning effect of type of operation on survival, mean survival in upper lobectomy was determined to be 50.7 months, mean survival in middle lobectomy was determined to be 54.9 months, mean survival in lower lobectomy was determined to be 34.7 months, mean survival in superior bilobectomy was determined to be 30.7 months, mean survival in inferior bilobectomy was determined to be 29.9 months and mean survival in pneumonectomy was determined to be 14.5 months. Although survival of upper and middle lobectomies were determined to be much longer compared to other groups, particularly pneumonectomy, in survival analysis performed with Kaplan-Meier method, no statistically significant difference was determined (P = 0.081) (Figure 1).

In patients whose site of operation was left hemithorax (43.8%, n: 42) some conclusion were drawn. Analysis concerning effect of type of operation on survival, mean survival in upper lobectomy was determined to be 55.6 months, mean survival was determined to be 32.7 months in lower lobectomy and mean survival in pneumonectomy was determined to be 40.8 months. Within these findings, although survival of upper lobectomy was determined to be much longer, a survival analysis performed with Kaplan-Meier method, found no statistically significant difference (P = 0.214) (Figure 2).

When the tumor was examined according to cell types; it was observed that pN2 was caused by adenocarcinoma at 51% (n:49) of time, squamous cell carcinoma (SCC) at 38.5% (n:37), adenosquamous carcinoma at 6.3 % (n: 6) and others 4.2% (n: 4). There were four cases in the other section. Two were caused by large cell carcinoma (2.1 %) and 2 other cases were atypical carcinoid tumor (2.1 %). Due to the low number of cases within other cell type group, these cases were excluded from the evaluation.

Mean survival for SCC was determined to be 47.7 months (median 35.9 months), mean survival in adenocarcinomas was determined to be 36.7 months (median 35.9 months) and survival in adenosquamous carcinomas was determined to be 34.1 months (median 23.5 months). Even though survival duration of SCC was much longer, no statistically significant difference was determined in survival analysis performed with Kaplan-Meier method (P = 0.740).

It was determined that lymph node station involvement (pN2) occurred both as single station (65.6 %, n:63) and multiple station (34.4 %, n:33). Whereas mean survival in patients with single station involvement was 55.6 months, it was determined to be 25.5 months in ones with multiple

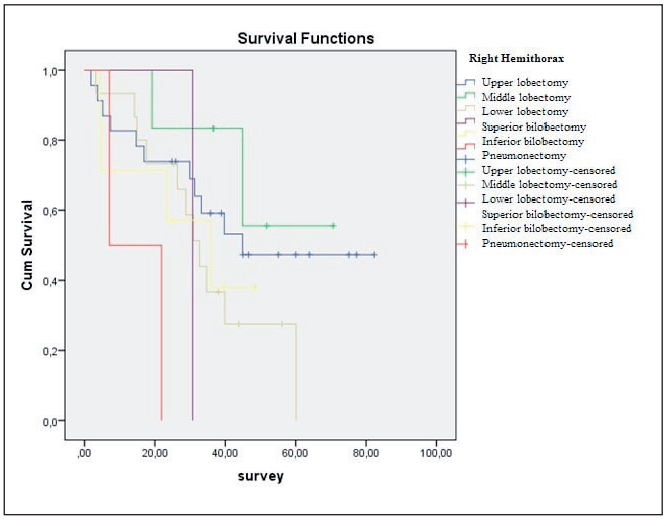

Figure 1: Effect of type of operation on survival in cases which were operated through right hemithorax.

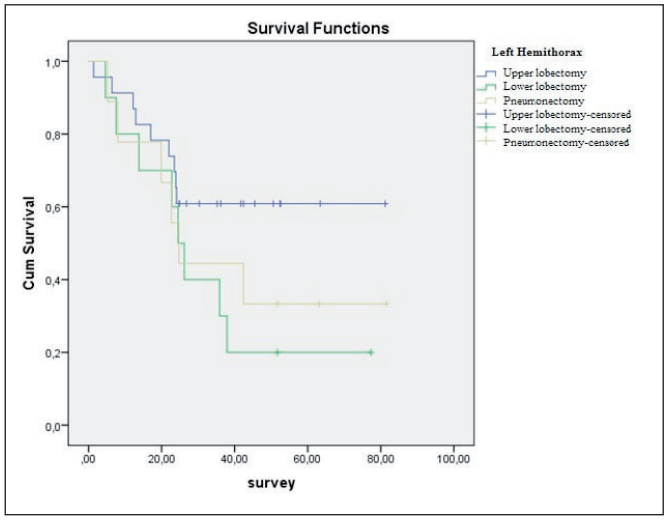

Figure 2: Effect of type of operation on survival in cases which were operated through left hemithorax.

station involvement. In Kaplan–Meier method and Log rank test, Chi-square value was determined to be 21.76 and p value was determined to be 0.01 ($P < 0.05$) and there was a statistically significant difference in survival analysis (Figure 3).

