

## Results of surgical resection in the treatment of small-cell lung cancer

Küçük hücreli akciğer kanseri tedavisinde cerrahi rezeksiyon sonuçları

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**Background:** This study aims to investigate the role of a surgical approach in the treatment of small-cell lung cancer (SCLC), and evaluate the possible effects of combining the surgical approach with other treatment modalities for survival.

**Methods:** Twenty patients (16 males, 4 females; mean age 58.3 years; range 41 to 76 years) who had a clinical and radiological suspicion of malignancy, who underwent an exploratory thoracotomy since diagnostic methods proved ineffective, and whose pathological results were reported as SCLC between January 1998 and January 2008 were reviewed retrospectively. Ten upper lobectomies, two lower lobectomies, six pneumonectomies and two inferior bilobectomies were performed along with radical lymph node dissection. All cases were evaluated according to age, gender, diagnostic methods, the operations performed, postoperative follow-up and survival results.

**Results:** The results of the postoperative histopathological assessments were reported as small-cell lung cancer and mixed type tumors were observed in 11 cases. Five of the cases were stage 1, six were stage 2, and nine were stage 3. During the postoperative period all cases received chemotherapy, and radiotherapy was applied to the cases with nodal metastases. The five-year survival rate was calculated as 76% for stage 1 and 2 cases, 13% for stage 3 cases and 86% and 15% for N<sub>0</sub> and N<sub>1-2</sub> cases, respectively.

**Conclusion:** Surgical treatment for SCLC can be considered in early stage (T<sub>1-2</sub> N<sub>0</sub>) cases. In the presence of N<sub>2</sub>, a surgical approach should be avoided. Postoperative chemotherapy should be applied after surgical resection, and mediastinal radiotherapy should be added in cases with nodal metastasis.

**Key words:** Lung cancer; lymph node dissection; small cell lung cancer; surgical.

**Amaç:** Çalışmada, cerrahi yaklaşımın küçük hücreli akciğer kanseri (KHAK) tedavisindeki önemi araştırıldı ve cerrahi yaklaşımla diğer tedavi yöntemlerinin bir araya getirilmesinin sağkalım üzerindeki muhtemel etkileri değerlendirildi.

**Çalışma planı:** Ocak 1998 - Ocak 2008 tarihleri arasında klinik ve radyolojik olarak malignite şüphesi taşıyan, tanısal yöntemler etkin olmadığı için eksplorasyon amacı ile torakotomi uygulanan ve patoloji sonucu küçük hücreli akciğer kanseri olarak bildirilen 20 hasta (16 erkek, 4 kadın; ort. yaş 58.3 yıl; dağılım 41-76 yıl) retrospektif olarak incelendi. Olgulara radikal lenf nodu diseksiyonu ile beraber, 10 üst lobektomi, iki alt lobektomi, altı pnömonektomi ve iki inferiyor bilobektomi yapıldı. Tüm olgular yaş, cinsiyet, tanı yöntemleri, uygulanan ameliyatlara, ameliyat sonrası takip ve sağkalım sonuçları ile değerlendirildi.

**Bulgular:** Ameliyat sonrası histopatolojik değerlendirme sonuçları küçük hücreli akciğer kanseri olarak bildirildi, 11 olguda miks tip tümör izlendi. Olgulardan beşi evre 1, altısı evre 2, dokuzu evre 3 idi. Ameliyat sonrası dönemde tüm olgulara kemoterapi ve nodal tutulumu olan olgulara radyoterapi uygulandı. Beş yıllık sağkalım evre 1 ve 2 için %76, evre 3 için %13; N<sub>0</sub> ve N<sub>1-2</sub> olgular için ise sırasıyla %86 ve %15 olarak hesaplandı.

**Sonuç:** Küçük hücreli akciğer kanseri de cerrahi tedavi erken evre (T<sub>1-2</sub> N<sub>0</sub>) olgularda düşünülebilir. N<sub>2</sub> varlığında cerrahi yaklaşımdan kaçınılması gerekmektedir. Cerrahi rezeksiyonun ardından ameliyat sonrası kemoterapi uygulanmalıdır ve nodal metastazlı olgularda mediastinal radyoterapi ilave edilmelidir.

**Anahtar sözcükler:** Akciğer kanseri; lenf nodu diseksiyonu; küçük hücreli akciğer kanseri; cerrahi.

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Small cell lung cancer (SCLC) accounts for 13-20% of all lung cancers.<sup>[1]</sup> It causes rapid local invasion and distant metastasis during the early period.<sup>[1]</sup> Chemotherapy is a generally accepted treatment method for this tumor due to a high positive response to treatment. Nevertheless, there are circumstances where this treatment has been found to be insufficient due to high rates of local recurrences which resulted in death despite combined chemotherapy and radiotherapy. Therefore, other treatment combinations which include surgical resection have started to receive attention.

