The Effect of the Isolated Aorticopulmonary Lymph Node on Survival in Lung Cancer

Akciğer Kanserinde İzole Aortikopulmoner Lenf Nodu Metastazının Sağkalıma Etkisi

Survival in Non-Small Cell Lung Cancer

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Özet

Amaç: Çalışmamızda özellikle sol üst lob tümörlerinde izole aortikopulmoner lenf nodu (LN) metastazı ve diğer N1 ve N2 LN tutulumlarının sağkalım süresi üzerine olan etkilerinin incelenmesi amaçlandı. Gereç ve Yöntem: Küçük hücreli dışı akciğer kanseri (KHDAK) nedeniyle opere edilen ve postoperatif patolojik inceleme sonucu lenf nodu metastazı tespit edilen 111 olgu retrospektif olarak incelendi. Komplet rezeksiyon ve mediastinal lenf nodu diseksiyonu uygulanan ve postoperatif mediastinal LN metastazı tespit edilen olgularda prognostik faktörlerin sağkalıma etkisi araştırıldı. Bulgular: Ortalama 21,41 ay takip edilen olguların 13'ü hayatını kaybetti. İzole aortikopulmoner LN metastazının diğer N2 hastalıklardan farklı olarak sağkalımı etkilemediği tespit edildi. Tartışma: Çalışmamızda sol üst lob yerleşimli KHDAK olgularında izole aortikopulmoner LN tutulumunun sağkalım üzerinde diğer N2 istasyonlardan farklı olarak olumsuz etkisi saptanmamıştır. Ancak kesin sonuç için daha ileri çalışmalara ihtiyaç vardır. Bu tür olgular inoperabl olarak görülmemeli, uygun hastalar komplet rezeksiyon için mutlaka değerlendirilmelidir.

Anahtar Kelimeler

Aortikopulmoner; Metastaz; Lenf Nodu; Akciğer Kanseri

Abstract

Aim: This study aims to investigate investigate the effects of aorticopulmonary LN metastasis and other N1 and N2 LN involvements on survival rates especially for left upper lobe tumors. Material and Method: 111 cases who underwent surgery due to NSCLC and were diagnosed with lymph node metastasis secondary to the postoperative pathological examination, were examined retrospectively. The cases on whom complete resection and mediastinal lymph node dissection were applied and who were diagnosed with postoperative mediastinal LN metastasis were examined with regard to the effects of some prognostic factors on survival. Results: 13 of the cases who were followed up for 21.41 months on average lost their lives. In the general survival analysis, it was found that isolated aorticopulmonary LN metastasis did not affect survival differently from other N2 diseases. Discussion: This paper claims that in cases with NSCLC located on the left upper lobe, isolated aorticopulmonary LN involvement does not have a negative effect on survival different from other N2 stations but further studies need for support this idea. Therefore, these cases should not be considered as inoperable and complete resection should be performed on the appropriate patients.

Keywords

Aorticopulmonary; Metastasis; Lymph Node; Lung Cancer

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Introduction

In the treatment of lung cancer, surgical resection in non-small cell lung cancer (NSCLC) is performed on the cases at early stages or cases with local advanced stages. In NSCLC cases, at the time of the diagnosis, generally a rate of about 30-38% of mediastinal lymph node (LN) involvement is detected [1]. While surgical treatment comes first in the early stages of lung cancer, in the presence of N2 disease, three-modality approaches come to the forefront in which surgical treatment is performed following induction chemotherapy and/or chemoradiotherapy [2]. In N2 disease, the metastatic LN station number and degree of invasion are important in terms of surgical evaluation. Today, resectable NSCLC patients who do not have bulky and multi-station LN metastasis and who have same side N2 positivity not showing capsule invasion undergo the surgical approach at well-recognized centers following neoadjuvant treatment [3,4]. There are some studies evaluating the survival rates of N2 disease on the left upper lobe tumors that have isolated station 5 and/or 6th involvements on which surgical operation have been applied among mediastinal lymph node involvements, and studies evaluating the survival rates of single station N2 disease. These studies illustrate that survival rate for left upper lobe tumors where there is 5 and/or 6th station lymph node involvement is higher compared to other mediastinal lymph node involvements [5-9].

