Review

Current Surgical Perspective on the Prognosis of Small Cell Lung Cancer

Hüseyin Fatih Sezer *

Posted Date: 17 September 2025

doi: 10.20944/preprints202509.1496.v1

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Hüseyin Fatih Sezer

Department of Thoracic Surgery, Kocaeli University Medical Faculty, Kocaeli, 41384 Turkey; hfs.hfs@gmail.com; Tel.: +0090 262 3037500

Abstract

Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine tumour that can metastasise early, may show resistance to systemic treatment, and has a poor prognosis. No satisfactory progress has been made in the prognosis with current treatment methods up to the present day. In this study, the prognosis and factors affecting prognosis in SCLC were investigated in light of current literature from a surgical perspective, and predictions were attempted to be made to lay the groundwork for personalised treatment approaches. Compared to non-small cell lung cancer, the number of studies is quite limited. Most of the surgical case series were conducted in the past, retrospectively, and involved a small number of patients. Advances in immunotherapy are promising. In the early stages, resection and subsequent chemotherapy may be the main treatment.

Keywords: small cell lung cancer; prognosis; survival

1. Introduction

Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine tumour that can metastasise early, may show resistance to systemic treatment, and has a poor prognosis.[1–7] It is estimated that there are 250,000 new cases worldwide each year, with 226,650 new cases and 124,730 deaths in the USA in 2025. [8,9] The use of tobacco products is closely related to the duration of their use, and approximately 95% of those diagnosed have a history of smoking.[6,8,10,11] So much so that initially, the proportion within lung cancers was 17-20%, but due to changes in smoking rates, this has now decreased to 13-15%. [1,12–19] (Figure 1) It is more commonly observed in males, but due to the increasing use of tobacco products among females, the prevalence among women is rising, and recent publications even report similar rates between the two sexes. [2,7,8,19] (Figure 1)

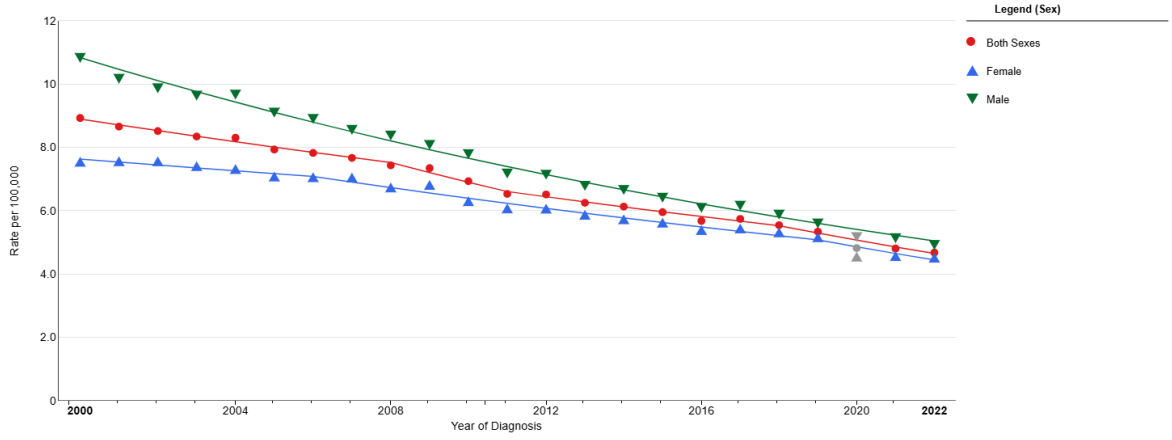

Figure 1. Incidence after the year 2000 in both sexes. National Cancer Institute (https://seer.cancer.gov)[67].

 doi:10.20944/preprints202509.1496.v1

Primarily the stage, as well as general medical condition, medical history, gender, race, and treatment summary can be listed as factors that may affect the prognosis.[2,13,20] As can be understood from here, it would be more beneficial to consider personal characteristics rather than generalisations when predicting prognosis. The treatment approach has traditionally involved long-term chemotherapy (CT) and radiotherapy (RT), and recent literature has focused on immunotherapy and genetic advancements. Surgery, however, can only be applied in cases detected at an early stage; considering that 70-80% of patients are diagnosed at an advanced stage, only a limited group are eligible for surgery. [2,6,12,21,22] Unfortunately, no satisfactory progress has been made in the prognosis with current treatment methods up to the present day. [23]

Due to the limited number of patients diagnosed at an early stage and the prejudices that surgical treatment will have a limited impact on prognosis, the number of patients who have undergone surgery, and consequently the literature related to surgical prognosis, is quite limited. In this study, the prognosis and factors affecting prognosis in SCLC were investigated in light of current literature from a surgical perspective, and predictions were attempted to be made to lay the groundwork for personalised treatment approaches.

