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Small-Cell Lung Cancer (SCLC)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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1 Summary

Lung cancer is the third most common malignant tumor in women and the second most common in men in German-speaking countries. In both men and women, lung carcinomas are the most common cause of cancer-related death. Median age of onset is about 70 years. The main risk factor is smoking.

Small cell lung cancer (SCLC) accounts for about 12-15% of all lung cancers. In Germany, approximately 7,000 - 8,500 people develop SCLC each year. The disease is characterized by a high cell division rate and rapid growth progression. These biological characteristics are the reason for the high sensitivity of the tumor to chemo- and radiotherapy. On the other hand, they also lead to early dissemination and high recurrence rates. In stages I - III (Very Limited Disease, Limited Disease) there is a curative treatment option. Therapy in these stages is multimodal with inclusion of surgery, systemic drug treatment and radiotherapy. In metastatic disease, the additional administration of immunotherapy in addition to chemotherapy has become established. With combined chemo-immunotherapy, 15-20% of patients reach a 3-year survival.

2 Basics

2.1 Definition and basic information

Lung carcinomas are malignancies arising from epithelial cells of the respiratory tract. Based on cell line differentiation, a distinction is made between small cell and non-small cell carcinomas, with non-small cell carcinomas being further differentiated according to immunohistological and, more recently, according to molecular parameters.

The lung is a predilection site for metastases of numerous malignancies. These, other rare pulmonary tumors and benign focal lesions must be clarified by history-taking and, if necessary, also histopathologically.

The following statements on epidemiology, risk factors, prevention and early detection refer to all forms of lung cancer. The topic of the following sections of this guideline are primary small-cell lung cancers. The first description of small-cell lung carcinoma is considered to be the observations in workers of the Schneeberg mines in the German Erzgebirge [1].

2.2 Epidemiology

The following results are based on cancer registry data from the regional German federal states, which are regularly compiled at the Center for Cancer Registry Data [2] for nationwide evaluations.

In 2017 - 2019, SCLC accounted for approximately 15% of all lung cancer cases reported to cancer registries via hospitals, practices, or pathologies, with no assignment possible in approximately 5% of cases due to nonspecific histology information.

Approximately 3,500 women and 4,800 men develop SCLC for the first time each year in Germany. Since the approximately 12% of cases known only via death certificates in the registry (DCO) generally do not allow histological differentiation and are therefore included in the incidence of lung cancer but not in that of the two subgroups, the figures given should be understood as minimum figures.

The age-specific incidence increases with age up to the 8th decade of life. In most recent data, the median age at diagnosis was 67 years, and only about 2% of those affected develop the disease before the age of 50 (Figure 1). The age-specific disease rates are declining in men in all age groups and in younger women, and are still increasing in women over 60. These trends reflect the gender-specific trends in smoking behavior with a latency of several decades; therefore, in the medium to long term, a decline is also expected in women. Similar to NSCLC, the absolute number of new cases has been almost constant since about 2015 with a total of about 8,300 cases per year, after having increased continuously in the years before.

In 71% of new cases (women: 68%, men: 73%) with sufficient documentation of tumor stages, distant metastases are already detected at first diagnosis of SCLC; in both sexes, only about 5% of cases are diagnosed in early stages I or II according to UICC (Figure 2).

Relative 5-year survival rate as an estimator of disease-specific survival for the 2017-2019 period for SCLC was 8.2%, only slightly higher than 10 years earlier (7.6%).

Figure 3 illustrates the dependence of survival prognoses on tumor stage. The significantly worse prognosis compared to non-small-cell lung cancers is partly explained by the less favorable tumor stage distribution, but also in the rare cases with early stages the results are worse than in NSCLC.

Figure 1: Annual incidence rates of SCLC per 100,000 persons by age and gender (Germany, 2017-2019)

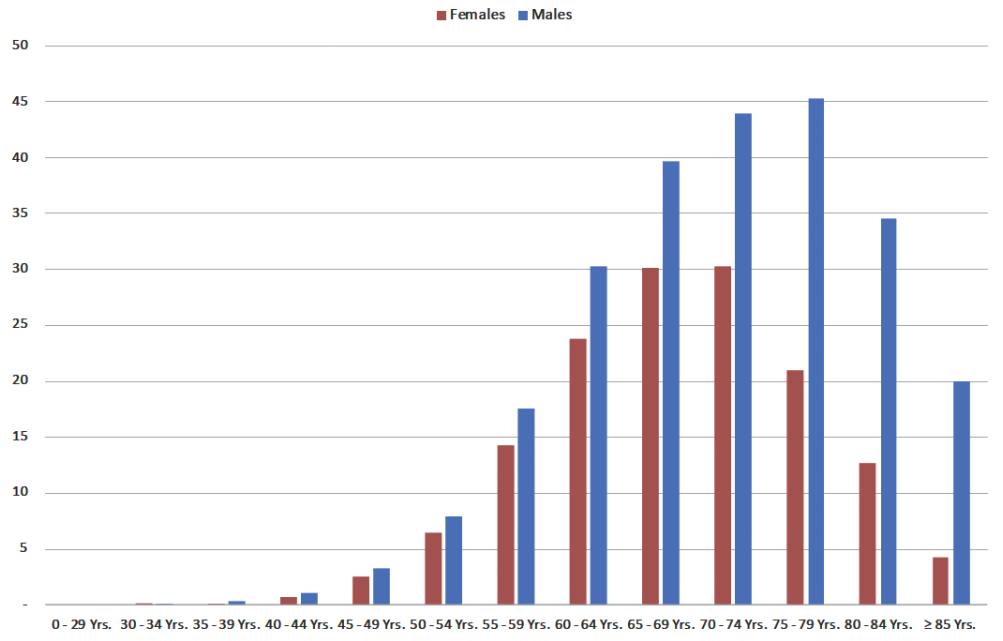


Figure 2: Distribution of UICC tumor stages by histology
(excluding DCO cases; no tumor stage could be assigned in 27% of cases)

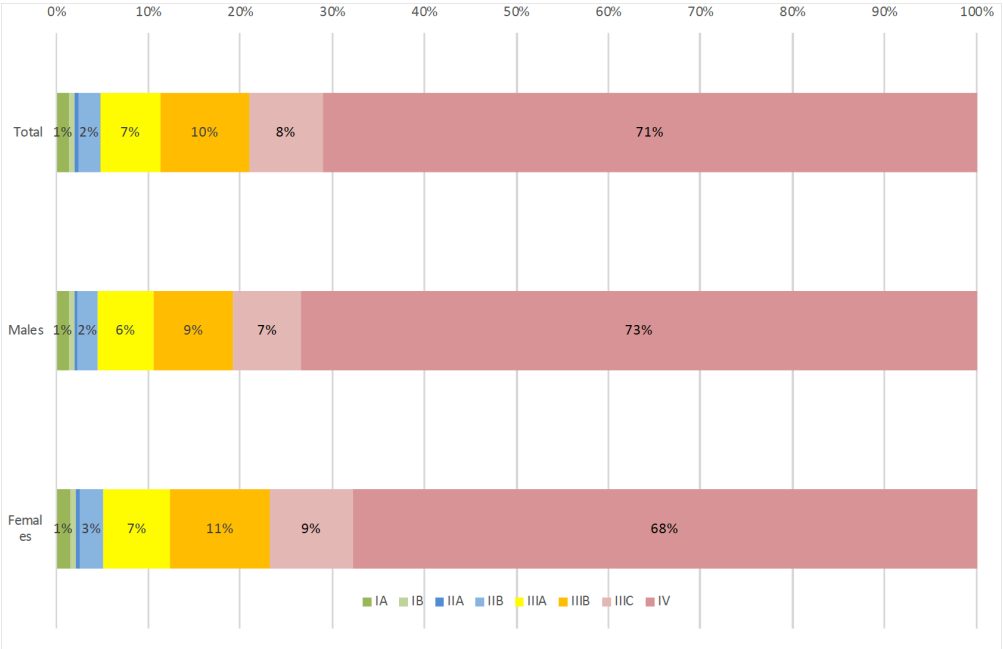
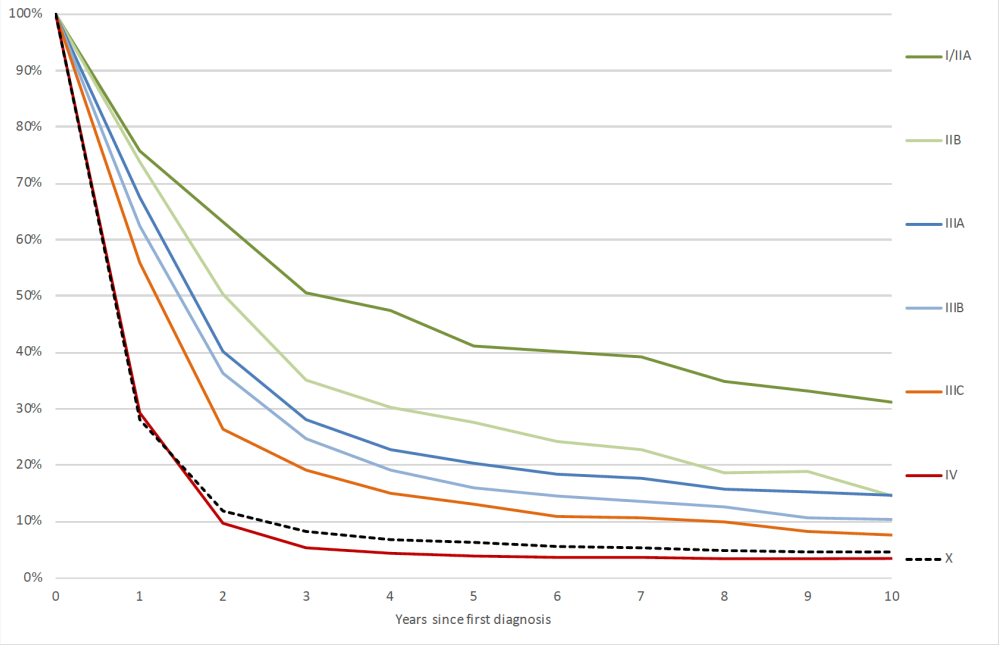


Figure 3: Relative survival (compared with age-matched general population) to 10 years after first diagnosis of SCLC, 2017-2019



2.4 Risk factors

The main risk factor is smoking. Further statements on risk factors of lung cancer can be found in Lung cancer, non-small cell (NSCLC).