We reviewed our own surgical experience in order to examine the role of surgery in the treatment of SCLC. Additionally, we discussed the follow-up results of our 20 SCLC cases who had resection surgery along with chemotherapy and/or radiotherapy while also reviewing the literature on the topic.

## PATIENTS AND METHODS

Twenty cases (16 males, 4 females, mean age 58.3 years; range 41 to 76 years) who underwent surgical resection for malignancy between January 1998 and January 2008 and who were diagnosed as having SCLC by a postoperative histopathological examination were retrospectively reviewed. The effects of combining a surgical approach together with other treatment modalities on survival were assessed. Preoperative assessment of all cases included a physical examination, routine laboratory tests, respiratory function tests, thoracic computed tomography (CT), cranial tomography, abdominal ultrasonography, bone scintigraphy, positron emission tomography (PET), and a bronchoscopy. Mediastinoscopy was performed for mediastinal lymph nodes with a length of 1 cm or above as seen on thoracic CT imaging and suspicious uptake as observed on positron emission tomography (PET). All cases were clinically and radiologically suspected to be malignant, and they underwent an exploratory thoracotomy because they could not be diagnosed using other methods.

Postoperative follow-ups of patients were performed through routine and periodic controls. The Kaplan-Meier method was used to acquire survival curves. The log-rank test was used in order to compare survival curves, and the chi-square test was used to compare group differences. A value of  $p < 0.05$  was accepted as significant.

## RESULTS

Nineteen cases had a history of smoking. Preoperatively, none of the patients was diagnosed with SCLC. Mediastinoscopy was performed on 10 patients with mediastinal lymph nodes 1 cm or above in length. The

tumors were diagnosed as malignant by intraoperative frozen section. Curative surgical resection was performed in all patients. There were 10 upper lobectomies (50%), two lower lobectomies (10%), six pneumonectomies (30%), and two inferior bilobectomies (10%) along with a radical lymph node dissection. Upon staging based on postoperative histopathological examination, two cases were classified as stage IA (10%), three cases as stage IB (15%), one case as stage IIA (5%), five cases as stage IIB (25%), seven cases as stage IIIA (35%), and two cases as stage IIIB (10%). Nine cases were N<sub>0</sub>, three cases were N<sub>1</sub>, and eight cases were N<sub>2</sub>. Eleven cases were diagnosed as "mixed small cell lung cancer" after a histopathological examination. Chemotherapy was administered to all patients, radiotherapy was also administered in eight patients, and prophylactic cranial radiotherapy was provided for one patient.

Taking into account all patients, the five-year survival rate was calculated at 41% with an average survival duration calculated as 56.8 months (Figure 1). The early stage (stage I and stage II, 11 patients in total) five-year survival rate was 76% with a mean survival of 90 months. On the other hand, for nine stage III patients, the five-year survival rate was only 13% with an average survival of 11.7 months. When early and late stage cases were compared, the statistical difference between those cases was significant ( $p = 0.004$ ; Figure 2). For N<sub>0</sub> cases, the five-year survival rate was 86%, and the average survival rate was 97.9 months. For N<sub>1</sub>-N<sub>2</sub> cases, the results were 15% and 15.8 months, respectively. When N<sub>0</sub> cases were compared with N<sub>1</sub>-N<sub>2</sub> cases, the statistical difference was significant ( $p = 0.021$ ; Figure 3).