In analysis of metastatic N2 lymph node stations according to groups; It was observed that Group 1 was composed of patients where superior (stations No 2 and 4) mediastinal lymph node metastases were determined (20.8%, n:20), Group 2 was composed of patients where aorticopulmonary window (stations No 5 and 6) lymph node metastases were determined (26%, n:25), Group 3 was composed of patients where central (station No 7) mediastinal lymph node metastasis was determined (13.5%, n:13), Group 4 was composed of patients where inferior (stations No 8 and 9) mediastinal lymph node metastases were determined (14.6%, n:14) and Group 5 was composed of patients where multiple mediastinal lymph node station metastases were determined.

In survival analysis performed according to the groups above; mean survival of the patients in Group 1 was determined to be 50.5 months, mean survival of the patients in Group 2 was determined to be 61.3 months, mean survival of the patients in Group 3 was determined to be 34.4 months, mean survival of the patients in Group 4 was determined to be 42.1 months and mean survival of the patients in Group 5 was determined to be 29.8 months. In Kaplan–Meier method and Log rank test, Chi-square value was determined to be 12.68 and p value was determined to be 0.0013 ($p<0.05$) and a statistically significant difference was determined in survival analysis. In conclusion of intra-group statistical evaluation; statistically significant ($p<0.05$) survival difference was determined among Group 1 and 2 and Group 3 and 5. However, it was determined that survival in Group 4 was much better compared to Group 3 and 5 however there was no statistically significant difference between them (Figure 4).

DISCUSSION

The most significant prognostic factor in patients which are operated due to NSCLC, is those that undergo complete resection and without distant organ metastasis is mediastinal lymph node metastasis (1). Selection of cases with possibility for operation still remains a controversial issue (2-5). When published articles are reviewed, survival rates have extreme variability. The reason for this is variability is the selection criteria for the patients which are to be candidates for surgery and there are inadequacies in preoperative and/or postoperative stages of this disease (2,6-8).

In NSCLC cases and those with N2 involvement, determination of the ones who have longer survival durations becomes crucial, especially if resection is considered. Since undesired morbidity and mortality following the surgery for such risky cases is possible. When these issues are considered as a whole, decision to perform surgery can be taken more appropriately in cases with N2 involvement. 5-year survival rates of patients diagnosed with NSCLC, for which complete resection was performed following a careful clinical staging and whose pathological stage was 1a, 1b, 2a and 2b are much lower than other solid organ tumours (1). Additionally, determining the effect of number of lymph node involvement on survival and which station involvement leads to better survival, are fundamental topics of this study, and are topical and significant issues in chest surgery area.

Good prognostic factors in cases with resection and N2 metastasis require complete resection, presence of single N2, lack of preoperatively determined N2, metastasis to

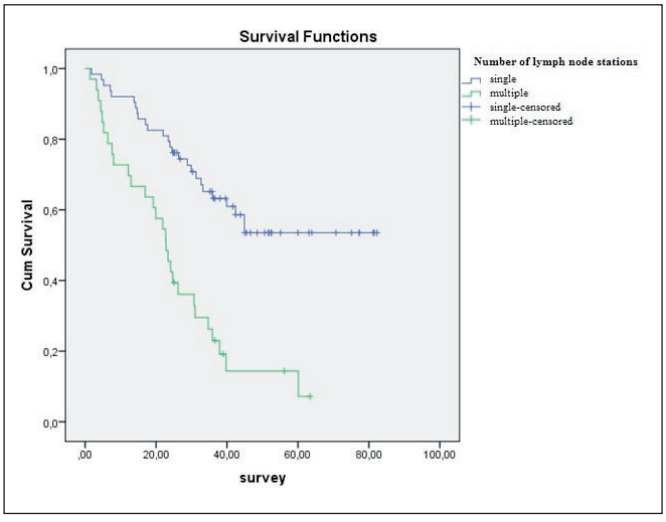

Figure 3: Effect of number of lymph node stations on survival.