2.5 Histopathology and molecular subgroups

Immunohistochemical detection of at least two neuroendocrine markers (TTF-1, CD 56, synaptophysin, chromogranin) is required for the diagnosis of small cell neuroendocrine lung carcinoma from biopsies, endobronchial ultrasound (EBUS), or cytology. The proliferation rate with Ki67 should be above 70% Ki67 positive cells. Differential diagnosis against small-cell basaloid squamous cell carcinoma or non-Hodgkin's lymphoma is particularly important.

Inactivating mutations in the tumor suppressor genes TP53 and RB1 are found in almost all SCLCs and can be understood here as a basic pathogenetic mechanism of malignant transformation. Among further molecular aberrations, mutations in TP73, CREBB genes of the NOTCH family and, less frequently, in additional oncogenes and suppressor genes are found in some cases [3]. The identified molecular aberrations are so far not amenable to targeted therapy.

More recently, a new classification has been proposed based on gene expression analysis in human and murine tumors [4]. This is based on the differential expression of 4 key transcription factors: *achaete-scute homologue 1* (*ASCL1 = ASH1*), *neurogenic differentiation factor 1* (*NeuroD1*), *yes-associated protein 1* (*YAP1),* and *POU class 2 homeobox 3* (*POU2F3*).

Accordingly, the new classification subdivides SCLC types SCLC-A, SCLC-N, SCLC-P, and SCLC-Y. SCLC-I (inflamed gene signature) has been proposed as a further subtype [5]. The delineation of these subtypes and their therapeutic relevance are the subject of current research and debate. Initial data suggest a higher efficacy of immunotherapy in the "inflamed" subgroup.

3 Prevention and early detection

3.1 Prevention

General recommendations for prevention relate to previously identified risk factors and private lifestyle, see lung cancer, non-small cell (NSCLC). Avoidance of smoking is the key preventive measure (WHO Framework Convention on Tobacco Control) [6]. Increased consumption of fruits and vegetables reduces the risk of lung cancer, especially in smokers.

3.2 Early detection

For SCLC, there is no recognized early detection in Europe in terms of national screening programs, see Lung carcinoma, non-small cell (NSCLC). In Switzerland, the Swiss Accident Insurance Fund (SUVA) offers a screening program to insured persons with occupational exposure to asbestos according to the NLST criteria.

4 Clinical characteristics

The clinical symptoms of patients with SCLC are not fundamentally different from those of patients with NSCLC, see lung cancer, non-small cell (NSCLC). Typically, SCLC originates in the central airways and often has a short history of tumor-related symptoms such as dyspnea, cough, or signs of superior Vena cava congestion. A distinctive feature of small-cell lung carcinoma is the more frequent occurrence of paraneoplastic syndromes, most commonly with endocrine disease patterns. Table 1 shows the frequency and distribution of paraneoplastic syndromes in patients with lung cancer. The leading symptom of SIADH (syndrome of inadequate anti-diuretic hormone secretion) is hyponatremia; in ACTH syndrome, the characteristic clinical Cushing's picture is often not fully developed because of the clinically short time of development. Lambert-Eaton syndrome is clinically manifested by weakness of the musculature with dysarthria, dysphagia, and proximal limb paresis. Antibody testing (anti-Hu (ANNA-1, Anti-Neuronal Antibody Type 1), anti-Ri (ANNA-2, Anti-Neuronal Antibody Type 2), anti-CRMP5, anti-Ma1, anti-amphiphysin, and others [7]) can confirm the clinical suspicion of a neurologic paraneoplastic syndrome.

Table 1: Paraneoplastic syndromes in patients with lung cancer [6]

Syndrome /Symptoms	SCLC (% of patients)	NSCLC (% of patients)
SIADH	10	< 0.1
Cushing's (ACTH)	2-4	< 0.1
Lambert-Eaton syndrome	1	< 0.1
Other neuropathies	to 5	< 0.1
Drumstick finger	< 1	5
Osteoarthropathy	< 1	5
Hypercalcemia	< 1	≤ 10

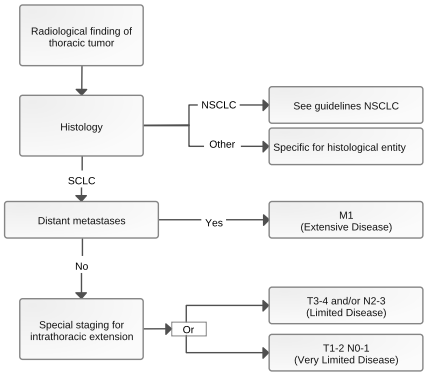
5 Diagnosis

5.2 Diagnostics

5.2.1 Initial diagnosis

The first step is to confirm the suspected clinical and/or imaging diagnosis, see Figure 4.

Figure 4: Diagnostic algorithm for SCLC



Legend:
NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer;

Diagnostic procedures should be performed until metastasis is detected or excluded, and in the absence of metastasis, until TNM criteria are defined, see Table 2.

Table 2: Diagnostics for suspected lung tumor

Procedure	Recommendation
Level 1 Imaging evidence of a thoracic mass	
Chest radiography in 2 planes	
Clinical chemistry	Blood count, electrolytes, uric acid, renal function parameters, liver parameters, LDH, coagulation tests, NSE, and optionally CEA (carcino-embryonic antigen)
CT[1] Thorax / Abdomen with contrast[6] / FDG-PET-CT[7]	First choice method
MRI[2] thorax / upper abdomen with contrast[6]	Alternative to CT[1]
Level 2 Histological or cytological diagnosis	
Bronchoscopy with transbronchial biopsy[3]	At suspect imaging finding
Transthoracic biopsy, mediastinoscopy, thoracoscopy	Optional alternative to obtain tissue samples if bronchoscopy is negative
Level 3 Exclusion of distant metastasis	
CT abdomen or MRI abdomen	Alternatively, sonography of the upper abdomen if there is unequivocal evidence of abdominal metastasis. Alternatively PET-CT, especially in curative approach
Cerebral MRI	Alternatively cerebral CT in case of unequivocal evidence of intracerebral metastasis
Bone scintigram	Alternatively PET-CT, especially in curative approach
Level 4 Detection of intrathoracic tumor spread	
PET-CT[4]	In the case of local option of radiotherapy or surgical resection, to exclude distant metastasis Only when PET-CT is not available, CT thorax/abdomen and bone scintigram are the alternative); PET-positive findings should be confirmed histo- or cytologically if a change the treatment concept would result
EUS / EBUS[5] with biopsy	In potentially resectable tumor with imaging enlargement of N2 lymph nodes (no bulk) to detect / exclude mediastinal lymph node involvement
Mediastinoscopy	In case of potentially resectable tumor with imaging enlargement of N2 lymph nodes (no bulk) to detect / exclude mediastinal lymph node involvement especially in case of negative EUS / EBUS
Pleural puncture	In case of pleural effusion and absence of organ metastasis
Thoracoscopy	in the absence of organ metastasis for the detection of pleuritis carcinomatosa in the case of pleural effusion and negative pleural puncture

Legend:
[1] CT = computed tomography;
[2] MRI = magnetic resonance imaging;
[3] Alternative for peripheral space lesions: brush, needle, or other;
[4] FDG-PET-CT = positron emission tomography with computed tomography;
[5] EBUS = endobronchial or endoesophageal ultrasound with fine needle biopsy;
[6] contrast = intravenous contrast agent;
[7] When there is a high probability of diagnosing NSCLC or SCLC;

FDG-PET-CT imaging upgrades patients from stage LD to ED in a significant percentage. In 8 studies with a total of 138 LD SCLC patients, the stage changed to ED in 29 cases, i.e., an aver-

age of 20% of patients [8]. This justifies performing PET-CT prior to planned curative therapy using simultaneous chemoradiation or surgery [9].

5.3 Classification

5.3.2 Staging

Since January 1, 2017, the new staging according to IASLC/UICC8 is effective [10]. The classification was revised based on data from almost 100,000 patients, including 5,002 patients with SCLC. Results were presented in late 2015/early 2016, see also Lung cancer, non-small cell (NSCLC). Formally, they became effective with the collaboration of IASLC/AJCC and UICC. The description of the TNM stages is summarized in Table 3.

Table 3: Description of TNM stages according to IASLC Lung Cancer Staging Project*

T (Primary Tumor)		**Label**
T0	No primary tumor	
Tis	Carcinoma in situ (squamous or Adenocarcinoma)	Tis
T1	Tumor ≤3 cm	
T1a(mi)	Minimally Invasive Adenocarcinoma	T1a*(mi)*
T1a	Superficial spreading tumor in central airways[a]	T1a*SS*
T1a	Tumor ≤1 cm	T1a*≤1*
T1b	Tumor >1 but ≤2 cm	T1b*>1-2*
T1c	Tumor >2 but ≤3 cm	T1c*>2-3*
T2	Tumor >3 but ≤5 cm or tumor involving:	
	visceral pleura[b],	T2*Visc Pl*
	main bronchus (not carina), atelectasis to hilum[b]	T2*Centr*
T2a	Tumor >3 but ≤4 cm	T2a*>3-4*
T2b	Tumor >4 but ≤5 cm	T2b*>4-5*
T3	Tumor >5 but ≤7 cm	T3*>5-7*
	or invading chest wall, pericardium, phrenic nerve	T3*Inv*
	or separate tumor nodule(s) in the same lobe	T3*Satell*
T4	Tumor >7 cm	T4*>7*
	or tumor invading: mediastinum, diaphragm, heart, greast vessel, recurrent laryngeal nerve, carina, trachea, esophagus, spine;	T4*Inv*
	or Tumor nodule(s) in a different ipsilateral lobe	T4*Ipsi Nod*
N (Regional Lymph Nodes)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral pulmonary or hilar nodes	
N2	Metastasis in ipsilateral mediastinal/subcarinal nodes	
N3	Metastasis in contralateral mediastinal/hilar, or supraclavicular nodes	
M (Distant Metastasis)		**Label**
M0	No distant mestastasis	
M1a	Melignant pleural/pericardial effusion[c]	M1a*Pl Dissem*
	or pleural/pericardial nodules	

	or separate tumor nodule(s) in a contralateral loe;	M1a$_{Contr\ Nod}$
M1b	Single extrathoracic metastasis	M1b$_{Single}$
M1c	Multiple extrathoracic metastases (1 or >1 organ)	M1c$_{Multi}$

Legend:
**after [10]*
TX, NX: T or N status not able to be assessed
[a] *Superficial spreading tumor of any size but confined to the tracheal or bronchial wall*
[b] *such tumors are classified as T2a if>3≤4 cm, T2b if>≤5 cm.*
[c] *Pleural effusions are excluded that are cytologically negative, non-bloody, transudative, and clinically judged not to be due to cancer.*

Categories N1 and N2 are further subdivided into N1a (single-station N1 involvement), N1b (multiple-station N1 involvement), N2a1 (single-station N2 without N1 involvement – “skip”), N2a2 (single-station N2 with N1 involvement) and N2b (multiple-station N2 involvement.