This study investigates the effect of 5 and/or 6th LN involvement, especially in cases with tumors located on the left upper lobe with the results obtained in the presence of the LN metastasis in NSCLC cases.

Material and Method

111 cases that underwent surgery due to NSCLC and diagnosed with lymph node metastasis as a result of the postoperative pathological examination in Atatürk Chest Diseases and Chest Surgery Training and Research Hospital Chest Surgery Clinic between 2009-2013 were included in the study. All of the cases were examined postoperatively with CT and PET/CT. In thorax CT, the caliber of the lymph node was more than 1 cm and in PET/CT in lymph node FDG involvement was more than 2.5 and they were accepted as threshold values for Endobronchial Ultrasonography (EBUS) and mediastinoscopy indication. The cases who were suspected to have lymph node metastasis were assessed with EBUS and/or mediastinoscopy. The cases diagnosed with N2 diseases and on whom neoadjuvant chemotherapy were applied, were excluded from the study. 97 of the cases whose average age was determined as 58.12 (30-78) were male and 14 of them were female. In 62 (55.9%) of the cases squamous cell carcinoma, in 28 (25.2%) adenocarcinoma, and in 21 (18.9%) other primary pulmonary malignancies were present.

In all cases, complete resection and mediastinal lymph node dissection were applied due to malignancy. Adjuvant chemotherapy/chemoradiotherapy were applied on all cases diagnosed with postoperative mediastinal LN metastasis. In all cases included in the study, the effect of the prognostic factors such as sex, tumor, histopathology, localizations of metastatic lymph node stations, single or multi lymph node station, lymph node metastasis, resection type, tumor stage and the location of the tumor on the left upper lobe were investigated. Additionally, survival rates of the cases diagnosed with aorticopulmonary LN metastasis, and other tumor cases located in the upper left lobe based on other prognostic factors were investigated.

Survive values were analyzed with Kaplan Meier statistical analyses methods. Differences were considered significant when the probability value of Kaplan Meier statistical analyses was less than 0.05.

Results

27 (24.3%) of the tumors were located on the upper left, 40 (36%) were located on the left lower lobe, 24 (21.6%) were located on the right upper lobe, 16 (14.4%) were located on the right lower lobe, and four (3.6 %) were located in the middle. Seven left lower lobectomies, 20 left upper lobectomies, 40 left pneumonectomies, five right lower lobectomies, 17 right upper lobectomies, five right bilobectomies, and 17 right pneumonectomies, were performed. In the postoperative histopathological examination, single N1 was detected in 46 cases, multiple N1 was detected in eight cases, single N2 was detected in 24 cases, multiple N2 was detected in two cases, N1 + N2 was detected in 31 cases, single aorticopulmonary was detected in 11 cases, and aorticopulmonary + tumor metastasis in other LN stations (N1/N2) were detected in 14 cases. 36 of the cases included in the study according to TNM 7 staging system were staged as Stage 2A, 10 were staged as 2B and 65 were staged as 3A (Table 1). The cases within the scope of the study were followed up for 21.41 (5-59) months postoperatively.

A significant relationship was detected between malignancy type and survival rate in the general survival analysis. It was observed that the survival rate was significantly lower in adenocarcinoma cases compared to other malignancies (11.2 months on average). It was found that single N1 and multiple N2 LN station metastasis had a significant effect on general survival. However, while a decrease in line with the multiple N2 LN positivity in survival rate was observed, it was detected that survival rate was higher in single N1 LN positive cases (26 months) compared to the negative cases (17.3), which was contrary to what was expected. In Stage 3A cases, it was found that the survival rate decreased significantly compared to other stages (17.3 months on average). Apart from the other factors, when male/female survival rates were examined, it was statistically determined in the general survival analysis that the survival rate of males (18.4 months) was significantly lower compared to females (32 months). The effect on general survival of the tumor location on the left upper lobe, the type of resection performed and aorticopulmonary metastasis, were not found to be significant (Table 1).

The isolated aorticopulmonary LN was localized on the left upper lobe in six cases out of 11 positive cases and was localized on the left lower lobe in five cases. The analysis performed on cases with isolated aorticopulmonary LN metastasis found that, regardless of the tumor localization, tumor histopathology and stage did not affect survival. It was detected that only in male cases with isolated aorticopulmonary LN metastasis caused a significant reduction in survival. Additionally, for tumors located on the left upper lobe, no negative effect on survival of aorticopulmonary LN metastasis was observed (Table 2).