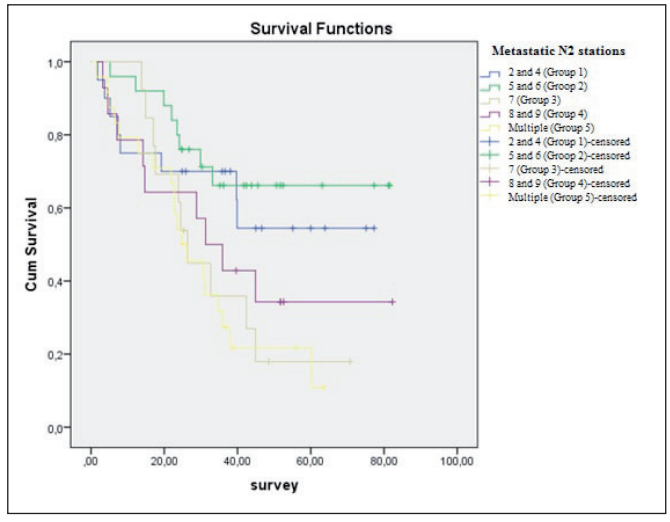

Figure 4: Effects of metastatic N2 stations on survival.

be intranodal, being T1 or T2 and station positivity other than subcarinal (2,9,10). All these variables have reported that cases with clinically determined N2 (cN2) have poorer prognosis compared to cases whose N2 diagnosis is determined during the surgical procedure (6,7,10,11). In case of determination of N2 during thoracotomy, it is likely to lead to resection if there is no perinodal infiltration or, lymph node is not fixated. It is possible to perform complete resection and pneumonectomy (especially right-sided) will not be performed. 5-year survival in these patients varies between 19% and 45% in various series (2,4,7). Presence of multiple N2 metastases has been defined as a negatively influencing factor for prognosis in many series (4,12,13). In the study in which Watanabe conducted in 1991 and investigated mediastinal lymph node metastasis pattern in patients with NSCLC which have N2 disease and received surgical treatment, he determined that 5-year survival was 34.4% in patients with single-station N2 lymph node involvement and 9.4% in patients with multi-station N2 lymph node involvement (4). Riquet et al. determined an extremely obvious difference as 26.3% and 8.3% in comparison of single-level lymph node involvement and multiple involvement, respectively (14). In staging study of IASLC, when relationship of lymph node involvement with survival was investigated, survival was determined to be much better in cases with single-region metastasis (median 35 months) compared to the ones with multiple-region metastasis (median 19 months) (15). In our study, whereas mean survival in ones with single-station N2 involvement was determined to be 55.6 months, it was determined to be 25.5 months in ones with multiple-station N2 involvement. In statistical analysis, p value was determined to be 0.01 ($p<0.05$) and a statistically significant difference was determined in survival analysis. This finding exhibits similarity with that in other studies in the literature.

Goldstraw et al. determined that the most commonly involved lymph node (45%) was subcarinal lymph node, followed by lymph nodes number 4R, 4L and 5, and reported that the least commonly involved lymph nodes were lymph nodes number 1, 2 and 6 (7). Martini et al. observed that the highest number of mediastinal lymph node involvements were localized in right upper mediastinum and the least number of nodes were localized in left upper mediastinum (2).According to the tumour localization of the cases; in 56% only superior mediastinum was involved, in 20% only inferior mediastinum was involved and in 28% both superior and inferior mediastina were involved. In our study, however, metastasis was determined to be with rate of 20.8% to Group 1 superior mediastinal lymph nodes, with rate of 26% to Group 2 aorticopulmonary window lymph nodes, with rate of 13% to Group 3 central mediastinal lymph node, with rate of 14.6% to Group 4 inferior mediastinal lymph nodes and with rate of 25% to Group 5 multiple mediastinal lymph nodes. The highest rate for metastasis was determined to be aorticopulmonary window (Group 2) station region and multiple N2 (Group 5) group. We think that the reason for the highest rate in Group 2 is difficulty of preoperative sampling of this station region but we also think that the reason for the second highest rate in Group 5 is due to patients in which there was clinical suspicion of N2 and/or invasive sampling is troublesome. In a relevant study, it was reported that in some of the cases which were thought to have clinical N0 it was inevitable for N stage to increase and 10% of them were found to have pN2 (16). Tsubota and Yoshimura. reported that 18% of the patients which had lymph nodes which did not seem to be metastatic during operation had metastatic lymph nodes (5). Furthermore, N2 was not intraoperatively suspected in 68% of the patients which were thought to have clinically stage 1 disease. Therefore, it should be always taken into consideration that intraoperative assessment of the surgeon concerning whether the lymph node is metastatic can be misleading and lymph node stage can be altered after pathology result of the resection material. In addition to this, it is a fact that theoretical information might not always be applied in practice. In NCCN 2010 survey, pollsters, who were all surgeons, were asked whether they may perform a surgery in case of single mediastinal lymph node station involvement less than 3 cm. Answer of the surgeons was that operation will be appropriate with a high rate of 90.5%. Rate of ones which told that they will perform a surgery in case of multiple stations larger than 3 cm were 47.5%, which is substantially high (17). Additionally, in conclusion of an extensive research including 729 tertiary level training hospitals and general hospitals, it was determined that mediastinoscopy was performed only for 27.1% of cases (18). Dogusoy et al. said that the mediastinoscopy is gold standart for staging of the NSCLC in their previous data (19) . In the light of these datas, we are in thought of that occurrence of multiple station involvements with a substantial rate reflects an important fact.