The revised staging is based on the TNM and the UICC 8 criteria [10], see Table 4. Based on the analyses of the IASLC, there is a minimal difference between the staging of SCLC and NSCLC: currently, the old staging from UICC 7 is still maintained for SCLC in M1a and M1b. For a distinction of IVA from IVB, which is to be performed already now, the data were not yet meaningful enough due to too small patient numbers in the subgroups.

Table 4: Classification of SCLC tumor stages according to UICC 8*

T/M	Label	N0	N1	N2	N3
T1	T1a$_{\leq 1}$	IA1	IIB	IIIA	IIIB
	T1b$_{>1-2}$	IA2	IIB	IIIA	IIIB
	T1c$_{>2-3}$	IA3	IIB	IIIA	IIIB
T2	T2a$_{Cent,\ Yisc\ Pl}$	IB	IIB	IIIA	IIIB
	T2a$_{>3-4}$	IB	IIB	IIIA	IIIB
	T2b$_{>4-5}$	IIA	IIB	IIIA	IIIB
T3	T3$_{>5-7}$	IIB	IIIA	IIIB	IIIC
	T3$_{Inv}$	IIB	IIIA	IIIB	IIIC
	T3$_{Satell}$	IIB	IIIA	IIIB	IIIC
T4	T4$_{>7}$	IIIA	IIIA	IIIB	IIIC
	T4$_{Inv}$	IIIA	IIIA	IIIB	IIIC
	T4$_{Ipsi\ Nod}$	IIIA	IIIA	IIIB	IIIC
M1	M1a$_{Contr\ Nod}$	IVA	IVA	IVA	IVA
	M1a$_{Pl\ Dissem}$	IVA	IVA	IVA	IVA
	M1b$_{Single}$	IVA	IVA	IVA	IVA
	M1c$_{Multi}$	IVB	IVB	IVB	IVB

Legend:
**after [10]*

For classification purposes, the division into Limited and Extensive Disease developed by the Veterans Administration Lung Study in 1957 was used for many decades [11], see Table 5.

Table 5: Veterans Administration Lung Study classification

Stage	Description
Limited Disease (LD)	Tumor confined to the initial hemithorax with or without ipsi- or contralateral mediastinal or supraclavicular lymph node metastases* and with or without ipsilateral pleural effusion regardless of cytologic result*.
Extensive Disease (ED)	any spread beyond "limited disease"

Legend:
** supraclavicular lymph nodes and cytologically malignant pleural effusion are also attributed to Extensive Disease stage by some groups.*

This classification was primarily based on the feasibility of radiotherapy. LD is defined as a tumor extent that can be completely detected and irradiated by means of a tolerable radiotherapeutic target volume. An addition is the subdivision of the "limited disease" stage into a "very limited disease" (VLD) group without evidence of mediastinal lymph node involvement and an LD group with mediastinal lymph node involvement.

Although the VA classification is usually sufficient for clinical purposes, the differentiated classification based on the TNM and UICC criteria [10] is now recommended for standardization of staging and because of its more accurate prognostic value, see above. The assignment of TNM features to the Veterans Administration Lung Study classification is summarized in Table 6.

Table 6: Assignment of TNM features to Veterans Administration Lung Study classification [9]

Stages of the Veterans Administration Lung Study	Assignment to TNM classification
Very Limited Disease	T1-2 N0-1
Limited Disease	T3-4 and / or N2-3
Extensive Disease	M1

5.6 General performance and comorbidities

Therapeutic options in patients with lung cancer are often limited by reduced general performance as well as cardiovascular, pulmonary, or other comorbidities, including those related to age. This applies to both curative and palliative therapy. Parameters for assessing operability can be found in Lung cancer, non-small cell (NSCLC).

For objective assessment of general condition, the use of geriatric assessment instruments is recommended for elderly patients, see Geriatric Assessment Knowledge Base. Tests for objectifying mobility and comorbidity are particularly suitable. The indication to perform further tests is based on the clinical impression and the planned treatment.

6 Therapy

6.1 Treatment structure

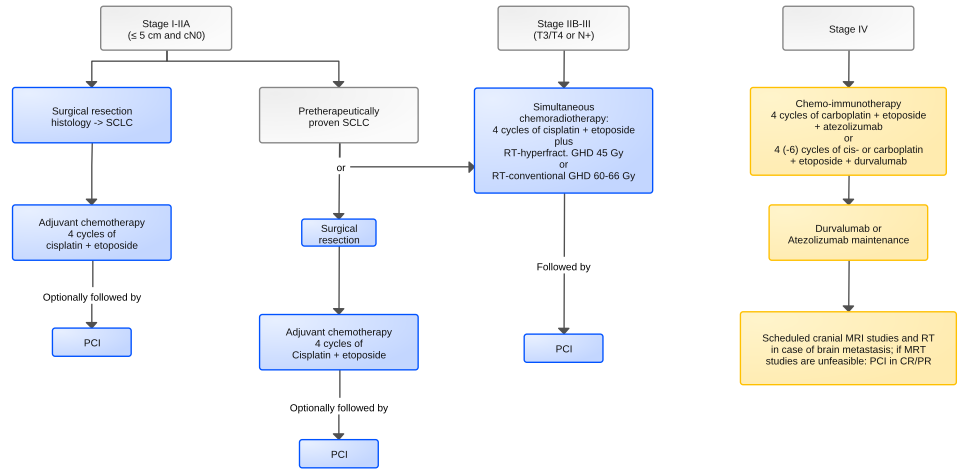
6.1.1 First-line therapy

The therapy recommendations are based on the UICC staging. However, the conventional classification into Very Limited, Limited and Extensive Disease will be continued in the description of therapy options, as clinical studies have generally been performed on the basis of this classification and it therefore represents the basis of therapy recommendations.

The most effective form of treatment for small-cell lung cancer is systemic drug therapy (chemotherapy and immunotherapy). In combination with surgery and/or radiation, treatment intent of limited disease is curative; in extensive disease, in addition to palliative symptom improvement, a significant prolongation of survival is now achieved for some patients.

An algorithm for primary therapy is shown in Figure 5. Whenever possible, patients should be treated in the framework of clinical trials.

Figure 5: Treatment structure for small-cell lung cancer (SCLC)



Legend:
curative intention, palliative intention.
SCLC = small-cell lung cancer, OP = surgery, PCI = prophylactic cranial irradiation; RT = radiation (radiotherapy); GHD = total therapeutic dose, hyperfraction RT = hyperfractionated radiotherapy 2 x daily, RT-conventional = conventional fractionated radiotherapy 1 x daily, Gy = Gray, CR = complete remission, NC = no change, PR = partial remission, MRI = magnetic resonance imaging.

6.1.1.1 Stage I-IIA (Very Limited Disease, VLD)

Approximately 5% of patients with SCLC are diagnosed in stages I and IIA (tumors less than 5 cm in size without lymph node involvement). In most cases, these are patients who undergo surgery for an incidental finding of a peripheral round tumor and histology shows the presence of SCLC. An analysis of the US National Cancer Database evaluated 1574 patients who were followed-up in various ways after such resection [12]. After surgery alone, 5-year survival rates were 40% (n=388), after additional adjuvant chemotherapy it was 52% (n=544), and after additional prophylactic cranial irradiation (PCI) nearly 70% (n=99). Mediastinal radiotherapy did not yield any further survival benefit. Based on the retrospective data, adjuvant chemotherapy with 4 cycles of cisplatin/etoposide can be recommended after surgical resection; the evidence of a PCI benefit is limited due to the small number of cases and possible patient selection.

The database analysis by Raman et al [13] examined the extent of resection required in a total of 1948 stage T1-2N0 SCLC cases undergoing surgical resection. These patients underwent either wedge resection (n=609), segmental resection (n=96), or lobectomy (n=1233). Patients were 75% stage IA, 10% stage IB, and 15% stage II. Adjuvant chemotherapy was given to 35% of patients, and 10% received additional cranial irradiation. Five-year survival rates were 31% and 35% for wedge resection and segmental resection, respectively, and were significantly higher for lobectomy at 45%. Thus, if primary surgery is performed, it should be in the form of lobectomy with systematic lymphadenectomy.

If stage VLD SCLC is detected via classical diagnostics prior to initiation of therapy, combined simultaneous radiochemotherapy is an alternative to primary surgery with adjuvant therapy.

This treatment modality and its results will be discussed in detail in chapter 6.1.1.2.

Unfortunately, there are no stage-specific randomized comparisons between the two treatment modalities of surgery or concurrent radiochemotherapy. Two older clinical trials randomized patients between surgery followed by radiotherapy or radiotherapy alone after neoadjuvant chemotherapy alone. No difference between arms was observed in 146 or 69 randomized patients, respectively. In case series and phase II trials, 5-year survival rates of 50-70% were observed for such a neoadjuvant therapy strategy in patients with stage N0 and between 35-40% for patients with N1.

The value of prophylactic cranial irradiation is not established in stages N0-1. However, registry data suggest an increase in 5-year survival by adjuvant PCI after surgical resection. Its use must be discussed on a case-by-case basis.

