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Original Article / *Özgün Makale*

Role of surgery in high-grade neuroendocrine tumors of the lung

Akciğerin yüksek dereceli nöroendokrin tümörlerinde cerrahinin yeri

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ABSTRACT

Background: This study aims to evaluate the surgical results for high-grade neuroendocrine carcinomas and to identify factors that influence prognosis.

Methods: Between January 2009 and December 2017, a total of 71 patients (58 males, 13 females; mean age: 62±9.6 years; range, 38 to 78 years) with a high-grade neuroendocrine carcinoma of the lung were retrospectively analyzed. Overall survival and five-year overall survival rates were evaluated.

Results: The mean overall survival was 60.7±6.9 months with a five-year survival rate of 44.3%. The mean overall survival and five-year overall survival rates according to disease stage were as follows: Stage 1, 67±10.8 months (46%); Stage 2, 61.4±10.8 months (45%); and Stage 3, 33.2±8.6 months (32%) (p=0.02). The mean overall survival and five-year overall survival rate according to histological types were as follows: in large cell neuroendocrine carcinoma, 59.4±9.2 months (45%); in small cell neuroendocrine carcinoma, 68.6±12.2 months (43%); and in combined-type neuroendocrine carcinoma, 40.9±10.1 months (35%) (p=0.34).

Conclusion: Thoracic surgeons should be very selective in performing pulmonary resection in patients with Stage 3 high-grade neuroendocrine carcinomas and combined cell subtype tumors.

Keywords: Large cell lung carcinoma, neuroendocrine tumor, small cell lung carcinoma, thoracic neoplasm.

ÖZ

Amaç: Bu çalışmada yüksek dereceli nöroendokrin karsinomların cerrahi sonuçları değerlendirildi ve prognozu etkileyen faktörler belirlendi.

Çalışma planı: Ocak 2009 - Aralık 2017 tarihleri arasında akciğerin yüksek dereceli nöroendokrin karsinomu olan toplam 71 hasta (58 erkek, 13 kadın; ort. yaş: 62±9.6 yıl; dağılım, 38-78 yıl) retrospektif olarak incelendi. Genel sağkalım ve beş yıllık genel sağkalım oranları değerlendirildi.

Bulgular: Ortalama genel sağkalım süresi 60.7±6.9 ay olup, beş yıllık sağkalım oranı %44.3 idi. Hastalık evresine göre ortalama genel sağkalım ve beş yıllık genel sağkalım oranları ise şu şekildedir: Evre 1'de 67±10.8 ay (%46), Evre 2'de 61.4±10.8 ay (45%) ve Evre 3'te 33.2±8.6 ay (%32) (p=0.02). Histoloji türüne göre ortalama genel sağkalım ve beş yıllık genel sağkalım oranları ise şu şekildedir: büyük hücreli nöroendokrin karsinomda 59.4±9.2 ay (%45), küçük hücreli nöroendokrin karsinomda 68.6±12.2 ay (%43) ve kombine tip nöroendokrin karsinomda 40.9±10.1 ay (%35) (p=0.34).

Sonuç: Göğüs cerrahları, Evre 3 yüksek dereceli nöroendokrin karsinom ve kombine hücre alt tipli tümörlü hastalarda akciğer rezeksiyonu yaparken oldukça seçici olmalıdır.

Anahtar sözcükler: Büyük hücreli akciğer kanseri, nöroendokrin tümör, küçük hücreli akciğer kanseri, torasik neoplazi.

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Surgery improves outcomes for early-stage lung cancers, while high-grade neuroendocrine carcinomas (HGNCs), including small cell lung carcinomas (SCLCs) and large cell neuroendocrine carcinomas (LCNECs), are rapidly progressive and most cases are inoperable, when they are diagnosed.[1] Neuroendocrine tumors (NETs) of the lung are a special subtype of lung cancer. According to the 2015 World Health Organization (WHO) Classification of Lung Tumors, LCNEC is distinct from large cell carcinoma and is grouped together with typical carcinoid (TC), atypical carcinoid (AC), and SCLC within the NETs of the lung.[2] Owing to their poorly differentiated features, LCNEC and SCLC are classified as high-grade NETs of the lung, as distinct from low-grade TC and intermediate-grade AC.