## DISCUSSION

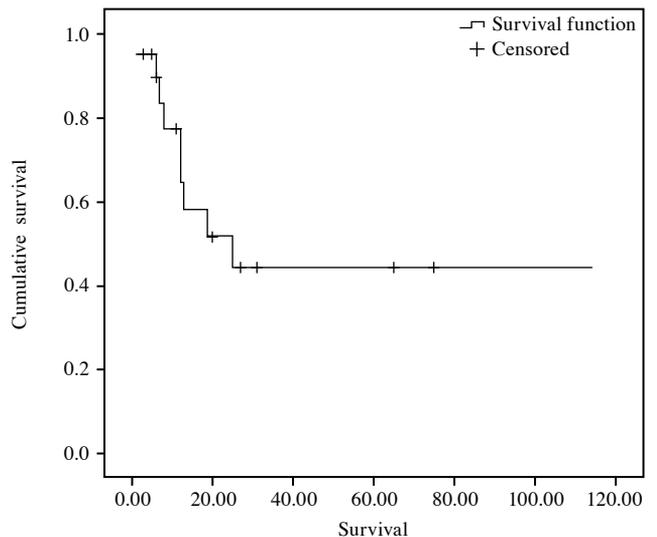
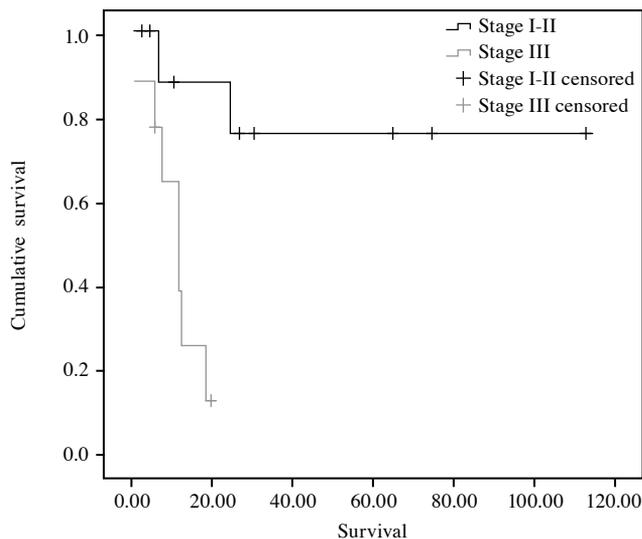
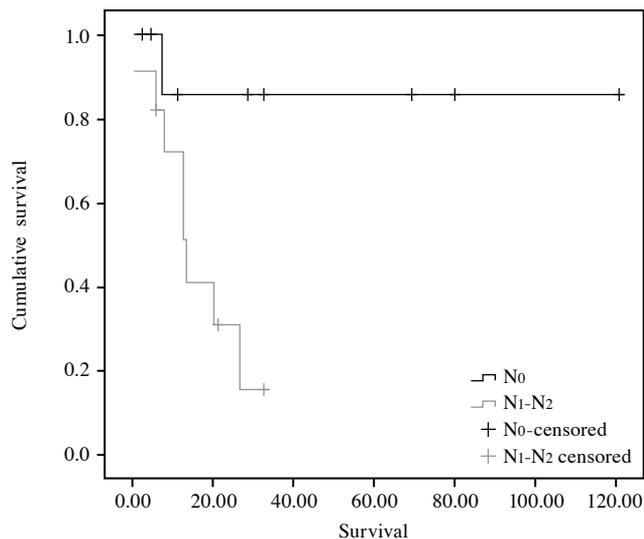


Figure 1. General survival chart for all cases.



**Figure 2.** General survival chart for stage I-II and stage III.



**Figure 3.** General survival chart for N0 and N1-2 cases.

The role of surgery for treatment of SCLC has been discussed frequently over the last three decades. The surgical approach has been avoided ever since a British Medical Research Council study in 1969 showed that the survival rate for radiotherapy was slightly better than the one for surgery.<sup>[1]</sup> During the same period, the efficiency of chemotherapeutic agents against SCLC has become evident.<sup>[2,3]</sup> The life span of patients has increased significantly with combined chemotherapy and combined chemotherapy-radiotherapy, and the median survival duration has been extended from 12 weeks to 12 months with two- to five-year survival rates starting to be reported during the limited disease stage.<sup>[4-6]</sup>

Although there has been an over 80% general response and 50% accurate response to treatment during the initial chemotherapy stage of SCLC, recurrences developed in a large majority of cases within two years. Along with the characteristic features of SCLC, mixed histopathologies have played an important role in the high incidence of local and systemic recurrence along

with, in some cases, an inaccurate treatment response to chemotherapy.<sup>[3]</sup> Approximately 30% of recurrences are local, about 30% are systemic and local, and the remaining recurrences are systemic.<sup>[3,7,8]</sup> Mixed type pathology, especially the resistance of the non-small cell lung cancer (NSCLC) component and other neuroendocrine pathologies to chemotherapy, negatively affects the success of chemotherapy. In 11 of our cases, mixed type pathology was determined.

