

Skip metastasis in non-small cell lung cancer: does it affect the prognosis?

Küçük hücreli dışı akciğer kanserinde skip metastazı: Prognozu etkiler mi?

Onur Akçay,¹ Tevfik İlker Akçam,² Şeyda Örs Kaya,³ Özgür Samancılar,³
Kenan Can Ceylan,³ Serpil Sevinç,³ Şaban Ünsal³

Institution where the research was done:

Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Turkey

Author Affiliations:

¹Department of Thoracic Surgery, Kızıltepe State Hospital, Mardin, Turkey

²Department of Thoracic Surgery, Medical Faculty of Ege University, İzmir, Turkey

³Department of Thoracic Surgery, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, İzmir, Turkey

ABSTRACT

Background: This study aims to examine skip metastases in patients who had resection due to non-small cell lung cancer.

Methods: A total of 111 patients (94 males, 17 females; mean age: 58.9±10.2 years; range 35 to 82 years) who were diagnosed with non-small cell lung cancer and in whom an ipsilateral mediastinal lymph node metastasis was detected based on the pathological examination of the R0 pulmonary resection samples between January 2005 and December 2011 in our clinic were retrospectively analyzed. The patients were divided into two groups: the skip metastasis group (sN2) (group 1, n=55) [N1(-), N2(+)] and non-skip ipsilateral mediastinal lymph node metastasis group (nsN2) (group 2, n=56) [N1(+), N2(+)].

Results: The median survival was 25 months and five-year overall survival rate was 13% for both study groups. Five-year overall survival rate was higher in group 1, compared to group 2 (20% vs. 7.4%, respectively), although the difference was not statistically significant (p=0.084).

Conclusion: Our study results show that five-year overall survival rates of operable patients with skip metastases are higher than those without skip metastases, although the difference is not statistically significant.

Keywords: Mediastinal lymph node; non-small cell lung cancer; skip metastasis.

ÖZ

Amaç: Bu çalışmada küçük hücreli dışı akciğer kanseri nedeni ile rezeksiyon yapılan hastalarda skip metastazları incelendi.

Çalışma planı: Kliniğimizde Ocak 2005 - Aralık 2011 tarihleri arasında küçük hücreli dışı akciğer kanseri tanısı konan ve R0 akciğer rezeksiyonu örneklerinin patolojik incelemesi sonucunda aynı taraf mediastinal lenf nodu metastazı saptanan toplam 111 hasta (94 erkek, 17 kadın; ort. yaş: 58.9±10.2 yıl; dağılım 35-82 yıl) retrospektif olarak incelendi. Hastalar skip metastazlı grup (sN2) (grup 1, n=55) [N1(-), N2(+)] ve skip metastazı olmayan aynı taraf mediastinal lenf nodu metastazlı grup (nsN2) (grup 2, n=56) [N1(+), N2(+)] olmak üzere iki gruba ayrıldı.

Bulgular: Her iki çalışma grubunda medyan sağkalım 25 ay olup, beş yıllık genel sağkalım oranı %13 idi. Beş yıllık genel sağkalım oranı grup 2'ye kıyasla grup 1'de daha yüksek olmakla birlikte (sırasıyla %7.4'e karşın %20), fark istatistiksel olarak anlamlı değildi (p=0.084).

Sonuç: Çalışma sonuçlarımız istatistiksel olarak anlamlı bir fark olmasa da skip metastazı olmayan hastalara kıyasla, skip metastazlı ameliyat edilebilir hastalarda beş yıllık genel sağkalım oranının daha yüksek olduğunu göstermektedir.

Anahtar sözcükler: Mediastinal lenf nodu; küçük hücreli dışı akciğer kanseri; skip metastazı.



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Correspondence: Tefvik İlker Akçam, MD, Ege Üniversitesi Tıp Fakültesi, Göğüs Cerrahisi Anabilim Dalı, 35100 Bornova, İzmir, Turkey.