6.1.1.2 Stage IIB and III (Limited Disease, LD)

Approximately one-third of patients with SCLC are first diagnosed in the Limited Disease stage (tumors with T3 or T4 features or N1/N2/N3 involvement). In this case, there is a curative therapeutic claim. The 5-year survival rates are in the range of 30-35%. The standard of care is simultaneous combined radiochemotherapy.
Most effective chemotherapy is the combination of cisplatin and etoposide over 4 cycles. Cisplatin/etoposide can be used concurrently with radiotherapy without dose restriction with tolerable side effect profile. Cisplatin has a well-documented radiosensitizing effect; fewer data are available on carboplatin. The standard dose of cisplatin should be 75-90mg/m^2 on day 1, but can be divided to 25-30 mg/m^2 day 1-3 for better tolerability. In cisplatin-unfit patients, carboplatin is an alternative. Radiotherapy should be started no later than the start of the third cycle. Possible radiotherapy options include hyperfractionated, accelerated radiotherapy with 1.5 Gy twice daily up to a total dose of 45 Gy (up to 60 Gy in phase II trials) or conventionally fractionated, once-daily radiotherapy with 1.8 to 2.0 Gy ED and a total dose of up to 66 Gy. A randomized comparison of these two options yielded no significant difference in the CONVERT trial by Faivre-Finn et al [15], in which the 3-year survival rate was 43% for hyperfractionated RT and 39% for conventional RT. The CALGB study by Bogart et al [16] also showed no significant differences. 638 patients received either concurrent chemoradiation therapy with twice daily RT up to 45 Gy or once daily RT with a GHD of 70 Gy. 60% received radiotherapy using the IMRT technique. Radiotherapy was started with the first cycle of chemotherapy in 45% of patients, and cisplatin was used as the chemotherapy base in 81%. The median survival was just under 2.5 years, and the five-year survival rate was 29% in the twice-daily radiation arm and 34% in the once-daily radiation arm. The rate of adverse events was not different; esophageal complications occurred in 17% of patients.

Dose-escalated hyperfractionated radiotherapy with twice daily hyperfractionated RT up to 60 Gy was used in the randomized phase II trial by Grønberg et al [16]. A total of 176 patients were treated, and two-year survival rates were 74% with 60 Gy compared with 48% with 45 Gy. The most common side effects were hematologic with neutropenia in 80% of cases. Neutropenic infection was seen in 27%. The esophagitis rate was 21 vs. 18%. In both treatment arms, three patients died from treatment-related complications. The concept is currently not a standard approach, and a validation in a randomized phase III trial is pending.

An overview of the results of randomized trials comparing conventional vs. hyperfractionated radiotherapy is shown in Table 7 below.

Table 7: Controlled trials of simultaneous chemoradiotherapy for locally confined SCLC

Authors	n	Therapy	3-year OS	5-year OS
Turrisi [14]	206	RT 45 Gy, 1.8 Gy x 25	33%	16%
	211	RT 45 Gy, 2 x 1.5 Gy x 15	27%	26%
Faivre-Finn CONVERT [15]	270	RT 66 Gy, 1 x 2 Gy x 33	39%	27%
	273	RT 45 Gy, 2 x 1.5 Gy x 15	43%	33%
Bogart CALGB [16]	325	RT 70 Gy, 1 x 2 Gy x 35	44%	34%
	313	RT 45 Gy, 2 x 1.5 Gy x 15	42%	29%
Grønberg [17]	89	RT 60 Gy, 2 x 1.5 Gy x 20	66% (2 years)	42% (4 years)
	81	RT 45 Gy, 2 x 1.5 Gy x 15	39% (2 years)	28% (4 years)

Legend:
RT = radiotherapy, Gy = Gray, OS = overall survival

Immunotherapy in combination with simultaneous chemoradiotherapy

The concept is currently being tested in several studies. So far, there are insufficient data on the side effect profile and also on the efficacy in LD-SCLC, so that the addition of immunotherapy to simultaneous chemoradiotherapy has not yet been established.

Immunotherapy maintenance after simultaneous chemoradiotherapy

The Stimuli trial by Peters et al [18] randomized LD-SCLC patients after concurrent chemoradiation therapy in the absence of progression to maintenance therapy with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for 4 administrations and then continuation of nivolumab therapy for 1 year vs observation. In a total of 153 patients, the rate of progression-free survival at two years was 40% in the nivolumab-ipilimumab arm and 43% in the placebo arm. Survival at three years was also no different, with 49% in the immunotherapy arm and 51% in the observation arm. Immunotherapy caused an SAE in 96% of patients, and grade 3/4 adverse events were observed in 61% of patients. 5% of patients (4 patients) died from complications. Immunotherapy had to be discontinued in 55% of patients due to toxicities.

Therefore, maintenance therapy with nivolumab and ipilimumab after simultaneous chemoradiotherapy for SCLC is currently not a therapeutic option. The high discontinuation rate limits the conclusion on the efficacy of the therapy to a considerable extent. The results of PD(L)-1 antibody maintenance alone in stage LD have not yet been published.

Details on simultaneous chemoradiotherapy

Simultaneous chemoradiotherapy is superior to the sequential approach and is therefore the preferred treatment option. Therefore, a sequential approach should only be used in individual patients with contraindications to simultaneous chemoradiotherapy.

Carboplatin-based adjuvant chemoradiotherapy protocols have not been adequately tested and should therefore be used here only in patients with clear contraindications to cisplatin. Initial chemotherapy with carboplatin and etoposide followed by consolidative radiotherapy may be a therapeutic option for patients in significantly impaired general condition, if standard therapy with cisplatin and etoposide is not feasible.

Another possible treatment option is simultaneous hyperfractionated chemoradiotherapy with cisplatin/etoposide in the first cycle and parallel RT with 2x1.5 Gy per day starting on the first day of treatment up to a total therapeutic dose (GHD) of 45 Gy and switch to the combination

cisplatin/irinotecan for the further three cycles of chemotherapy alone. This approach is equivalent to the standard approach with continuation of cisplatin/etoposide [19].

Administration of anthracycline-containing protocols should be avoided in the setting of concurrent chemoradiation therapy due to poorer efficacy and higher toxicity. Similarly, dose intensification approaches are not recommended outside of trials.

6.1.1.3 Prophylactic cranial irradiation (PCI) in stage LD

Prophylactic cranial irradiation reduces the risk of brain metastases from 40% in non-irradiated patients to less than 10% in cranial irradiated patients and improves 5-year survival by 5% [20].

PCI is therefore an established therapeutic component for patients after simultaneous chemoradiotherapy.

PCI may cause cognitive impairment. Several studies have therefore attempted to reduce this side effect by omitting the hippocampus. A Spanish study by Rodríguez de Dios et al [21] included 150 patients, 75 received classical PCI with 25 Gy in 10 fractions and the other half received the same PCI with hippocampus sparing. Here, better protection of neurocognitive function could be demonstrated by hippocampal sparing. The rates of significant impairment were 8.7% vs 20.6%. A second study from the Netherlands by Belderbos et al [22] included 168 patients. Again, 25 Gy was used in 10 fractions with and without hippocampal sparing. Here, the rates of significant neurocognitive impairment were 29% vs 28% and thus not different. In both studies, the rate of subsequent emergence of brain metastases was not different and survival was also the same.

Thus, hippocampal sparing does not reduce the efficacy of PCI and does not worsen survival. However, the effect on reducing neurocognitive impairment is not clearly established.

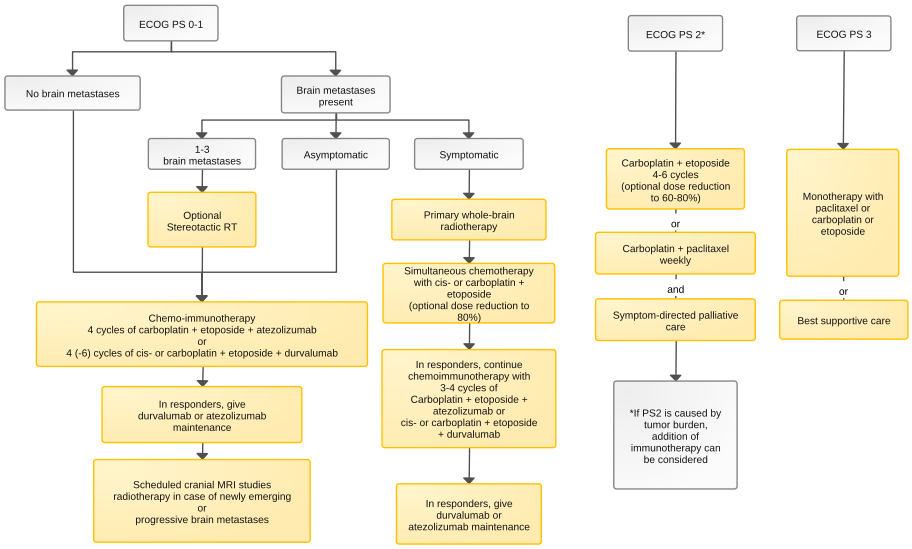
6.1.1.4 Extensive Disease (ED)

60-70% of patients with SCLC are first diagnosed in the Extensive Disease stage. Systemic chemotherapy plus immunotherapy is the standard of care. In addition to improving symptom control and thus quality of life, it leads to a significant prolongation of survival. With chemo-immunotherapy, the median survival of ED patients is approximately 12 months, 2-year survival is 20-25%, and 3-year survival is 15-20%. Thus, the addition of immunotherapy has tripled the 3-year survival rates of patients compared to chemotherapy alone.

Systemic drug treatment in ED

An algorithm for the selection of chemo-immunotherapy in stage IV is shown in Figure 6.

Figure 6: Algorithm for first-line therapy in stage IV SCLC



Legend:
palliative intention
[1] ECOG PS = classification of general condition
[2] the interval between chemotherapy cycles should be 3 weeks
[3] in patients with symptomatic brain metastases, monitoring of response should be performed after completion of cranial RT and at the latest after 2 cycles of chemotherapy

The recommendation for therapy management in patients with brain metastases is based on retrospective data on the efficacy of stereotactic radiotherapy and on subgroup analyses of first-line trials of combined immunotherapy. Therefore, these recommendations are not supported by prospective controlled trials.