Table 1. The effects of prognostic factors to overall survive

Prognostic factors		N	N (%)	Survive (mo)	P
Gender	Male	97	87,4	18,44	0,003
	Female	14	12,6	32	
Histopathology	Adeno Ca	28	25,2	11,20	0,017
	SCC	62	55,9	24	
	Others	21	18,9	24,86	
Stage	IIA	36	32,4	26,67	0,037
	IIB	10	9	24	
	IIIA	65	58,6	17,37	
Single N1 LN	-	65	58,6	17,37	0,032
	+	46	41,4	26	
Multiple N1 LN	-	103	92,8	21	0,955
	+	8	7,2	18	
Single N2 LN	-	87	78,4	21,13	0,769
	+	24	21,6	18,86	
Multiple N2 LN	-	109	98,2	21	0,041
	+	2	1,8	17,76	
N1+N2 LN	-	80	72,1	21,82	0,148
	+	31	27,9	17,25	
Aorticopulmonary LN	-	100	90,1	21,43	0,111
	+	11	9,9	11	
Aorticopulmonary + other LN	-	97	87,4	21,64	0,104
	+	14	12,6	10,5	
Left upper lobe tumor	-	84	75,7	20,31	0,685
	+	27	24,3	22,5	
	LLL	7	6,3	15	0,645
	LP	40	36	24	
	LUL	20	18	16	
Resection type	RBİ+RBS	5	4,5	30	
	RLL	5	4,5	27	
	RP	17	15,3	18	
	RUL	17	15,3	19	

LLL: Left lower lobectomy, LP: Left pneumonectomy, LUL: Left upper lobectomy, RBİ: Right bilobectomy inferior, RBS: Right bilobectomy superior, RLL: Right lower lobectomy, RP: Right pneumonectomy, RUL: Right upper lobectomy, LN: Lymph node

Table 2.The effect of single aorticopulmonary lymph node metastasis to survive

	p
Gender	0,004
Resection type	0,714
Histopathology	0,777
Left upper lobe tumors	0,714
Stage	0,083

In the examination performed by taking the tumor localization as a base, in non-left upper lobe localized malignancies, it was identified that sex, tumor histopathology single N1 LN positivity, and the other LN positivity along with aorticopulmonary and tumor stage, significantly reduced survival. In tumors in the left upper lobe, it was found that resection type, tumor histopathology, LN metastasis combinations and tumor stage had no effect on survival at all (Table 3).

In the analysis conducted by tumor histopathology in malignants that have left upper lobe and lymph node metastases, the survival effect of histopathologic type was not observed. However, in the analysis made in all locations, a significant decrease (p:0,009) was observed in survival of patients with adenocarcinoma, who have single station N1 lymph node metastases, when compared with other types of squamous cell carcinoma (27 months) and histological type of tumor patients (28,88 months) (Table 4). In cases diagnosed with adenocarcinoma in left upper lobe, survival time of negative and positive cases according to aorticopulmonary LN metastasis was determined respectively as 18 and 13.5 months, in cases with squamous cell carcinoma as 31.5 and 36 moths, and in other histological types as 36 months and 4.5 months. According to the statistical analyzes of the tumor histopathology, LN metastasis of aorticopulmonary have not made a significant difference in survival. (p: 0,501) (Table 4). Similarly, in the analysis of the left upper lobe tumors considering the tumor histopathology, among different histological types, no lymph node metastasis was found not make a difference in survival.