Tel: +90 232 - 390 49 19 e-mail: tevfikilkerakcam@hotmail.com

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The stage and the associated lymph node involvement are the most important factors affecting survival in patients with lung cancer.^[1] The accepted model for the lymphatic drainage in non-small cell lung cancer (NSCLC) is the spread from the tumor to the intraparenchymal lymph nodes and, then, to the hilar lymph nodes. The next station is the ipsilateral mediastinal lymph nodes.^[2] In some cases with unexplained mechanisms, the mediastinal lymph node metastasis occurs without the intraparenchymal and hilar lymph node involvement, which is known as a skip metastasis.^[3-5]

In this study, we aimed to examine skip metastases in patients who had resection due to NSCLC and compare the results with those without a skip metastasis.

PATIENTS AND METHODS

A total of 111 patients (94 males, 17 females; mean age 58.9 ± 10.2 years; range 35 to 82 years) who were diagnosed with NSCLC and in whom an ipsilateral mediastinal lymph node metastasis was detected based on the pathological examination of the R0 pulmonary resection samples between January 2005 and December 2011 in our clinic were retrospectively analyzed. All patients were preoperatively evaluated using chest X-ray, while 54 patients (48.6%) underwent thoracic computed tomography (CT) and 57 patients (51.4%) operated after the year of 2008 underwent whole body positron emission tomography (PET)/CT. Preoperative invasive staging methods such as endobronchial ultrasound (EBUS) or mediastinoscopy were performed for possible mediastinal lymph node metastases on PET/CT or CT scan. When pathological N2 disease was detected, the patients were referred to neoadjuvant therapy and were excluded from the study. Only the patients with an incidental ipsilateral mediastinal lymph node metastasis based on the postoperative histopathological examination results were included in the study. Anatomic resection and mediastinal lymph node dissection were performed for all patients with no evidence of mediastinal lymph node involvement or distant metastasis. Three cycles of platinum-based adjuvant chemotherapy were applied to all patients following surgery. The patients were divided into two groups: the skip metastasis group (sN2) (group 1, n=55) [N1(-), N2(+)] and non-skip ipsilateral mediastinal lymph node metastasis group (nsN2) (group 2, n=56) [N1(+), N2(+)].

The study was conducted in accordance with the ethical standards of the related committee on Human Experimentation (institutional and national) and with the Helsinki Declaration.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). The quantitative data were analyzed using the Kolmogorov-Smirnov test for compatibility with normal distribution. Parametric methods were used to analyze normally distributed homogeneous variables, while non-parametric methods were used to analyze abnormally distributed homogeneous variables. The categorical data were compared using the Pearson's chi-square test. Survival analysis was made using the Kaplan-Meier plot and log-rank tests. A *p* value of <0.05 was considered statistically significant with 95% confidence interval.

RESULTS

Of 111 patients, 28 had possible N2 disease by preoperative examinations either by CT or PET/CT scan. Sixteen patients had mediastinoscopy and 12 had both EBUS and mediastinoscopy. The histological assessment revealed a squamous-cell carcinoma in 59 (53.1%), adenocarcinoma in 50 (45.1%), and large-cell carcinoma in two patients (1.8%). The five-year survival rate was 14% in adenocarcinomas, 13.6% in squamous-cell carcinomas, and 0% in large-cell carcinomas, indicating no statistically significant difference ($p=0.078$). There was no statistical significant difference in age, gender, comorbidities, and smoking history between the groups. However, the incidence of subcarinal lymph node metastasis was significantly higher in patients with skip metastases ($p=0.018$) (Table 1).

Sixty-four patients had upper lobe (57.6%), 44 had lower (39.7%), and three patients had middle lobe tumor (2.7%). There was no difference in survival rates between the patients with upper and lower lobe tumors ($p=0.091$). In addition, in the sN2 group, 31, 23 and 1 patient had tumors located at the upper, lower and middle lobes, respectively. There was no association between the presence of sN2 and the upper-lower lobe distinction ($p=0.695$) (Figure 1). Additionally, the prognoses of the patients with upper and lower lobe tumors were examined in the sN2 group. We found that the mean survival was 38 months in the patients with upper lobe tumors and 21 months in those with lower lobe tumors, although the difference was not statistically significant ($p=0.114$). Lymph node distribution of is shown in Table 2.