The results for systemic therapy in Extensive Disease can be summarized as follows:

- Chemotherapy in SCLC
  - Platinum-containing regimens achieve significantly higher complete remission rates than non-platinum combination therapies. With respect to overall survival, results from meta-analyses are inconsistent. In one meta-analysis of 5,530 patients, no significant difference was found in survival rates at 6, 12, or 24 months [23].
  - When selecting the platinum agent, the majority of studies show slightly higher efficacy of cisplatin compared with carboplatin. In a meta-analysis based on individual data, cisplatin and carboplatin were equieffective and remission rates were equal. The side effect profile of carboplatin is more favorable. The two platinum derivatives are equivalent in the treatment of stage ED SCLC.
  - Achievement of the full platinum target dose is an important prognostic factor.
  - The combination of cisplatin / etoposide achieves remission rates of 60-70% in patients with extensive disease.
  - In platinum-containing combination therapy, irinotecan and etoposide are equieffective in patients in Central Europe and North America.
  - In platinum-containing combination therapy, topotecan and etoposide are also equieffective in patients in Central Europe and North America. Topotecan can be administered intravenously or orally.
  - Anthracycline-containing protocols such as ACO or ACE (doxorubicin or epirubicin plus cyclophosphamide / vincristine or etoposide) are effective but are no longer used in primary therapy because of anthracycline-associated cardiotoxicity, possibly intensified by additional radiotherapy.
  - Dose escalation increases remission rates but does not prolong overall survival.

- Polychemotherapy with addition of ifosfamide and anthracyclines or taxanes to platinum/etoposide increases the remission rate and slightly prolongs survival, but is associated with significantly higher toxicity. These combination therapies are therefore no standard protocols.
- Alternating administration of different combination therapies also does not improve survival compared with sequential therapy.

- Immunotherapy in SCLC
  - Results of several randomized phase III trials comparing chemotherapy alone vs. chemotherapy plus immunotherapy are now available.
  - The addition of ipilimumab (anti-CTLA-4 antibody) alone did not prolong patient survival [24].
  - The IMpower133 trial [25] randomized 403 patients to either carboplatin/etoposide alone or the same regimen plus the PD-L1 antibody atezolizumab. Remission rates were not different (60% vs. 64%), but the 12-month PFS rate was significantly higher in the atezolizumab arm, 12.6% vs. 5.4%. Median survival was significantly prolonged by 2 months from 10.3 to 12.3 months (hazard ratio 0.76). The 2-year survival rates were 22% vs. 18%. Longer follow-up is not available.
  - In the CASPIAN trial [26], the anti-PD-L1 antibody durvalumab in combination with platinum/etoposide versus platinum/etoposide also resulted in an increase in overall survival from 10.3 to 13.0 months (hazard ratio 0.73). The 2-year survival rates were 22% vs. 14%. CASPIAN is the only study with available 3-year survival rates. These were 18% vs. 6%.
  - The addition of tremelimumab as a CTLA-4 antibody did not improve patient survival in the CASPIAN trial.
  - The Keynote 604 trial [27] studied pembrolizumab added to platinum and etoposide. While the difference was not significant according to the statistical approach of the trial, the 2-year survival rates were 23% vs. 11% (HR 0.80, p=0.016).
  - The ASTRUM-005 trial [28] tested the PD-1 antibody serplulimab in combination with platinum + etoposide. A total of 585 patients *from China* were enrolled. Median survival was significantly prolonged at 15.4 vs. 10.9 months. 2-year survival data are not yet available at short follow-up.
  - The phase III CAPSTONE-1 trial, also only recruiting Chinese patients [29], showed an OS benefit for the anti-PD-L1 antibody adebrelimab in combination with carboplatin/etoposide compared with chemotherapy alone (15.3 months vs. 12.8 months; HR 0.72).
  - All studies with PD-(L)-1 addition thus show a clear advantage for immunotherapy, so that the combination is now standard in first-line therapy.
  - Atezolizumab is approved in combination with carboplatin and etoposide, and durvalumab is approved in combination with cisplatin or carboplatin plus etoposide for first-line therapy. In the CASPIAN trial, the addition of durvalumab to cisplatin/etoposide was 10% more effective compared with carboplatin/etoposide. Whether selection effects or interaction contribute to this is not clear from this setting. According to the approval, the duration of treatment is not limited; the combination of chemotherapy and immunotherapy should be administered over 4 to 6 cycles, after which immunotherapy is continued until progression.
  - The study results for primary combined chemo-immunotherapy are shown in Table 8.

Table 8: Controlled trials of combined chemo-immunotherapy in advanced SCLC

Study	Arm	n	RR	PFS (mo)	HR PFS	OS (mo)	OS 24 mo	OS 36 Mo	HR OS
IMpower133 [25]	Atezolizumab	201	60	5.2	0.72	12.3	22%		0.76
	Placebo	201	64	4.3	0.62- 0.96	10.3	18%		0.6 – 0.95
CASPIAN [26]	Durvalumab	268	68	5.1	0.80	12.9	22%	18%	0.75
	Placebo	269	58	5.4	0.70 – 1.01	10.6	14%	6%	0.68-1.00
KEYNOTE- 604 [27]	Pembrolizumab	228	71	4.5	0.75	10.8	23%		0.80 n.s.
	Placebo	225	62	4.3	0.61 – 0.91	9.7	11%		0.64 – 0.98
ASTRUM-005 [28]	Serplulimab	389	80	5.7	0.46	15.4			0.49 – 0.82
	Placebo	196	70	4.3	0.38 – 0.59	10.9			
CAPSTONE-1 [29]	Adebrelimab	230	70.4		0.67	15.3			0.72
	Placebo	232	65.9			12.8			

Legend:
n = number of patients, RR = remission rate, PFS = progression-free survival, OS = overall survival, mo = months, HR = hazard ratio, n.s. = not significant

Patients with CNS metastases

The efficacy of systemic chemotherapy is lower intracerebrally than outside the central nervous system. In early studies, chemotherapy alone was associated with shorter survival compared with additional radiotherapy.

Thus, as a rule, there is an indication for additional radiotherapy when intracerebral metastasis is detected. The extent and timing of additional local therapy have come under discussion due to recent study results.

The FIRE study [30] is a case collection of 710 patients with brain metastases from SCLC treated by stereotactic radiotherapy. In one third of patients each, 1 or 2-4 or more than 4 brain metastases were present. Median OS times were 11 months, 8.7 months, and 8.0 months in the respective groups. New brain metastases developed in 55% of patients with initially one metastasis and 70% of patients with multiple brain metastases. A matched-pair analysis with patients undergoing whole-brain irradiation (187 vs. 178 patients) showed an overall survival advantage for patients with stereotactic radiotherapy, although the intracerebral recurrence rate of approximately 60% was twice as high as after whole-brain radiotherapy at 30%.

Stereotactic radiotherapy alone was associated with significantly less neurocognitive impairment compared with stereotaxy plus whole-brain radiotherapy in patients with 1-3 brain metastases of different etiologies (60% lung carcinomas) [31].

Whole-brain radiotherapy can also be performed in the form of hippocampus-sparing irradiation in patients without metastases in the hippocampal region. The NRG study [32] showed less neurocognitive impairment with the same efficacy and survival in over 500 patients with brain metastases of different etiologies (60% lung carcinomas).

In the IMpower133 study, patients with brain metastases did not benefit from atezolizumab administration, and in the KEYNOTE-604 study, patients with brain metastases were even more likely to have a disadvantage in the pembrolizumab group. In CASPIAN, progression-free survival was identical in patients with and without brain metastases; median survival was more

favorable for the durvalumab group (8.7 vs. 11.8 months), but the curves converge again during progression.

While IMpower133 and KEYNOTE-604 included pretreated (usually irradiated) and stable brain metastases, 90% of patients with brain metastases were not pretreated in CASPIAN.

Both atezolizumab and durvalumab did not reduce the incidence of new brain metastases. Approximately 15% of patients without initial brain metastases developed new brain metastases during the course of therapy.

Among patients with brain metastases in CASPIAN, 3 patients in the durvalumab arm and 4 patients in the durvalumab plus tremelimumab arms achieved 3-year survival, whereas this was not seen in any patient with chemotherapy alone [32].

Therefore, performing combined chemo-immunotherapy and initially foregoing additional radiotherapy is an option in asymptomatic patients, as is stereotactic radiotherapy in patients with a limited number of brain metastases. Symptomatic patients with multiple intracerebral lesions, on the other hand, should receive early whole-brain radiation.

Elderly patients and patients with performance score 2

In older patients in good general condition, the results are comparable to those in younger patients. Thus, age per se does not represent a negative prognostic parameter. Poorer efficacy of immunotherapy in patients of older age has not been proven so far. The higher hematologic toxicity of therapy in older patients, which requires dose adjustments, should be noted.

Only patients with performance score (PS) 0 and 1 were included in the trials of combined chemo-immunotherapy. Whether PS2 patients benefit from the addition of immunotherapy is unclear. Further studies are needed in this patient subgroup. The approval does not exclude PS2 patients. In the case of PS2 due to tumor burden, the administration of additional immunotherapy is warranted despite the lack of study data.

In patients in reduced general condition due to significant comorbidity, purely symptom-oriented therapy or, at most, monotherapy with a chemotherapeutic agent is recommended. Mono-immunotherapy has not been tested and should not be used.

Predictors of immunotherapy efficacy

Predictors for the efficacy of immunotherapy have not yet been adequately defined. Tumor cells in SCLC rarely express PD-L1, more often immune cells in the environment of the tumor are positive.

PD-L1 expression was not predictive of PD-L1 antibody efficacy in either IMpower133 or CASPIAN; in fact, in IMpower133, PD-L1 negative patients tended to benefit more from atezolizumab.

In CASPIAN, PD-L1 positivity and the HLA type DQB1*03:01 were favorable parameters for achieving 3-year survival with durvalumab plus tremelimumab. For durvalumab administration alone, HLA type DQB1*03:01 was not predictive.

Tumor mutational burden was also not a predictive factor for PD-L1 antibody efficacy in either IMpower133 or CASPIAN.

- Maintenance therapy
    - Maintenance therapy with cytostatic drugs or other agents does not prolong survival [33].