2. Staging System

The staging that forms the basis of clinical use was established by the Veterans' Administration Lung Study Group (VALSG) (1957), and tumours limited to one hemithorax (treatable with a single radiotherapy field) were classified as limited stage (LD), while others were classified as extensive stage (ED). Subsequently, the International Association for the Study of Lung Cancer (IASLC) (2009) recommended the use of the TNM staging system.[24] However, the idea that the staging cannot be effectively determined, or the fact that previous studies have used the first staging, has left the issue of which staging should be used open to discussion.[1,2,6,12,25] From a practical clinical perspective, roughly speaking, when we synchronise both systems, patients with limited (Stage 1-2-3) and radiotherapy-eligible hilar mediastinal lymph nodes in a single hemithorax are limited; others are considered extensive (Stage 4), and it is observed that TNM classification is more frequently used in surgical decisions. [9,11,12,14,18,26,27] Recent studies on the subject of stage are focusing on subclassifications based on genetic and molecular material. [25,26,28–30]

3. Small Cell Lung Cancer Prognosis and Survival

The variable reasons for the prognosis are that the disease's clinical presentation is influenced by multifactorial parameters and the response to treatment is not homogeneous. The most important prognostic factor is the stage. Besides the stage, important epidemiological parameters include the patient's overall performance status and medical history, age, male gender, and smoking habits. The effectiveness of treatment methods, the extent of the performed surgery, lymph node metastasis, recurrence, presence of pleural effusion, weight loss of more than 10%, elevated LDH levels, a neutrophil/lymphocyte ratio of 4 or higher, and electrolyte disturbances such as hyponatraemia can also be considered as additional factors affecting prognosis. [5,9,13,20,31–34] In prognosis estimation, histological or molecular features that are accepted by all sectors have not yet been identified.[10]

The areas most frequently affected by metastasis are the contralateral lung, brain, liver, adrenal glands, and bones. [2] Initially, cranial metastases are observed in 10-18% and generally in 40-60%. [1,2,12] As expected, a single metastasis has a better prognosis compared to multiple metastases, while liver and brain metastases have a poor prognosis. [21,35] Within two years after treatment, approximately 75% of locally advanced disease and over 90% of metastatic disease experience recurrence or progression. [2] [19] Despite treatment processes, recurrence is observed in less than 10% of patients within 2 years. [9]

The survival time in untreated widespread disease is approximately 2-4 months. [5,9,20] Between 1973 and 2002, the 2-year survival rate in the limited stage was reported as 15-22%, while in the extensive stage it was 3.4-5.6%. [6] When all stages of patients are considered, the five-year

 doi:10.20944/preprints202509.1496.v1

survival rate was initially 4.3%, but at the beginning of the 2000s, this rate increased to 6.3%. [1] In more recent publications, the median survival is reported as 14-24 months in limited stage, 6-12 months in extensive stage, and an average survival of 13 months. [7,9,17,31,35] The 2-year survival rate is reported as 30-40%, the 3-year survival rate is 56.5% (limited stage) - 17.6% (advanced stage), and the 5-year survival rate is 0-47%. [5,7,9,11,12,14,20–22,25,28,29,31,36–42] Heterogeneous results among the studies are due to treatment options and universal change. From a traditional perspective, the 5-year survival rate in the limited stage (LD) is 22.8%, while in the advanced stage (ED) it is below 2%. [19] In terms of TNM staging, the survival times are as follows: stage 1a 60 months, 1b 43 months, 2a 34 months, 2b 18 months, 3a 14 months, 3b 10 months, 4 6 months.[11]