The mean follow-up was 31.8 ± 2.4 (range 2 to 105) months. The median overall survival was 25 (range 0 to 105) for both groups and five-year overall survival rates were 20% and 7.4% in group 1

Table 1. Characteristics of patients

	sN2 (n=55)		nsN2 (n=56)		p
	n	Mean±SD	n	Mean±SD	
Age (year)		57.1±11.1		60.8±8.8	0.74
Gender					0.71
Male	50		44		
Female	5		12		
Comorbidities					0.473
Yes	15		12		
No	40		44		
Smoking					0.057
+	40		35		
-	15		21		
SCC/AC/LCC	33/21/1		26/29/1		0.091
Upper/middle/lower	31/1/23		33/2/21		0.695
Subcarinal					0.018
+	17		7		
-	38		49		

sN2: Skip metastasis; nsN2: non-skip metastasis; SD: Standard deviation; SCC: Squamous-cell carcinoma; AC: Adenocarcinoma; LCC: Large-cell carcinoma.

and group 2, respectively. Although five-year overall survival rate was higher in group 1, there was no statistically significant difference between the groups (p=0.084) (Figure 2).

DISCUSSION

The presence or absence of mediastinal lymph node metastasis is one of the most important factors determining the prognosis alone in patients with NSCLC.^[1,5] Therefore, the examination of lymph nodes is critical step.^[6,7] The incidence of pathological N2 disease following surgical resection and systematic mediastinal lymph node dissection varies between 17.6 and 26.5%.^[8] In addition, the incidence of sN2 in the N2 group varies between 20 and 40%.^[4,7] In our study, the incidence of N2 disease was 13.9% and the incidence of sN2 in the N2 group was 49.5%, consistent with the literature.

Some N2(+) cases may not have N1 involvement. This is known as a skip metastasis, as previously described. However, there is no precise data about the pathway of sN2 occurrence, and various mechanisms have been discussed, to date. One of these mechanisms is the presence of direct lymphatic channels extending through the mediastinum.^[4] It has been reported that the spread of upper lobe-based tumors directly to the mediastinal lymph nodes is more common.^[8] In addition, Takizawa et al.^[9] attempted to demonstrate the pathways of skip metastases to the mediastinum.

There are several thoughts on the examination of mediastinal lymph nodes during the operation; however, it has been shown that the systematic mediastinal lymph node dissection is much effective than the mediastinal lymph node sampling in detecting sN2, as it is more sensitive in detecting micro-metastases.^[5] In the present study, we used systematic mediastinal lymph node dissection

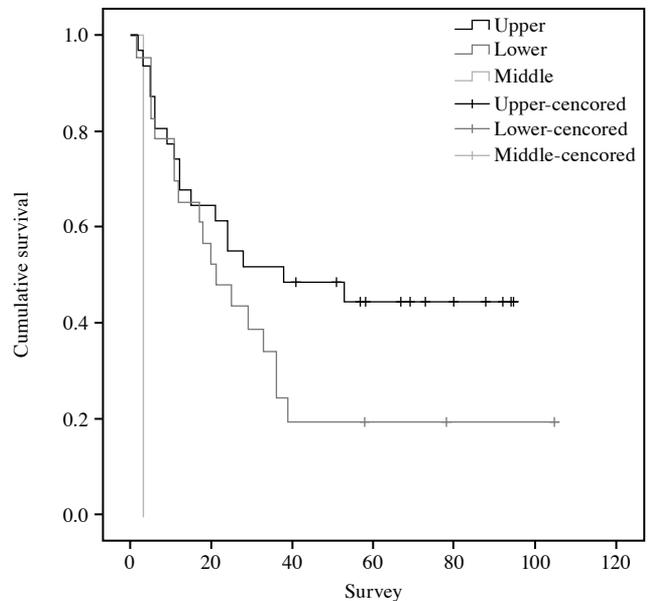


Figure 1. Long-term survival curves of skip metastasis/non-skip metastasis patients.

Table 2. Lobe-specific lymph node distribution

	#2	#4	#5	#6	#7	#8	#9
Right upper lobe	3	20	0	0	6	1	0
Right middle lobe	1	1	0	0	3	1	1
Right lower lobe	0	8	0	0	19	9	4
Left upper lobe	1	7	25	17	7	2	3
Left lower lobe	0	1	5	5	6	1	3

Lymph node station.

rather than mediastinal lymph node sampling, and accordingly, ipsilateral mediastinal lymph node dissection was performed in all patients.