It has been reported in various studies that subcarinal lymph node involvement influences survival negatively (20,21). When Naruke compared survival in subcarinal lymph node involvement with those of other N2s, he obtained a result of 21.7% vs 4.3% (22). However, Watanabe did not determine any significant difference among survivals of multiple N2 patients with and without subcarinal lymph node involvements (4). Patterson et al. expressed that in case of preoperative determination of subcarinal node involvement patient should be considered as inoperable (23). In our study, mean survival of the patients in Group 1 was determined to be 50.5 months, mean survival of the patients in Group 2 was determined to be 61.3 months, mean survival of the patients in Group 3 was determined to be 34.4 months, mean survival of the patients in Group

4 was determined to be 42.1 months and mean survival of the patients in Group 5 was determined to be 29.8 months. Survivals of ones with Group 3 lymph node involvement and Group 5 lymph node involvement were determined to be close. Survival was determined to be significantly reduced in Group 3 and 5. It was also determined that this two groups fell into statistically same interval and led to poorer (statistically significant) survival than Group 1 and Group 2 ($p<0.05$). It was determined that survival in Group 4 was better than Group 3 and 5 but no statistically significant difference developed.

The most common type of NSCLC that causes mediastinal lymph node metastasis is adenocarcinoma (2). However, Goldstraw observed SCC as the most common type in 76 cases in N2 series comprised of 172 cases (7). Although many researchers determined that cell type did not have any influence on survival in N2 disease, general thought is in direction of that better survival is achieved in SCC. This better survival achieved in SCC has been expressed with lower rate of metastasis to contralateral mediastinum and higher rate of intranodal invasion rather than perinodal invasion (6-8,20,21). Naruke reported close survivals for patients with T1N2 SCC and adenocarcinoma (30% - 35%) but in T2N2 and T3N2 cases there was a difference on behalf of SCC (8). When our data were investigated according to tumour cell types; the rates of accompanying to N2 disease were determined to be; 51% (n:49) for adenocarcinoma, 38.5% (n:37) for SCC, 6.3% (n:6) for adenosquamous carcinoma and 4.2% (n:4) for others. Determination of adenocarcinoma as the most common was found to be consistent with the literature. In our study, mean survival in patients diagnosed with SCC was determined to be 47.7 months, mean survival in adenocarcinomas was determined to be 36.7 months and mean survival in adenosquamous carcinomas was determined to be 34.1 months. Although SCC found to have longer survival duration among the group, no statistically significant difference was determined in conducted survival analysis ($p=0.740$). As these determined data were consistent with the literature, it exhibited that in N2 disease cell type did not have any statistically significant effect on survival but survival duration of SCC was much longer.

CONCLUSION

We are in thought of that surgical treatment with complete resection can be performed without hesitation from morbidity and mortality due to thoracotomy in case of single-station N2 involvement that may develop during or after thoracotomy, especially if involved stations are superior mediastinal or aorticopulmonary window lymph node stations.

Also we are in thought of that as survival durations expected in case of multiple and central (station No 7) station N2 involvement statistically significantly decrease, while resection for NSCLC is being considered, the mediastinum should be evaluated for number 7 and multiple station involvements, if a clinical suspicion is present.

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