Because of cases in which combined chemotherapy and radiotherapy treatment was insufficient along with incidences of high local recurrences which resulted in death, attention was redirected to the treatment combinations that include surgical resection. Early reports of sporadic cases that received surgical treatment were followed by results of retrospective and prospective series. Shields et al.,<sup>[9]</sup> Meyer and Parker<sup>[2]</sup> and Shepherd et al.<sup>[10]</sup> were pioneers of such studies (Table 1).<sup>[11-13]</sup>

Early stage (T1-2, N0) SCLC patients in whom surgical resection is planned should be subject to a thorough preoperative evaluation in accordance with the

**Table 1. Five-year survival rates of small cell lung cancer cases where chemotherapy was applied after resection**

Name of author	Number of cases	5-year survival (%)	Stage I (%)	Stage II (%)	Stage II (%)
Shepherd et al. <sup>[3]</sup>	79	39	51	28	29
Davies et al. <sup>[5]</sup>	32	36	50	35	21
Coolen et al. <sup>[11]</sup>	30	33.3	60	-	-
Rea et al. <sup>[12]</sup>	51	32	52	30	15
Inoue et al. <sup>[13]</sup>	91	37.1	Ia 56.1 Ib 30	IIa 57.1 IIb 42.3	-
Granetzny et al. <sup>[12]</sup>	95	43	20	44	31

system based on tumor (T), node (N), metastasis (M) staging. Stage I SCLC is less than 5% of all SCLC cases. Cases that have clinically exceeded the T1-2, N0 stage are not expected to benefit from surgery.<sup>[14]</sup> For cases that are clinically stage I (T1-2, N0), surgery could be considered after an evaluation with thoracic CT, upper abdominal tomography, bone scintigraphy, cranial tomography, and PET. In order to eradicate hidden nodal metastasis before resection, mediastinoscopy should be performed, or for lymph nodes which cannot be assessed by mediastinoscopy, another surgical evaluation should be undertaken.<sup>[15]</sup> The possibility of small lymph nodes in SCLC being metastatic is higher compared with NSCLC. Moreover, the postoperative pathological stage in cases where mediastinoscopy was performed is generally more advanced than the preoperative clinical stage. N2 existence has been determined in about 30% of the cases where N2 could be identified neither clinically nor mediastinoscopically.<sup>[3,5,9]</sup> Similarly, N2 that was not identified mediastinoscopically or by other diagnostic surgical methods was present in eight of our cases. In these, it was only identified through a postoperative histopathological review. The probability of such a situation is higher, especially in central tumors.<sup>[5]</sup>

Medullary bone uptake is a very rare possibility in cases not in the extensive stage and where systemic metastasis is not identified. In a series of 403 cases, the medullary bone uptake could only be identified in seven of the cases (1.7%). Accordingly, performing a medullary bone biopsy for the purpose of staging is accepted as an optional examination.<sup>[16]</sup>

Surgical resection significantly reduces the probability of local recurrence in SCLC and is not naturally expected to have an impact upon systemic recurrences.<sup>[4,17]</sup> It is known that having the combined systemic effects of chemotherapy and the local control effects of surgical resection increases the success of treatment. Moreover, impeding the progress of disease via chemotherapy will increase the feasibility of surgical resection. Past studies demonstrate that chemotherapy induction before surgical resection is obviously a beneficial approach in diagnosed stage I cases.<sup>[2,14]</sup> For patients who have been preoperatively diagnosed and have undergone neoadjuvant chemotherapy before resection, re-staging should be performed after chemotherapy and before surgery.<sup>[4,15]</sup>

Complete resection should be the preferred surgical approach. Even in cases where curative resection is believed to have been performed, micrometastasis probability should always be kept in mind, and chemotherapy should be applied after surgery. It has been reported that chemotherapy following surgical

treatment in N0 and N1 cases is a proper treatment approach and a proper treatment option to extend survival.<sup>[3,5,7]</sup> In cases having nodal metastasis, mediastinal radiotherapy should be applied in addition to postoperative chemotherapy.<sup>[3]</sup> In our series, all of the patients underwent curative resection and adjuvant chemotherapy with additional radiotherapy given to eight cases identified as N2. Prophylactic cranial radiotherapy (given in one case) should be considered after complete resection and adjuvant chemotherapy. It is assumed that prophylactic cranial radiotherapy has positive effects on disease-free and general survival.

Very few cases of SCLC have a chance for surgical resection because the pathological stage is always more advanced than the clinical stage. Therefore, preoperative clinical staging should be done very accurately. Surgery should be avoided in patients that clinically exceed stage I (T1-2, N0). For stage I cases, mediastinoscopy or other mediastinal surgical evaluation should be performed first, and surgery should be considered afterwards. Small-cell lung cancer-diagnosed surgical candidates should undergo neoadjuvant chemotherapy, and chemotherapy should be continued after resection. Patients that underwent surgery without any diagnosis and were postoperatively diagnosed with SCLC should undergo chemotherapy after surgery as well as radiotherapy as needed. For those for whom complete resection could not be performed, partial resection does not contribute to survival. In our study, the five-year survival rate was 86% and the average survival duration was 97.9 months for N0 cases, and 15% and 15.8 months for N1 and N2 cases, respectively. Our results support the publications that suggest surgical treatment is needed in early stage SCLC.