In the literature, there is a limited number of studies investigating the prognosis and surgical results for HGNCs. In the present study, we aimed to evaluate surgical results for HGNCs and to identify the factors that influence prognosis.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Thoracic Surgery between January 2009 and December 2017. The data cut-off date for clinical survey was January 2019. During the study period, 3,946 anatomic pulmonary lung resections due to lung carcinoma were performed. A total of 65 (1.65%) patients who underwent pulmonary resection followed by mediastinal lymph node dissection due to HGNCs and six additional patients who underwent pulmonary wedge resection due to poor cardiopulmonary condition were included in the study. Finally, a total of 71 patients (58 males, 13 females; mean age: 62±9.6 years; range, 38 to 78 years) were recruited. Tumor-free margins were obtained in the six (6.5%) patients who underwent pulmonary wedge resection without lymph node dissection. Patients who underwent exploratory thoracotomy, received neoadjuvant treatment or were lost to follow-up were excluded.

All patients were smokers and stopped smoking at least one week before surgery. Preoperatively, all patients underwent thoracic computed tomography (CT), cranial magnetic resonance imaging (MRI), and positron emission tomography (PET). Transthoracic needle aspiration and/or bronchoscopy was performed at least once in all patients for diagnosis. In 32 (45%) patients, histological diagnosis could not be achieved preoperatively. Decisions regarding operability were made based on CT and PET. Eleven of the patients (15.5%) were diagnosed incidentally during routine medical check-ups.

Mediastinoscopy was performed in 39 patients who had a preoperative diagnosis of lung carcinoma. Mediastinoscopy was also performed in 15 patients without a carcinoma diagnosis who had mediastinal lymph nodes greater than 1 cm in diameter spotted in CT and/or positive PET scans, hilar lymph node positivity, or tumors necessitating pneumonectomy. Mediastinoscopy was not performed in patients with undiagnosed T1 tumors (n=11). All patients received chemotherapy and radiotherapy, when N2 disease was identified. Patients with small cell carcinoma and combined carcinoma HGNCs including the small cell component received cranial irradiation. All cases were routinely followed by CT at a six-month interval.

The 8th edition of the Tumor, Node, Metastasis (TNM) classification of malignant tumors, assessed by the International Association for the Study of Lung Cancer (IASCL) Committee, was used for staging.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. Survival curves were estimated using the Kaplan-Meier analyses, and log-rank tests were performed to determine the significance of differences in survival between groups. A p value of <0.05 was considered statistically significant.

RESULTS

Overall, 24 of 71 cases were high-grade SCLCs (33.8%) and 35 (49.3%) were high-grade LCNEC. The remaining 12 cases (16.9%) were combined carcinomas. The combinations were as follows: small cell with large cell HGNC in eight cases, small cell HGNC with non-small cell lung cancer (NSCLC) in two cases, and large cell HGNC with NSCLC were in two cases (Table 1).

In all, 31 of 71 tumors were T1 (43.6%). Of 31 patients with T1 tumors, nine (29%) had preoperative diagnosis and 22 patients did not. A total of 31 cases were Stage 1 (43.6%), 23 were Stage 2 (32.3%), and 17 were Stage 3 (24.1%). Stage distribution is shown in Table 1.

Of 65 patients who had anatomical pulmonary resection, 54 (76.1%) underwent lobectomy

Table 1. Data of patients

Parameter	HGNC (n=71) n	%
Sex		
Male	58	82
Female	13	18
Large cell carcinoma	35	49.3
Small cell carcinoma	24	33.8
Combined carcinoma	12	16.9
Stage		
1	31	43.6
2	23	32.3
3	17	24.1
N0	41	57.7
N1	23	32.3
N2	7	10
Lobectomy	54	76
Pneumonectomy	11	15.4
Wedge resection	6	8.6

HGNC: High-grade neuroendocrine carcinoma.

and 11 (15.5%) underwent pneumonectomy. Mediastinoscopy was performed in 54 patients (83%) before anatomic pulmonary resection. No mortality was observed either perioperatively or postoperatively.