Furthermore, the histological type was reported to have no effect on the long-term survival in the studies by Yoshino *et al.*^[10] and Gunluoglu *et al.*^[11] between the long-term survival and tumor histology of sN2 patients and nsN2 patients. Nevertheless, there is no consensus about the presence of a predominant histological type in sN2 patients.^[8,10-12] Squamous-cell carcinomas are more common in the sN2 group in several studies,^[5,13,14] whereas the incidence of adenocarcinomas is higher in the other studies.^[3,8,10] The squamous-cell carcinomas were reported to cause sN2 more commonly in our patient group; however, we found no statistically significant difference in the sN2 rates between the squamous-cell carcinomas and adenocarcinomas.

In the majority of studies, sN2 patients have been reported to have a better prognosis, compared

to those with sN2 and nsN2.^[5,10,15-17] Riquet *et al.*^[8] showed that the five-year survival outcomes were significantly higher in patients with skip metastases. However, Tanaka *et al.*^[13] compared the five-year survival rates of sN2 patients and nsN2 patients, and found no significant difference. Similarly, Yoshino *et al.*^[10] reported no statistically significant difference, although the five-year survival rates of the patients with and without sN2 were 35% and 13%, respectively. In our study, similarly, we found that the five-year overall survival rate was higher in sN2 patients; however, it did not reach statistical significance. On the other hand, the difference can reach statistical significance in larger-scale studies.

There are also several studies investigating the lobes causing skip metastases, and the upper lobe tumors have been reported to cause sN2 more commonly.^[4,12,18] Although there was a higher number of sN2 in the upper lobe tumors in the present study, the difference was not statistically significant ($p=0.695$). Additionally, the mean survival time of the patients with upper lobe tumors was longer compared to those with lower lobe tumors, the difference was not statistically significant.

When the lymph node stations in the sN2 patient group were evaluated, it can be seen that the involvement of the upper mediastinal lymph node stations, particularly, were more common. However, there is no definite conclusion on this involvement in the literature.^[4,5,14] It can be attributed to the fact that sN2 involvement is more common in the upper lobe tumors. In addition, there is no final consensus on the number of sN2 stations. As aforementioned, particularly in the study by Misthos *et al.*,^[5] the subcarinal lymph node involvement was at a lower rate; however, this type of involvement was significantly higher as a single station in the present study, which makes this finding quite interesting.

In conclusion, our study results show that five-year overall survival rates of operable patients with skip metastases are higher than those without skip metastases, although the difference is not statistically

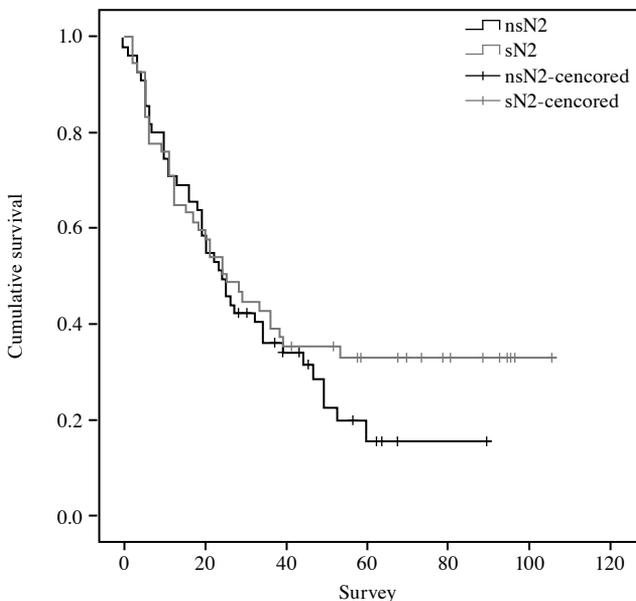


Figure 2. Prognosis-survival curves of lower lobe/upper lobe tumor patients in the skip metastasis group.

significant. However, there is a need for further large-scale studies. In addition, the present study focused on the localization and number of lymph node stations particularly in patients with skip metastases, different from previous studies. Based on our study results, sN2 involvement is more common in the subcarinal lymph node station as a single station, and lower survival rates of the lower lobe tumors with sN2 should not be ignored.

Declaration of conflicting interests

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