#### Declaration of conflicting interests

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#### REFERENCES

1. Miller AB, Fox W, Tall R. Five-year follow-up of the Medical Research Council comparative trial of surgery and radiotherapy for the primary treatment of small-celled or oat-celled carcinoma of the bronchus. *Lancet* 1969;2:501-5.
2. Meyer JA, Parker FB Jr. Small cell carcinoma of the lung. *Ann Thorac Surg* 1980;30:602-10.
3. Shepherd FA, Ginsberg RJ, Feld R, Evans WK, Johansen E. Surgical treatment for limited small-cell lung cancer. The University of Toronto Lung Oncology Group experience. *J Thorac Cardiovasc Surg* 1991;101:385-93.

4. Zatopek NK, Holoye PY, Ellersbroek NA, Hong WK, Roth JA, Ryan MB, et al. Resectability of small-cell lung cancer following induction chemotherapy in patients with limited disease (stage II-IIIb). *Am J Clin Oncol* 1991;14:427-32.
5. Davis S, Crino L, Tonato M, Darwish S, Pelicci PG, Grignani F. A prospective analysis of chemotherapy following surgical resection of clinical stage I-II small-cell lung cancer. *Am J Clin Oncol* 1993;16:93-5.
6. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. *J Clin Oncol* 1990;8:1563-74.
7. Shepherd FA, Ginsberg RJ, Evans WK, Feld R, Cooper JD, Ilves R, et al. Reduction in local recurrence and improved survival in surgically treated patients with small cell lung cancer. *J Thorac Cardiovasc Surg* 1983;86:498-506.
8. Fleck JF, Einhorn LH, Lauer RC, Schultz SM, Miller ME. Is prophylactic cranial irradiation indicated in small-cell lung cancer? *J Clin Oncol* 1990;8:209-14.
9. Shields TW, Higgins GA Jr, Matthews MJ, Keehn R. Surgical resection in the management of small cell carcinoma of the lung. *J Thorac Cardiovasc Surg* 1982;84:481-8.
10. Shepherd FA, Ginsberg RJ, Haddad R, Feld R, Sagman U, Evans WK, et al. Importance of clinical staging in limited small-cell lung cancer: a valuable system to separate prognostic subgroups. The University of Toronto Lung Oncology Group. *J Clin Oncol* 1993;11:1592-7.
11. Coolen L, Vanden Eeckhout A, Deneffe G, Demedts M, Vansteenkiste J. Surgical treatment of small cell lung cancer. *Eur J Cardiothorac Surg* 1995;9:59-64.
12. Rea F, Callegaro D, Favaretto A, Loy M, Paccagnella A, Fantoni U, Festi G, Sartori F. Long term results of surgery and chemotherapy in small cell lung cancer. *Eur J Cardiothorac Surg* 1998;14:398-402.
13. Inoue M, Miyoshi S, Yasumitsu T, Mori T, Iuchi K, Maeda H, Matsuda H. Surgical results for small cell lung cancer based on the new TNM staging system. *Ann Thorac Surg* 2000;70:1615-9.
14. Veronesi G, Scanagatta P, Leo F, De Pas T, Pelosi G, Catalano G, et al. Adjuvant surgery after carboplatin and VP16 in resectable small cell lung cancer. *J Thorac Oncol* 2007;2:131-4.
15. Granetzny A, Boseila A, Wagner W, Krukemeyer G, Vogt U, Hecker E, et al. Surgery in the tri-modality treatment of small cell lung cancer. Stage-dependent survival. *Eur J Cardiothorac Surg* 2006;30:212-6.
16. Campling B, Quirt I, DeBoer G, Feld R, Shepherd FA, Evans WK. Is bone marrow examination in small-cell lung cancer really necessary? *Ann Intern Med* 1986;105:508-12.
17. Gürsoy S, Yazgan S, Yıldız S, Yapucu MU, Üçvet A, Kul C ve ark. Küçük hücreli akciğer kanserlerinde cerrahi tedavi sonuçlarımız. *İzmir Göğüs Hastanesi Dergisi* 2006;3:55-60.