The patients who underwent anatomic pulmonary resections were considered in survival analyses. The mean overall survival was 60.7±6.9 months, with a five-year survival rate of 44.3%. In addition, patients with Stage 3 disease had the worst prognosis (p=0.02). The mean overall survival and five-year overall survival rates were 67±10.8 months (46%) for Stage 1, 61.4±10.8 months (45%) for Stage 2, and 33.2±8.6 months (32%) for Stage 3 (Figure 1). In six patients with wedge resections, the mean survival was 60.3±12.8 months, and the five-year survival rate was 55%.

When overall survival was compared according to histopathological types, combined neuroendocrine carcinomas were associated with the poorest overall survival; however, the difference was not statistically significant (p=0.34). The mean overall survival and five-year overall survival rates were 59.4±9.2 months (45%) for LCNEC, 68.6±12.2 months (43%) for small cell NETs and 40.9±10.1 months (35%) for combined NETs (Figure 2).

When the five-year overall survival rates were analyzed by N status, the mean rates were 65.9±8.3 months (50%) in patients with N0 disease, 53.6±10.6 (42%) for N1 disease, and 37.1±15.3 months (35%) for N2 disease, (p=0.103). As expected, the patients

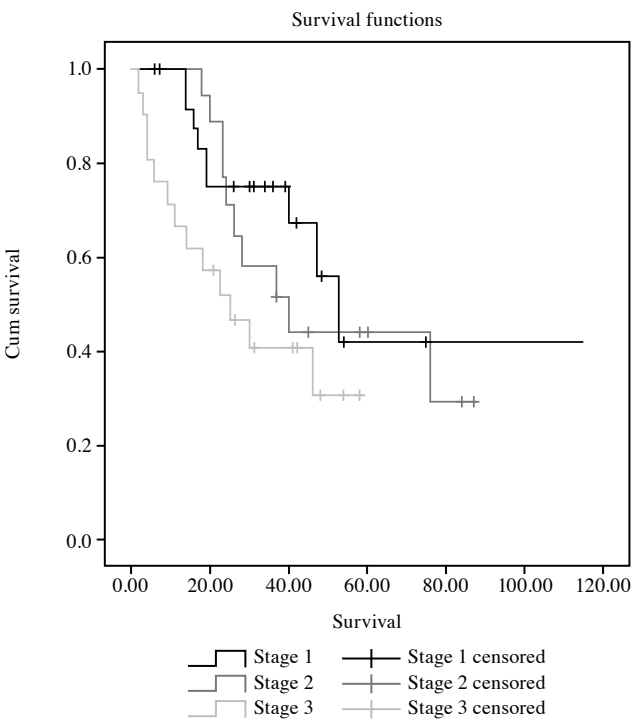

Figure 1. Overall survival of patients according to pathological stages.