- After combined chemo-immunotherapy, immunotherapy should be continued as maintenance until progression or intolerance.
- Starting immunotherapy only after completion of induction chemotherapy is not very effective. The corresponding maintenance therapy study CheckMate-451 [34] with nivolumab and nivolumab plus ipilimumab vs. placebo in patients without progression after 4 cycles of platinum/etoposide failed to show any benefit. In a total of 854 patients, neither nivolumab alone nor the combination of nivolumab plus ipilimumab significantly prolonged survival.

- Implementation of therapy and duration of therapy
  - Response to chemotherapy and immunotherapy can be assessed after 2 cycles of therapy. In case of response, the combination therapy should be performed for a total of 4 cycles. In case of good tolerability and expected further clinical benefit, an extension up to 6 cycles with subsequent immune maintenance therapy can be considered.
  - In the absence of response to first-line therapy, the prognosis is very unfavorable. An early switch to second-line therapy can be made. Inclusion in clinical trials of innovative therapeutic concepts is recommended.
  - An important negative prognostic biomarker is an elevated serum lactate dehydrogenase (LDH).
  - Tumor lysis syndrome may occur or be exacerbated at the start of chemotherapy.

6.1.1.5 Local therapeutic procedures in stage IV (ED) SCLC

- In patients without primary chemo-immunotherapy, thoracic radiotherapy consolidation did not significantly improve overall survival (hazard ratio 0.84; p=0.066) in patients without progression after first-line therapy in a randomized EORTC trial [35]. However, it did increase the 2-year survival rate from 3% to 13%. Female patients aged less than 70 years with thoracic residual tumor had particularly benefited from radiotherapy consolidation.
- In the case of primary use of combined chemo-immunotherapy, consolidative primary tumor irradiation has not been tested. This was not included in either IMPOWER-133 or CASPIAN. Whether consolidative radiotherapy increases long-term survival in patients with residual thoracic tumor and very good remission of distant metastasis, even with primary use of combined chemo-immunotherapy, is unclear. Given the expected thoracic and pulmonary toxicity with ongoing immune maintenance therapy, this approach is not a standard procedure and should be restricted to clinical trials.
- There are different study results on prophylactic cranial irradiation in extensive disease SCLC. In the EORTC study [36] in patients without progression after first-line therapy and without clinical signs of brain metastasis, PCI improved overall survival compared with observation (hazard ratio 0.68; median 1.3 months). However, systematic cranial MRI controls were not performed in this study, and cranial irradiation was initiated in the control arm only when clinical symptoms of CNS involvement were present. Second-line chemotherapy was given to only 45% of patients in the non-PCI arm vs. 68% in the PCI arm; data on the proportion of patients undergoing cranial irradiation in the control arm are lacking.
- A randomized Japanese trial [37] included only patients without MRI-based evidence of brain metastases. Here, cranial MRI follow-up was performed every 3 months in the control arm and cranial irradiation was initiated if there was imaging evidence of brain metastases. In this study, 89% of non-PCI patients received second-line chemotherapy, and of 51 patients with new-onset brain metastases, 81% were treated with radiotherapy

or surgery. There was a slight, statistically nonsignificant survival disadvantage from PCI in this study, with a median of 11.6 vs. 13.7 months (hazard ratio 1.27; p=0.094).

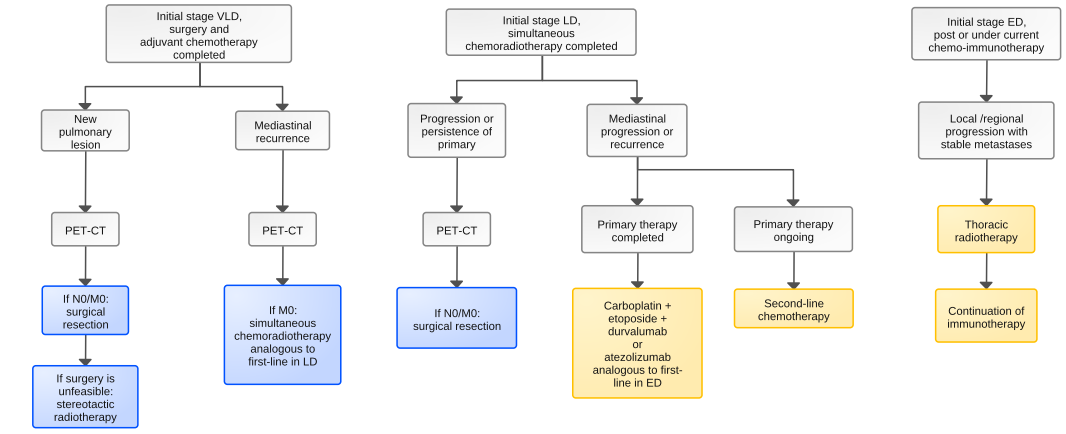
- Therefore, omitting PCI combined with regular cranial MRI follow-up is the usual and most commonly used approach. If regular MRI checks are not feasible, PCI can be discussed with the patient.

6.1.2 Second-line therapy

The indication and selection of second-line therapy in SCLC is based on stage, general condition and comorbidity, prior therapy, and the time of re-progression or therapy-free period. The algorithm is shown in Figure 7 and Figure 8, distinguishing between local progression (Figure 7) and systemic progression (Figure 8).

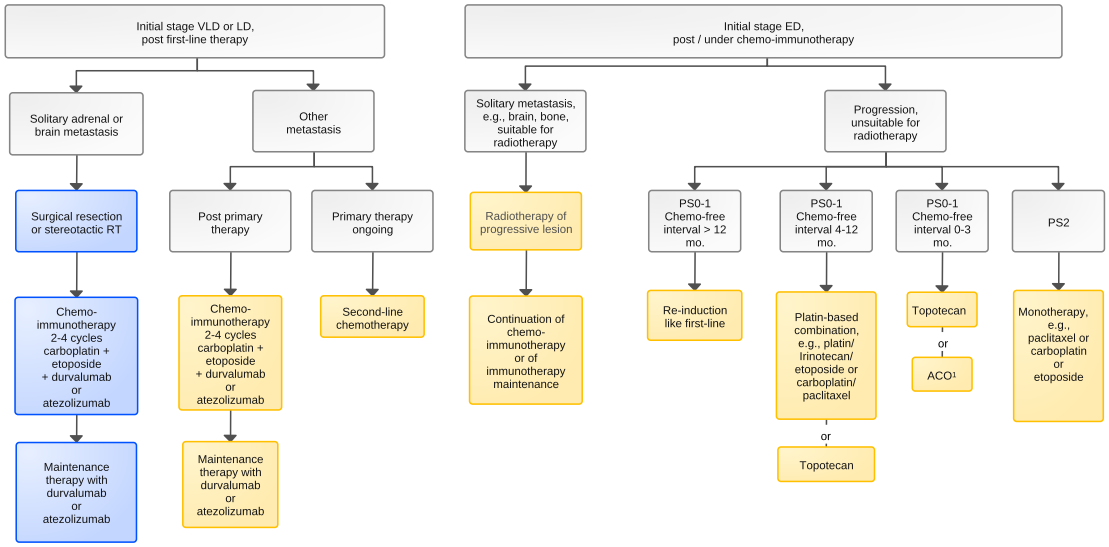
Especially for the setting of local recurrence, only retrospective analyses, case compilations, and clinical experience are available. Therefore, the recommendations are not backed-up by prospective studies, but represent a clinically feasible approach.

Figure 7: Algorithm for therapy of recurrent SCLC - part 1: local progression / recurrence



Legend:
curative intention, palliative intention.
** Thoracic irradiation during ongoing immunotherapy has not been appropriately studied to date. A possible higher risk for pulmonary toxicities has to be considered.*

Figure 8: Algorithm for therapy of recurrent SCLC - part 2: disseminated progression



Legend:
curative intention, palliative intention.
[1] Therapy regimens: ACO = doxorubicin/epirubicin, cyclophosphamide, vincristine;
Note: the optional recommendation for surgical resection or stereotactic radiotherapy of an isolated adrenal or cerebral metastasis is based on individual case reports and clinical experience. It is not supported by prospective studies or case series with larger numbers of patients.

6.1.2.1 Local and regional progression - second-line therapy

If patients develop a second intrapulmonary tumor after surgical resection and adjuvant chemotherapy, the possibility of a second primary with a different histology must be considered. In case of a new nodular lesion without lymph node involvement or distant metastasis (by PET-CT and further mediastinal staging if appropriate), another primary resection can be considered. If again histologically SCLC is evident, it is unclear whether repeat adjuvant chemotherapy will be beneficial.
If surgical resection is not performed, histologic confirmation should be sought pre-therapeutically. If SCLC histology is proven pre-therapeutically, simultaneous chemoradiotherapy can be performed as an alternative to surgery. If histology is different, histology- and stage-specific therapy should be initiated.

If patients develop a locoregional recurrence with mediastinal lymph node involvement after surgical resection and adjuvant chemotherapy, simultaneous chemoradiotherapy can be performed after histologic confirmation and exclusion of distant metastasis by PET-CT, analogous to the procedure for LD.

If complete remission of lymph node involvement is achieved in stage LD after simultaneous chemoradiotherapy, but the primary tumor persists or shows local progression again, surgical resection of the primary tumor may be considered in individual cases. Prior to this, PET-CT and, if appropriate, further mediastinal staging should be performed to exclude N2 or N3 involvement, as well as cranial MRI to exclude cerebral metastasis. A pneumectomy should be avoided. Stereotactic radiotherapy may also be considered in individual cases.

If locoregional recurrence with mediastinal lymph node involvement occurs after completion of concurrent chemoradiation therapy, systemic therapy with chemotherapy and immunotherapy analogous to first-line therapy in stage ED is recommended.

If local progression is observed in primary metastatic disease with stable distant metastasis, local irradiation of the progressive tumor can be performed. In this case, chemo-immunotherapy or immunotherapy can be continued initially and a switch to second-line chemotherapy can

be made if systemic progression is observed again. It should be noted that primary tumor irradiation during ongoing immunotherapy has not been studied in larger trials and may cause a higher risk of pulmonary toxicity.