Table 3. The effect of tumor localization to survive

	Left upper lobe tumors (p)	Other locations (p)
Gender	0,108	0,020
Tumor histopathology	0,880	0,003
Single N1 LN	0,718	0,023
Multiple N1 LN	0,817	0,777
Single N2 LN	0,907	0,695
Multiple N2 LN	0,304	0,103
N1+N2 LN	0,832	0,103
Aorticopulmonary LN	0,483	0,145
Aorticopulmonary + other LN	0,811	0,039
Stage	0,20	0,050
Resection type	0,473	0,647

Table 4. Analysis of survival on the basis of histopathology according to tumour localization in metastatic disease

Metastatic lymph nodes	Left upper lobe	All localizations
Single N1 LN	0,506	0,009*
Multiple N1 LN	0,221	0,806
Single N2 LN	0,827	0,141
Multiple N2 LN	0,992	0,317
N1+N2 LN	0,800	0,387
Aorticopulmonary LN	0,501	0,777
Aorticopulmonary + other LN	0,632	0,364

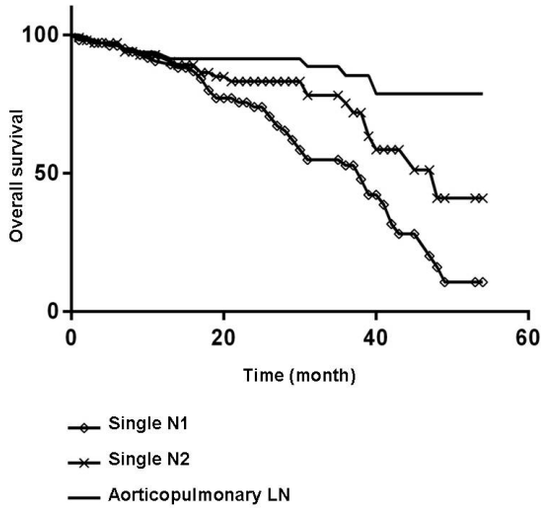
*Adenocarcinoma

The general analysis of our study illustrated that left upper lobe tumors had better survival results compared to single N1 and/or single N2 LN station metastasis seen in similar tumor cases of isolated aorticopulmonary LN metastasis (Chart 1).

Discussion

Debates on the role of surgery in non-small-cell lung carcinoma with metastatic N2 LN still continue. Additionally, the fact that the N2 disease group is rather heterogeneous renders ideal treatments controversial for these patients. For example, the survival rates of patients with bulky N2 disease and microscopic N2 patients diagnosed following the resection are quite different. Therefore, treatment strategies of such patients should be different. A similar controversial discussion exists on the

Chart 1. Overall survival analysis according to the lymph nodes



isolated involvements of N2 stations. However, There has not been any comprehensive study investigating the effects of mediastinal lymph nodes on prognosis except for subcarinal lymph node so far [10].

Many factors that affect survival rate are being studied in resected N2 patients. Among these factors, the effects of the method of diagnosis for N2 disease, evaluation with mediastinocopy, intraoperative evaluation of lymph nodes, place/number of tumor positive lymph nodes and metastasis type on survival are being investigated. The generally accepted approach suggests that changing survival rates in N2 disease could be associated with metastatic lymph node level and involvement amounts. For example only Kirsh and Sloan [11] reported better survival results in patients with upper mediastinum LN metastasis. Miller et al. [12], also reported that prognosis was better in patients with upper mediastinum involvement compared to patients with lower mediastinum involvement irrespective of the primary tumor localization. On the contrary, results of the study by Nakanishi et al. [7], illustrates that the presence of superior, inferior, aorticopulmonary or extended lymph node metastasis in patients with N2 did not make a difference in terms of prognosis. Similarly, it was also asserted that no difference was identified between single N2 and multi N2 in terms of the survey. Riquet et al. [13], also suggested that distribution of metastatic mediastinal limp nodes is not important for the prognosis. However, there are some studies reporting that prognosis is worse in patients with N2 positivity compared to patients with single N2 positivity [12,14].

Subaortic lymph nodes are of importance for the left upper lobe in lymphatic drainage. Many studies conducted on N2 metastasis found that LN metastasis created an exceptional case in terms of survival among other N2 metastasises. When patients with single N2 positivity were compared, it was identified that patient survey rates with aorticopulmonary lymph involvement were significantly different from the patients with single N2 involvement. Patterson et al. [3], reported that 5-year survival after resection was 42% in 35 cases with single subaortic LN metastasis. Martini and Flinger [15] reported the 5-year survival rate for similar patients as 35%. A study by Miller et al. did not find a significant difference in terms of the 5-year survival between patients with negative and positive aortic lymph node. Okada et al. [9], reported the five-year survival rate as 0% in patients with subcarinal LN involvement from right or left upper lobe tumors and as 37% in patients with only upper mediastinal or aortic LN involvement. Similarly, this study found that isolated aorticopulmonary lymph node metastasis caused significant decrease in the survival rates in only male cases independent from other factors. However, this result could be because of the disparity in numbers of males/females included in the study. Therefore, in male cases with aorticopulmonary LN involvement, conclusion that survival is low is a bit challenging. The researchers of this study are of the opinion that comprehensive studies to be conducted in the future can remove the uncertainties with regard to this issue.