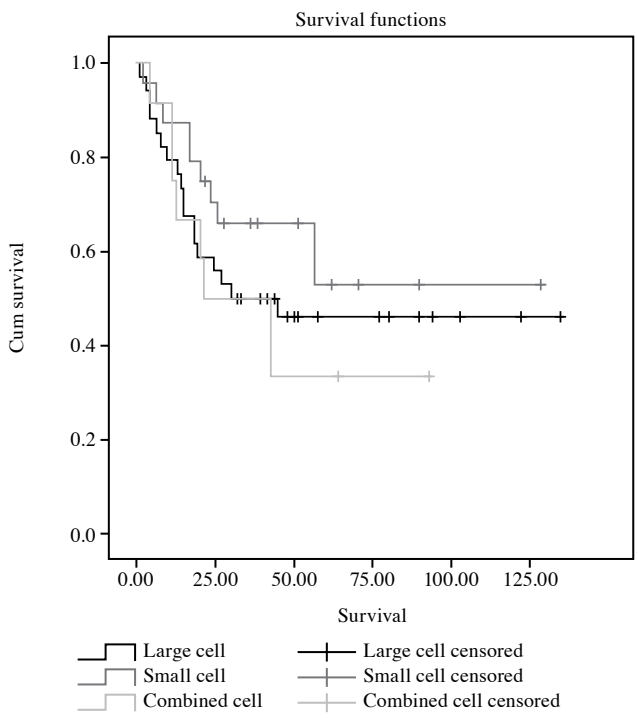

Figure 2. Overall survival of patients according to histological subtypes.

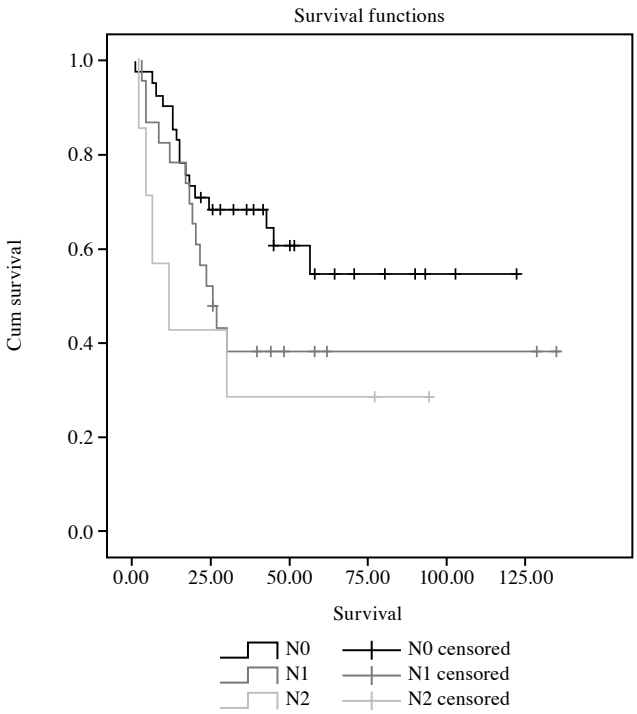

Figure 3. Overall survival of patients according to N status.

with N0 disease had a significantly better prognosis, compared to patients with N2 disease (p=0.009) (Figure 3).

DISCUSSION

Long-term survival is possible in small cell carcinoma of the lung in some cases, particularly in patients in whom tumor-free margin is achieved and there is no N2 disease.[3] Adjuvant chemotherapy is mandatory for this group of patients.[4] Mediastinal radiotherapy is necessary in patients with N2 disease. Despite the relatively positive results achieved in surgery for small cell lung cancers, the value of surgery for the treatment of HGNCs is still unclear.[5]

Chemotherapy alone seems to be an insufficient treatment for SCLC. Although it is associated with favorable initial results, there is a local relapse rate of 90% after chemotherapy.[6] Median survival after treatment of limited disease is 15 to 20 months. For higher-stage diseases, median survival is 8 to 13 months, with a two-year survival rate of 5%.[7] Namikawa et al.[8] reported that the five-year survival rate of patients with Stage 1 small cell carcinoma was 75%. Therefore, treatment must always include systemic measures to control locoregional recurrence and treat distant tumor cells, if present.

Small cell and LCNECs are classified as high-grade NETs based on the 2015 WHO criteria.[2] Aggressive clinical progress is correlated with histopathological parameters. Cytological characteristics are clearly identified; however, it is not always possible to clearly differentiate between these two tumor types pathologically.[9] Moreover, it is not always possible to discriminate between NSCLC and AC tumors after immunohistochemical and morphological analyses.[10] Molecular studies have revealed that these tumors share common mutations.[11]

While there is a local relapse rate of 90% after chemotherapy in small cell tumors, the rate of local recurrence is lower in LCNECs, as these tumors are usually peripherally located.[5] In our study, overall survival was higher than expected, possibly as many patients had T1 tumors. A similar cause-and-effect relationship was observed by Welter et al.[5] Although high-grade NETs of the lung have poor prognosis, compared to other NSCLCs,[12-14] satisfactory survival rates were observed in our study.