Factors affecting survival in the treatment process include concurrent chemoradiotherapy, early radiotherapy, and prophylactic cranial irradiation. [22,36,41] In patients who are at stage 1 and have not undergone surgical treatment, the two-year survival rate is below 5%, whereas in those who have undergone surgery, this rate can reach up to 30%. [43] In stage 2 patients, the median survival time with a combination of surgery and chemotherapy is 24 months, whereas for patients receiving only chemotherapy or radiotherapy, this period is 13-16 months.[43] In Stage 3 patients, the median survival with combined therapy is 20 months (previously 15 months), while in Stage 4 patients, the group receiving only chemotherapy has a median survival of 8 months, whereas with combined therapy it is 12 months.[43] The 5-year survival rate in early-stage patients who undergo surgery combined with chemotherapy is 30-58%. [44] In recent studies, the 5-year survival rate for patients who did not undergo surgery within a limited group between 2018 and 2022 is reported as 53.9%.

4. The Role of Surgery in Treatment and The Impact of Surgical Treatment on Survival and Prognosis

Since the majority of patients are in an advanced stage at the time of diagnosis, the treatment processes are primarily shaped by medical treatment, radiotherapy, and conservative approaches. [1,2,35] Although both chemotherapy and radiotherapy are indispensable options for most patients, their impact on prognosis and survival is limited.[6,9,11,17–19,23,28,45,46] So much so that the two-year survival rate in patients resistant to chemotherapy is below 10%. [1] Chemotherapy treatment is also applied in addition to surgery in patients who have undergone early-stage resection. Treatment models have remained the same for a long time until the developments in immunotherapy. Although promising developments are expected in immunotherapy, its impact on survival is still very limited, lasting only about 2 months. [1,2,4,17,23,26,37,42,45,47,48]

Surgical treatment can only be applied in limited stages, which corresponds to less than 5% of patients (T1-2 N0 M0), and among lung cancer cases, it is approximately 1.53%. [1,9,12,18,44,49] A diagnosis is often made incidentally during surgery for most of these patients. [21,50] In cases operated on due to solitary nodules, SCLC is detected in 4-12% of the cases. [51]

If we consider the last 30 years, one of the notable studies related to surgical treatment is a prospective study conducted by Lad et al. in 1994 regarding the role of surgery, but no difference was found in survival. [11] Results from this and similar studies have caused bias among surgeons, leading to less frequent application of surgery in SCLC cases. However, in subsequent studies [7,19,52], especially in patients who underwent surgery at an early stage, the significantly better survival outcomes have somewhat broken this prejudice.

4.1. Results Related to Surgical Application

Ideally, surgical treatment involves lobectomy and lymph node excision, followed by chemotherapy. [8,25] Anatomical resections have a significant advantage in terms of survival compared to non-anatomical resections. [43] There are only a few studies reporting the effectiveness of lymph node sampling in surgical applications for SCLC patients. Sampling more lymph nodes in two studies has been reported to prolong expected survival. [53,54] However, another study reports that increasing the number of lymph nodes sampled does not affect survival. [55]

 doi:10.20944/preprints202509.1496.v1

Another issue is that the clinical and pathological stages can differ significantly. In some studies, it has been reported that pathological staging is significantly more advanced than clinical staging, and therefore, some have recommended that the case should be considered as a more advanced stage when making surgical decisions. [21] For these reasons, mediastinal lymph node sampling is recommended as much as possible before the operation. [56]

4.2. Surgical Survival-Recurrence Outcomes

In patients undergoing surgical resection as part of their treatment, overall survival (OS) ranges from 34 to 69 months.[49,50,54,57] OS for 1 year is 84.8-93.8%, for 3 years is 60-71.2%, and for 5 years is 51.1-63.8%. [32,54] The five-year survival rates are reported as follows: stage I 31-63.8%, stage II 25-65.5%, stage III 15-27.8%, and stage IV 0%. [2,12,43,49,54,57–59] (Figures 2 and 3) In N0-N1-N2 lymph node metastases, overall survival (OS) was 120-28-40 months, with 2-year survival rates of 88.3%, 57.8%, and 60.8%, and 5-year survival rates of 65.5-69.4%, 40.6-41.9%, and 31.2-35.7% respectively.[54,60] In cases where lobectomy was performed, the OS was 84 months; in cases of pneumonectomy, 69 months; and in wedge resection, 21 months. [54] In cases where early-stage patients are predominant, the five-year survival rates are 55.6% for sublobectomy, 50.3-68.8% for lobectomy, and 70.6% for pneumonectomy. [32,36] In advanced stages, these rates are 28.8% for lobectomy, 12.5% for sublobar resection, 8.7% for pneumonectomy, and 13.5% for unknown types. [61]