6.1.2.2 Systemic progression - second-line therapy

If a solitary adrenal or brain metastasis occurs as a recurrence after the initial stage VLD or LD, there is an option of local therapy. In the case of an adrenal metastasis, this can preferably be performed as a resection, and in the case of a brain metastasis, it can preferably be performed as stereotactic radiotherapy. Whether subsequent systemic chemotherapy improves the prognosis is unclear. Given the metastatic disease situation now present and the positive data on chemo-immunotherapy, additional chemo-immunotherapy analogous to primary therapy in stage IV is recommended.
As an alternative to a local approach followed by systemic chemo-immunotherapy, the latter can also be used primarily. Prospective studies on the value of the local approach are not available, the optional recommendation is based on individual case reports and clinical experience.

In case of disseminated progression or relapse, second-line systemic therapy is indicated in patients with ECOG PS 0-2 and those with disease-related ECOG PS 3. It results in symptom relief and prolongation of survival. Depending on the timing of re-progression, a distinction can be made between sensitive progression with freedom from therapy of more than 90 days and refractory progression with freedom from therapy of less than 90 days. This distinction is prognostically relevant and may have an impact on the choice of second-line therapy. The later the progression or relapse occurs, the more effective the second-line therapy and the longer the survival benefit can be expected.

The results for systemic therapy in Extensive Disease can be summarized as follows:

- Second-line chemotherapy in ED-SCLC
    - Drugs with proven efficacy in the second-line setting include topotecan, irinotecan including the nanoliposomal formulation, paclitaxel, ifosfamide, anthracyclines (including amrubicin), and lurbinectedin.
    - A randomized trial compared topotecan vs. best supportive care [38]. Topotecan resulted in a significant prolongation of survival from 14 to 26 weeks. The benefit was seen in both sensitive and refractory relapse. Oral and intravenous administration of topotecan are equivalent.
    - Topotecan is the only therapy currently approved specifically for the second-line treatment of SCLC and has therefore been used in trials as the standard of care in the comparator arm.
    - In a study comparing cisplatin/etoposide/irinotecan vs. topotecan in patients with sensitive recurrence [39], combination therapy prolonged median survival from 12 to 18 months, but without achieving long-term survival beyond 3 years, and with significantly higher toxicity.
    - Similarly, in the French study by Baize et al [40], an advantage for repeat therapy with carboplatin/etoposide over topotecan was observed in patients with sensitive recurrence and more than 90 days off therapy before relapse.
    - Orther studies showed no superiority for the ACO protocol and for single agents such as amrubicin, lurbinectedin, and nanoliposomal irinotecan compared with topotecan therapy.
    - The Atlantis study [41] comparing adriamycin plus lurbinectedin vs. topotecan or ACO in the control arm in 600 patients also showed no advantage for the combination. The preceding therapy-free interval had to be at least 30 days. Median sur-

vival was 8.6 months in the lurbinectedin arm and 7.6 months in the control. The survival curves were almost identical.

- The RESILIENT trial comparing nanoliposomal irinotecan vs. topotecan in 450 patients also showed no advantage for the nanoliposomal encapsulated agent [42].

- Second-line immunotherapy in ED-SCLC
  - The administration of immunotherapy in the second-line setting has achieved remission rates of approximately 12% in phase II trials (CheckMate-032) [43], but has not been successful in randomized trials. In the CheckMate-331 trial, there was no difference between nivolumab vs. topotecan in progression-free and overall survival in the overall population [44].
  - Due to the use of first-line immunotherapy, second-line immunotherapy is no longer important today.
- Targeted substances
  - Antiangiogenic agents are not indicated in either first- or second-line settings after negative studies of aflibercept, bevacizumab, thalidomide, vandetanib, and others.
  - Furthermore, negative randomized phase II studies are available on mTOR inhibitors, HDAC inhibitors, BCL-2 antisense agents and PARP inhibitors.
  - The maintenance therapy trial with the PARP inhibitor niraparib showed no difference in either progression-free survival or overall survival between the two treatment arms.
  - Studies with rovalpituzumab tesirine (Rova-T), a drug conjugate directed against DLL-3, were also negative. TAHOE [45] included 442 patients and compared topotecan with Rova-T in DLL3 high-positive metastatic SCLC. Median survival was 6.3 months in the Rova-T arm and 8.6 months in the topotecan arm. The HR was 1.46. As a result, the study was terminated early. MERU [46] randomized 748 patients to Rova-T maintenance therapy or placebo after completion of chemotherapy and lack of progression. Again, the Rova-T arm tended to be less favorable than the placebo arm with a median of 8.5 vs 9.8 months. The drug was also associated with a higher rate of treatment-related adverse events, including pleural effusions in nearly 30% of patients, peripheral edema, and photosensitivity reactions.
  - Combinations of Rova-T with nivolumab with/without ipilimumab achieved remission rates of 30%, but were associated with high toxicities, leading to discontinuation of the studies.
  - A newer compound under investigation is AMG-757 (Tarlatamab), a bispecific antibody (BiTE molecule) that binds to DLL-3 on the surface of small-cell tumor cells on the one hand and to CD 3 on cytotoxic T cells on the other. The compound was used in 66 patients [47] and achieved a response rate of 20% in a heavily pretreated patient population. Main side effects were the occurrence of CRS (cytokine release syndrome) in 44% of patients. Further studies are currently ongoing in this regard.
- Indication for therapy and differential therapy
  - In PS 0-1 patients, the use of repeat combination treatment in the second-line setting is warranted after outweighing the treatment goals against therapy-associated toxicity.
  - If progression occurs after a therapy-free period of more than (6-) 12 months, the first-line regimen can be used again.
  - With a therapy-free interval of 4-12 months, combination of cisplatin/irinotecan and etoposide can be used (see study results). Alternative combinations include cis- or carboplatin with irinotecan or topotecan, but also carboplatin with paclitaxel.

Repeat therapy with carboplatin/etoposide is also an option. Platinum-free combinations include ACO or AIO (adriamycin, ifosfamide, vincristine) or ACE (adriamycin, cyclophosphamide, etoposide).

- In cases of treatment refractoriness with progression during therapy or within 3 months after the end of therapy, topotecan is the only substance tested with an advantage over best supportive care. In this case, the value of repeated combination therapy is not certain.
- In case of limited general performance or deliberate avoidance of renewed combination therapy, topotecan as monotherapy is the approved standard (cave myelosuppression). An alternative is weekly paclitaxel treatment.
- If available, lurbinectedin and liposomal irinotecan are also alternatives.
- If the general performance is severely reduced, a best-supportive-care approach is usually indicated. A possible option here is, at best, oral etoposide or trofosfamide administration with the aim of symptom relief.

6.1.3 Surgery

If surgery is performed without previous histological diagnosis to remove a peripheral pulmonary nodular lesion, and histologic workup reveals SCLC, these patients should receive adjuvant chemotherapy postoperatively, and PCI if appropriate, see Figure 5. Postoperative mediastinal radiotherapy should be avoided in patients with stage pN0, since retrospective studies have shown evidence of a negative impact on long-term survival.

In patients with preoperatively proven SCLC and very limited disease, especially in N0 patients, resection with adjuvant chemotherapy is an alternative to radiochemotherapy. Resection should be performed according to the same standard as in patients with non-small cell lung cancer. After lobectomy in stage pT1/2, 5-year survival rates of 53% and a median survival of 65 months can be achieved.

Prior to surgery, the best possible exclusion of distant metastasis and a careful examination of the mediastinal lymph nodes are required. Patients with pre-therapeutically proven N2 or N3 involvement should primarily not undergo surgical resection. In patients with stage N1 disease, the value of surgery is controversial. Exclusion of mediastinal lymph node involvement should be performed by PET-CT, EUS/EBUS, or mediastinoscopy. The goal of surgery is R0 resection. Lobectomy is recommended. Pneumectomy should be avoided in SCLC. Postoperatively, adjuvant chemotherapy and PCI should be performed in case of LD.

A neoadjuvant approach is also feasible in the VLD group. Surgery is particularly important if there is still residual tumor after simultaneous chemoradiotherapy and no mediastinal lymph node involvement is detectable. Here, too, a pneumectomy should be avoided.

Local therapy of a solitary adrenal metastasis is an option especially for those patients who achieve complete remission after combined chemoradiotherapy and who subsequently develop a solitary adrenal metastasis as recurrence site after a prolonged therapy-free period.

6.1.4 Radiotherapy

6.1.4.1 Thorax

Radiation is an effective therapy for SCLC. In stage VLD after primary surgery and adjuvant chemotherapy, registry data from the National Cancer Data Base show no advantage for con-

solidative mediastinal irradiation. It should not be performed in N0 and N1; in N2, mediastinal reirradiation can be performed. Controlled studies on this are not available.

Radiotherapy is used in combination with chemotherapy in patients with LD and in VLD without surgery.

Chemotherapy should consist of cisplatin and etoposide whenever possible. Carboplatin is less effective or insufficiently tested in the setting of chemoradiation therapy. Simultaneous chemoradiotherapy results in 5-year survival rates of 20-30%, making it a potentially curative therapy. Compared with sequential therapy, 5-year survival is increased by approximately 5-10%. In the case of concurrent administration, an early start of radiotherapy should be aimed for, starting no later than the beginning of the 3rd cycle. This ensures that two complete cycles of cisplatin/etoposide are applied concurrently with radiotherapy. Early initiation of radiotherapy is associated with a higher rate of neutropenia. It is imperative to avoid dose reductions or even treatment discontinuations when simultaneous chemoradiotherapy is used early. Off-protocol therapy implementation worsens the results. Therefore, optimal supportive therapy is of great importance in the context of simultaneous chemoradiation therapy protocols.

When conventional fractionation with daily single doses of 1.8-2.0 Gy is applied, a total dose of radiotherapy of 60-66 Gy is recommended. Hyperfractionation with twice daily application of 1.5 Gy was superior to conventional fractionation with the same total dose of 45 Gy in a randomized study. However, the biologically effective dose is significantly different between the two therapeutic approaches. Comparisons of accelerated-hyperfractionated radiotherapy (AHF) with twice daily 1.5 Gy up to a total dose (GD) of 45 Gy vs. conventional fractionated radiotherapy with daily single doses of 1.8-2.0 Gy up to 70 Gy showed no statistically significant difference. Both treatment regimens are appropriate, although the burden to normal tissue may occasionally suggest an advantage for the AHF regimen.