The relatively high overall survival in the present study may be attributable to the fact that most patients had early-stage high grade neuro-endocrine (HGNE) lung cancers. Overall, 31 of our 71 patients (43.6%) had T1 tumors. Among 31 patients with T1 tumors, only nine (29%) had a preoperative diagnosis. Twenty-two patients with undiagnosed T1 tumors had peripheral tumors, and diagnostic procedures such as bronchoscopy and transthoracic thin needle aspirations were inadequate. Operability was assessed by CT and PET scans in this group of patients.

In a study by Mochizuki et al.[3] that included 21 cases, 20 patients with tumors were detected after routine check-up procedures. Large cell carcinomas were the most common subtype (49.3%) in the HGNC group, while combined cell carcinomas were in the minority (16.9%). Patients with SCLCs had the highest five-year overall survival rate (43%); patients with combined cell carcinomas had the lowest (35%). Stage 3 patients including those with N2 disease had by far the worst prognosis. Our survival analyses demonstrated that a conservative approach may be necessary while evaluating patients with Stage 3 HGNC, combined cell subtype.

The difference in prognosis between high-grade LCNEC and SCLC was not well-defined. Several retrospective studies have reported similar prognoses between high-grade LCNEC and SCLC patients who

underwent surgical resection.[8,15-17] However, Varlotto et al.[18] showed that overall survival for high-grade LCNEC patients undergoing surgery without radiation was higher to a non-significant degree than for high-grade SCLC patients. Isaka et al.[19] also found that Stage 1A LCNEC patients undergoing surgery had an increased overall survival rate, compared to small cell cases.

We performed sublobar wedge resection in six cases, due to poor cardiopulmonary status with no preoperative diagnosis. Interestingly, improved survival was observed in this group of patients. This apparent effect may be due to the small number of cases. Meanwhile, two retrospective studies reported that sublobar resection did not affect survival in LCNEC patients;[20,21] however, the authors were unable to draw any definitive conclusions based on the data. Regarding SCLC, a retrospective study by Brock et al.[22] showed that sublobar resection was an independent negative prognostic factor. Furthermore, Schreiber et al.[23] reported that the prognosis of the patients who underwent lobectomy was better than that of those who underwent sublobar resection and, thus, recommended lobectomy for this group of patients.

Nonetheless, the present study has several limitations. First, it has a single-center, retrospective, non-randomized design. Although our study included a relatively large number of patients, most cases did not have a preoperative diagnosis, which may have introduced a strong selection bias. Second, the adjuvant chemotherapy regimens were not standardized, as the patients received their treatments at different institutions. Disease-free interval was not obtained due to lack of follow-up data.

In conclusion, favorable survival rates can be achieved in patients with high-grade neuroendocrine carcinomas tumors who are surgically operated and receive postoperative adjuvant chemotherapy, mediastinal radiation therapy when necessary, and protective cranial radiotherapy. It should be noted that Stage 3 disease, N2 disease, and combined high-grade neuroendocrine tissue type are associated with poor prognosis. Therefore, thoracic surgeons should be very selective while performing pulmonary resections in this limited subgroup of patients.

Ethics Committee Approval: The study was approved by the Yedikule Chest Disease and Thoracic Surgery Hospital Ethics Committee (Date: 10.3.2022, no: 2022-199). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept, writing the article, supervision: M.A.B.; Analysis, interpretation: N.Ü.; Literature review, critical review: Y.S.; Data collection, references: N.A.; Materials: N.F.; Design, analysis: L.C.; Review: M.K.; Supervision: S.A.

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