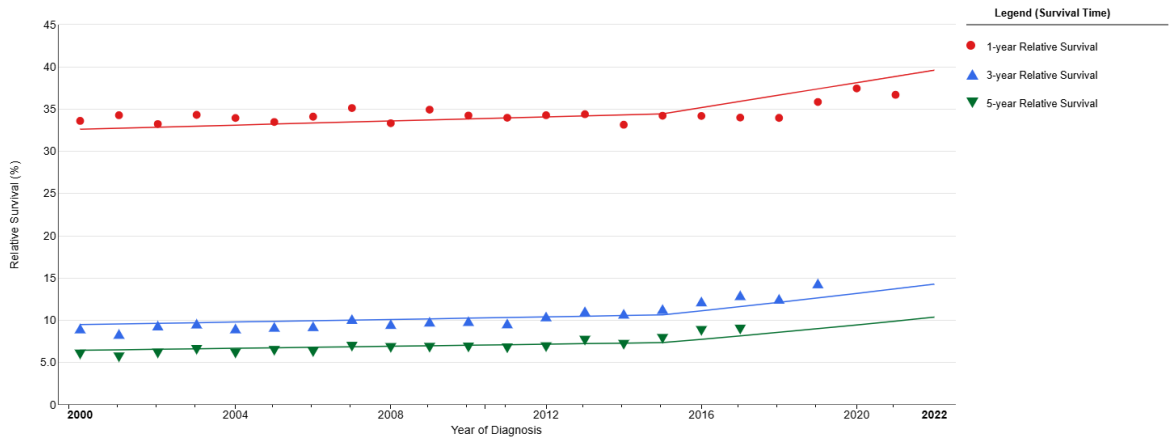

Figure 2. 1-3-5 year survival rates. National Cancer Institute (https://seer.cancer.gov)[67].

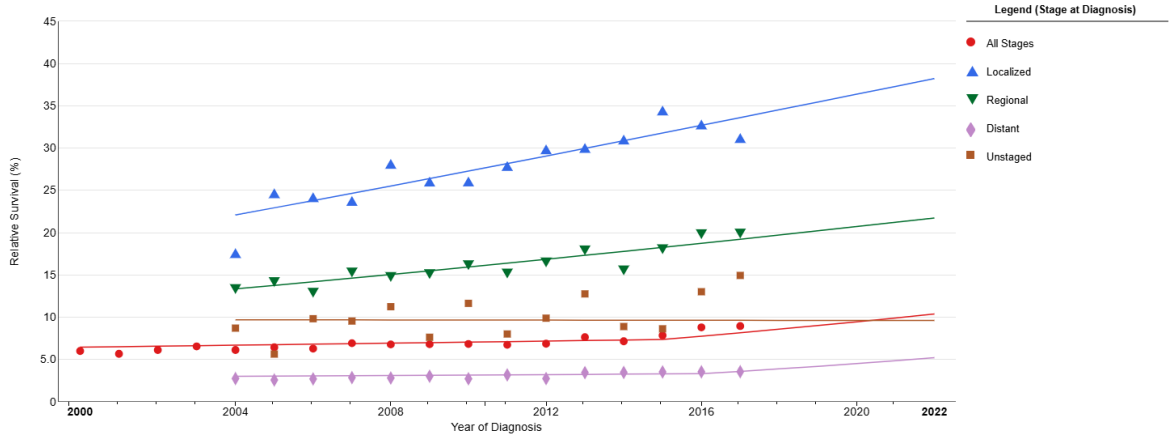

Figure 3. Survival according to stage. National Cancer Institute (https://seer.cancer.gov) [67].