The survival results after complete resection performed in the presence of LN metastasis in NSCLC secondary to left upper lobe, in particular, are quite positive compared to other N2 metastasis. The same study by Okada detected 5-year survival as 57% in cases with only aortic LN involvement in left upper lobe tumors and as 36% in cases with upper or lower mediastinum LN involvement. A study by Patterson et al. [3], detected that the survival of patients with a left upper lobe tumor having 5 and 6 LN metastasis have similar tumor sizes and in patients with N1 positivity tumor sizes are nearly the same. Nevertheless, Miller et al. [12], did not find difference in terms of 5-year survival in subaortic LN positive and negative patients. Similarly, this study did not find any negative effect of isolated aorticopulmonary LN positivity on survival rate irrespective of the tumor localization. Although any difference was not detected in survival rates of cases with adenocarcinoma with single-station N1 lymph node metastasis located in the the left upper lobe compared to other histopathological types, cases with adenocarcinoma with one station N1 lymph node metastasis in other locations had significant survival rates compared to other histopathological types.

The results obtained in this study illustrate that prognostic factors including LN metastasis in left upper lobe localized tumors did not affect survival and these results are in parallel with the literature. Although a significant decrease was observed in the general survival analyzes of adenocarcinoma patients, in tumors with lymph node metastasis localized in the left upper lobe, histological type was found to have no effect on the survival.

According to the results of this study, long survival rates were obtained by complete resections performed in the cases with N2 positivity in the aorticopulmonary field. In left upper lobe malignancies, subaortic lymph node metastasis is considered to be equivalent to hilar lymph nodes for survival different from other N2 stations. Therefore, primarily, in the case of subaortic metastacity, left upper lobe cancers should not be considered as inoperable. Survival obtained when complete resection is performed is not different from the survival obtained from N1 disease.

In the light of general theory of malignancy, there is a common belief among researchers that LN metastasis decreases survival, prognosis is adversely affected. Although researchers of this study share the same belief, in overall survival analyzes, this study reveals that patients with single station N1 lymph

node metastasis have a long survival time compared to patients without single station N1 lymph node metastasis. This situation is not possible to be accidental because there is sufficient number of cases. Thus, it is difficult to explain the unexpected situation, which is contrary to malignity physiology. In this sense, a more comprehensive and detailed research on this subject is believed to provide more accurate information.

The fact that aorticopulmonary LN involvement had better survival compared to other lymph node stations is strongly supported by all the studies performed so far. Complete resection should be performed on these patients when possible.

Keller et al. [6], did not find a significant difference between single station N2 and N2 LN positivity about survival rates of patients with a left upper lobe tumor. Similarly, the general survival analysis of this study illustrated that multiple N2 LN involvement decreased survival rate. A study by Inoune et al. [8], reported 5-year survival as 70% in the presence of single N2 lymph node involvement in patients with a left upper lobe tumor and 55.4% in the presence of N2 positivity in patients with a right upper lobe tumor.

This study revealed that survival rates for adenocarcinoma cases were lower compared to other tumor histopathology's. However, Nakanishi reported that there is no difference between the patients with adenocarcinoma and patients with squamous cell carcinoma in terms of survival. Also, there is no difference between the patients with T1, T2, and T3 tumors in terms of the survival [7]. Moreover, no matter whether aorticopulmonary lymph node metastasis exists or not, a significant effect of histopathological type on survival was not observed in the left upper lobe tumors.

In the scope of this study, it is understood that isolated aorticopulmonary LN involvement had no negative effect on the survival in cases with left upper localized NSCLC different from the other N2 stations. Therefore, all cases should not be considered as inoperable and complete resection should be performed on appropriate patients.

Competing interests

The authors declare that they have no competing interests.

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