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It may be of interest to consider the contribution of surgery alone or chemotherapy applied in addition to surgery to survival. Early-stage survival with only surgical intervention is 31-42.1 months, with a 5-year overall survival rate of 13-43.8%. [21,40,54,62] In cases receiving surgery combined with adjuvant chemoradiotherapy, overall survival (OS) ranged from 48.6 to 84 months, with 3-year survival rates of 68% for Stage 1, 56% for Stage 2, and 13% for Stage 3a. The 5-year survival rate was between 27% and 52.7%.[21,40,52,54,62][36] In studies comparing the contribution of surgery, the average survival ranged from 22 to 11 months (Stage 1: 38.6-22.9, Stage 2: 23.4-20.7, Stage 3a: 21.7-16), with a 5-year survival rate of 63% to 11%. [52,58] In patients who underwent lobectomy, the 5-year survival rates ranged from 34.6% to 50.3%, whereas in non-surgical treatments, it ranged from 9.9% to 14.9%.[54]

The recurrence rate after surgery is 13-15%. (58) The disease-free survival (DFS) following surgery is 30.63 months, with 1-, 3-, and 5-year DFS of 72.4%, 54.6%, and 31.5-51.8%, respectively. (32,49)

From the rates reported above, the contribution of surgical treatment to prognosis in selected patients is observed. The varying reports of survival rates may be due to different study concepts; however, they also indicate that the disease is individualised.

If the topic that comes up is salvage surgery. It is a management method that has been published as a few cases (a total of 17) used in limited-stage patients as an alternative to second-line chemotherapy after radical chemoradiotherapy, with an estimated survival rate of 92% at 2 years and 66% at 5 years. [63]

4.3. Factors Affecting Prognosis During and After the Surgical Process

Since patients who can undergo lung resection independently of their performance status are in better general condition than others, it is expected that these patients will have higher survival rates. Factors that may affect the prognosis related to surgery include epidemiological factors or the patient's general condition; stage, age, gender, tumour localisation, number and rate of lymph node metastases, smoking, coronary disease, nodular involvement, and tumour thrombosis. [32,49,50,54,57,60,64] Factors during the surgical process; performing systematic lymph node dissection (more than 19, with a metastatic lymph node rate below 21.4%), surgical method (lobectomy is good, sublobar resection is poor), R0 surgery, complete resection. [8,32,49,54,64] Factors related to the post-surgical process include receiving postoperative chemotherapy. [50,54,64]

There have been studies proposing nomograms that include personal characteristics for survival prediction beyond the existing staging systems in patients.[65,66] A prediction based on a score was obtained by separately scoring each parameter that could affect prognosis, such as age, gender, resection size, T stage, lymph node dissection, lymph node metastasis, chemotherapy, and radiotherapy. [59,65,66] However, there are some limitations or weaknesses in these nomograms. In studies with a surgical concept, chemotherapy and radiotherapy have been examined as the main variables. These studies are also not randomised and have limitations in using patients' medical history, disease characteristics, and postoperative complication data. For these reasons, these studies are subject to debate.

4.4. Limitations of Surgical Case Series

Compared to non-small cell lung cancer, the number of studies is quite limited. Most of the surgical case series were conducted in the past, retrospectively, and involved a small number of patients. Those with sufficient patient numbers used non-standard data obtained from datasets. Additionally, these studies have standardisation limitations, such as the influence of additional treatments (e.g., chemotherapy) on survival outcomes or heterogeneity among the groups.

5. Conclusion

 doi:10.20944/preprints202509.1496.v1

Although there are different options currently available for the treatment of SCLC, their effects are limited; therefore, preventive methods should be prioritised. Advances in immunotherapy are promising. In the early stages, resection and subsequent chemotherapy may be the main treatment. As SCLC begins to be seen at increasingly older ages, and when we do not consider age as the sole factor, we believe that in the next decade, the decline in cardiopulmonary reserve, the increase in accompanying comorbidities, and advancements in radiotherapy will lead to a decreasing rate of surgical resection even if SCLC is detected at an early stage. Randomised studies that include the results of surgical treatments and treatment algorithms acceptable to all disciplines should be established. For this, large prospective studies with a high number of surgical cases are needed.

Table 1. Recession Articles and Their Key Features Over the Last 10 Years.

	n	**STAGE**	**SURGICAL METHOD**	**SURVIVAL**	**SURGICAL PROGNOSIS: POOR OR GOOD**
Guo et. al. (2020)	297	Limited 286 (96.3%) Extend 11 (3.7%)	Lobectomy: 236 (79.5%) Pneumonectomy: 20 (6.7%) Sublober: 19 (6.4%)	OS 5 years: 63.8% DFS 5 years: 51.8%	(-) sublober rezeksiyon (+) Lobectomy
Fu et. al. (2023)	196	Stage 1-71(36.22%) Stage 2-45 (22.96%) Stage 3-58 (29.59%) Unknown- 19 (9.69%)	Lobectomy: 144 (73.5%) Pneumonectomy: 10 (5.1%) Sleeve: 3 (1.54%) Bilobectomy: 20 (10.2%) Wedge: 9 (4.5%)	OS 5 years: 49%	(-) smoking, advanced age, T-N advanced stage
Guo et. al. (2022)	120	Stage 1-39(32.5%) Stage 2-37 (30.83%) Stage 3-42 (35%) Stage 4- 2 (1.67%)	Lobectomy: 87 (71.3%) Pneumonectomy: 5 (4.17%) Bilobectomy: 6 (5%) Sublober: 9 (11.67%)	OS 5 years: 46% DFS 5 years: 30.63%	(-) Advanced age, advanced TNM stages, sublobar resection-pneumonectomy, vascular thrombus
Yang et. al. (2018)	681	T1 410 (60.2%) T2 195 (28.6%) T3 13 (1.9%) T4 12 (1.8%) N0 461 (79.4%) N1 90 (15.5%) N2 29 (5.0%) N3 <10	Lobectomy: 458 (67.3%) Pneumonectomy: 23 (3.4%) Segmentectomy: 22 (3.2%) Wedge: 178 (26.1%)	OS 5 years: 48.1%	

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Zhou et. al. (2021)	164	Stage 1: 82 (50%) Stage 2: 43 (26.22%) Stage 3: 39(23.78%)	Lobectomy 101 (61.59%) > Lobectomy 17 (10.37%) Sublober 46 (28.05%)	OS (month) 26 (1986-1989) 37 (1990-1999) 60 (2000-2010) 59 (2010-2019)	(-) Coronary artery disease, nodal disease (+) Lobectomy, adjuvant chemotherapy
Gao et. al. (2021)	418	Stage 3	Lobectomy: 224 (53.59%) Pneumonectomy: 31 (7.41%) Sublober: 147 (35.17%) Unknown: 16 (3.83%)	OS 5 years: 20.90%(19 months) Lobectomy: 28.8% Pneumonectomy 8.7% Sublober 12.5% Unknown 13.5%	(-) Advanced age, male gender, T-N advanced stage, sublobar resection-pneumonectomy. (+)lobectomy, chemotherapy-radiotherapy
Yang et. al. (2016)	954		Lobectomy: 666 (69.8%) Pneumonectomy: 18 (1.9%) Segmentectomy: 26 (2.7%) Other 45 (4.7%) Wedge: 199 (20.9%)	OS: 5 years 47.4%(55.6 months)	(-) Advanced age, tumor size (+)Lobectomy
Motas et. al.* (2023)	17	Stage 1-11(64.71%) Stage 2- 2 (11.76%) Stage 3- 3 (17.65%)	Lobectomy: 10 (58.82%) Pneumonectomy: 2 (11.76%) Segmentectomy: 1 (5.88%) Bilobectomy: 2 (11.76%) Wedge: 2 (11.76%)	OS: 86 months 2 years 92%, 3 years 80%, 5 years 66%	
Wakeam et. al. (2017)	2089	Stage 1-1310(60.27%) Stage 2- 335 (16.37%) Stage 3- 401 (19.60%)	Lobectomy: 741 (35.5%) Pneumonectomy: 87 (4.2%) Sublober: 1261 (60.4%)	OS: Stage 1 38.6 months, Stage 2 23.4 months, Stage 3a 21.7 months	(-)Lymph node metastasis (+) Lobectomy, R0 surgery, chemotherapy - radiotherapy

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Zhao et. al. (2019)	205	Stage 1-79(38.5%) Stage 2-42 (20.5%) Stage 3-61 (29.8%) Stage 4- 9 (4.4%) NA 14 (6.8%)	Lobectomy: 151 (73.7%) Pneumonectomy: 20 (9.8%) Wedge: 34 (16.6%)	.OS: 69 months .1-3-5 years survival rates: 84.8% - 60% - 51.1%. .5-year survival: Stage 1 63.8%, Stage 2 65.5%, Stage 3 34.9%, Stage 4 0%.	(-)smoking, lymph node metastasis, PD-L1 positivity (+) R0 resection, T and B cell tumour
* Salvage Surgery		n: number	NA: Unknown	OS: Overall survival	DFS: Disease-Free Survival

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