Patients with ED usually receive primary chemo-immunotherapy with immunotherapy maintenance today. The use of consolidating primary tumor irradiation has not been tested in the context of such a therapeutic strategy and should therefore be reserved for study concepts.

6.1.4.2 Prophylactic cranial irradiation

Prophylactic cranial irradiation leads to a significant reduction in brain metastasis as a recurrence site. In stage LD, this is reduced from approximately 40% to 10%. Here, PCI also leads to a prolongation of overall survival and a 5% increase in 5-year survival. In a meta-analysis of 7 trials involving 987 limited-disease SCLC patients, survival at 3 years was 20.7% compared with 15.3% in the control arm. Possible radiation regimens include.

- 20 Gy in 5-8 fractions
- 24 Gy in 12 fractions
- 25 Gy in 10 fractions
- 30 Gy in 10-15 fractions

A randomized trial comparing a PCI dose of 25 Gy in 10 fractions with a dose of 36 Gy in 18 fractions showed a reduction in brain recurrence rate from 30% to 24% by the higher dose in 760 patients, but was associated with a less favorable survival curve. Surprisingly, the intrathoracic recurrence rate was increased in the group with the higher PCI dose. Doses above 30 Gy are therefore not a common approach, they are also associated with a higher risk of CNS toxicities including cognitive deficits. These are less pronounced with smaller individual doses and lower total doses.

Divergent study results are available for PCI in patients with extensive disease who had responded to induction chemotherapy. The EORTC trial driven solely by clinical symptoms showed a prolongation of median survival from 5.4 to 6.7 months, while the MRI-driven trial from Japan observed a statistically non-significant survival disadvantage with PCI with a median of 11.6 vs. 13.7 months (hazard ratio 1.27; p=0.094). In the EORTC clinically driven trial, the proportion of patients receiving second-line chemotherapy was significantly lower in the non-PCI arm at 45% compared to 69% in the PCI arm. This may have contributed to the survival benefit for PCI in this study. In the MRI-guided Japanese study, the rate of second-line therapy in both arms ranged from 80% to 90%, and overall survival was also significantly more favorable. PCI in ED may be an option to consider if regular MRI cranial controls are not performed.

6.1.4.3 Symptom-oriented radiotherapy

Local radiotherapy is an effective therapy for symptom relief, e.g., in multiple brain metastases or in symptomatic bone metastases.

6.1.5 Systemic drug treatment

Chemotherapy is the basis of therapy in patients with SCLC. It is used at every stage of the disease, see Figure 5 and Figure 6.

6.1.5.1 Substances (in alphabetical order)

6.1.5.1.1 Amrubicin

Amrubicin is a fully synthetic anthracycline with potentially reduced cardiotoxicity. It has efficacy in SCLC, but the randomized second-line trial failed to demonstrate an advantage over topotecan. Therefore, the compound is not approved for the treatment of SCLC.

6.1.5.1.2 Atezolizumab

Atezolizumab is an anti-PD-L1 monoclonal antibody and belongs to the immune checkpoint inhibitor class. Atezolizumab led to an improvement in overall survival in first-line therapy of patients with stage extensive disease SCLC in combination with carboplatin/etoposide compared to therapy with carboplatin/etoposide alone (improvement OS 2.0 months; HR 0.70; p=0.007). Clinically relevant adverse events included an increase in grade 3/4 diarrhea (2% vs 0.5%) and infusion-related reactions (2% vs 0.5%). Exacerbation of paraneoplastic phenomena may occur with atezolizumab and should be monitored thoroughly.

6.1.5.1.3 Carboplatin

Carboplatin is a platinum derivative. It has a more favorable side effect spectrum than cisplatin. In stage ED, remission rates are equal to those with cisplatin, and survival rates are probably not different, see Chapter 6.1.5.1.4. Specific severe side effect is hematotoxicity with thrombocytopenia, anemia, and neutropenia. Nausea, vomiting, and neurotoxicity occur but are less severe than with cisplatin. Carboplatin is administered intravenously.

6.1.5.1.4 Cisplatin

Platinum derivatives are among the most effective single agents. The combination of cisplatin and etoposide is the standard worldwide protocol in stage VLD and LD SCLC and the most commonly used regimen in stage ED patients besides carboplatin / etoposide. Specific serious side effects (grade 3/4) include nausea and vomiting, nephrotoxicity, polyneuropathy, ototoxicity, hematotoxicity, electrolyte shifts, cardiotoxicity, and diarrhea. Cisplatin is administered intravenously.

6.1.5.1.5 Cyclophosphamide

Cyclophosphamide is used primarily in combination with anthracyclines; see doxorubicin.

6.1.5.1.6 Doxorubicin (Adriamycin)

Anthracycline-containing regimens are an alternative first-line treatment in EDs with contraindications to platinum-containing combinations. They are also frequently used as second-line treatment. Doxorubicin and epirubicin have been tested in trials. The anthracyclines are used in combination with cyclophosphamide plus etoposide or vincristine (ACE and ACO, respectively). Remission rates for first-line therapy are 50-60%, and for second-line therapy are 20%. Serious adverse events (grade 3/4) of combination therapy, which occurred in more than 5% of patients in randomized trials, are primarily hematologic: neutropenia (52-87%), febrile neutropenia (5-10%), anemia (5-15%), thrombocytopenia (1-20%). Doxorubicin is administered intravenously.

6.1.5.1.7 Durvalumab

Durvalumab is an anti-PD-L1 monoclonal antibody and belongs to the immune checkpoint inhibitor class. Durvalumab resulted in an improvement in overall survival compared to chemotherapy alone in first-line treatment of patients with stage extensive disease SCLC in combination with cis- or carboplatin/etoposide. (Improvement OS 2.3 months; HR 0.75; p=0.007). The 3-year OS rates were 18% vs. 6%. Immunotherapy-related side effects should be thoroughly monitored.

6.1.5.1.8 Etoposide

Etoposide is a topoisomerase II inhibitor. It is a treatment standard in combination with cisplatin for SCLC. In patients with extensive disease, remission rates with combination therapy are 60-70%. Oral monotherapy with etoposide is less effective than intravenous combination therapy and has poorer bioavailability. In first-line palliative therapy, the following serious adverse events (grades 3-4) occurred with cisplatin/etoposide: Neutropenia (68-76%), anemia (11-12%), thrombocytopenia (8-15%), nausea/vomiting (11-12%), %), fatigue (11%), and anorexia (5%). Etoposide can be administered intravenously or orally.

6.1.5.1.9 Ipilimumab

Ipilimumab is a CTLA-4 antibody and thus also belongs to the group of checkpoint inhibitors. Ipilimumab alone was not effective as an adjunct to chemotherapy in extensive disease SCLC. Under maintenance therapy with nivolumab and ipilimumab after combined chemoradiotherapy, severe side effects occurred, leading to discontinuation of therapy in approximately 50% of patients. When used as maintenance therapy in combination with nivolumab, no significant survival benefit was detectable. Therefore, the substance has not yet been approved for the treatment of SCLC.

6.1.5.1.10 Irinotecan

Irinotecan is a topoisomerase I inhibitor. In combination with cisplatin, remission rates of 60-70% are achieved in first-line therapy, and survival rates are comparable to the cisplatin/ etoposide combination. Serious adverse events (grade 3/4) occurring in more than 5% of patients on this combination therapy include neutropenia (34%), febrile neutropenia (5%), diarrhea (19%), nausea/vomiting (14%), fatigue (14%), anorexia (13%), dyspnea (8%), and anemia (5%). Irinotecan is administered intravenously.

The nanoliposomal formulation of irinotecan was not superior to topotecan in a randomized phase III study in the second line and therefore will not be available for second-line treatment of SCLC.

6.1.5.1.11 Lurbinectedin

Lurbinectedin is structurally similar to trabectedine. The compound inhibits the transcription of tumor cell genes. Phase II studies demonstrated good efficacy of lurbinectedin in second-line SCLC treatment with remission rates of 35% and progression-free survival of 5.3 months. As a result, the compound was approved for SCLC second-line therapy in the United States. However, the subsequent randomized phase III trial failed to show an advantage over topotecan. Lurbinectedin is not approved for the treatment of SCLC in the EU.

6.1.5.1.12 Paclitaxel

Paclitaxel belongs to the taxanes. Taxanes are effective drugs in the advanced/metastatic stage of SCLC. They are used in combination with platinum derivatives or as monotherapy. Side effects include neutropenia, anemia, thrombocytopenia, nausea/vomiting, diarrhea, nephrotoxicity, neuropathy, and fatigue. Other side effects include edema, alopecia, onychodystrophy, and allergic reactions. Paclitaxel is administered intravenously.

6.1.5.1.13 Topotecan

Topotecan is a topoisomerase I inhibitor. Topotecan is a standard substance in second-line therapy of SCLC. Remission rates of 20% are achieved here. In combination with cisplatin, topotecan is also effective in first-line therapy and achieves comparable survival rates to cisplatin / etoposide. Serious adverse events (grade 3/4) occurring in more than 5% of patients on this combination therapy include neutropenia (33-88%), anemia (25-31%), thrombocytopenia

(7-43%), fatigue (8%), and dyspnea (10%). Topotecan can be administered intravenously or orally.

6.1.5.1.14 Vinca alkaloids

Vinca alkaloids, most commonly vincristine, are used primarily in combination with anthracyclines; see doxorubicin.

6.1.6 Palliative therapy, symptom-oriented

Palliative therapy includes the treatment of physical and psychological complaints. It required a multidisciplinary setting. The need for and options of palliative therapy should be discussed early and comprehensively with patients affected. The following specific symptoms occur particularly frequently in patients with SCLC.

6.1.6.1 Bone metastases

Local and systemic measures are available for the therapy of patients with bone metastases. In case of pain or fracture risk, radiotherapy is the treatment of choice. It can be hypofractionated under continuous systemic therapy. An additional option is surgical treatment for pathologic fractures, unstable vertebral body fractures, or as a relief for spinal compression.

Systemic measures include tumor-directed therapy and administration of bone-modifying agents (bisphosphonates, RANKL antibodies). Bone-modifying agents may reduce the risk of skeletal complications in bone metastasis of solid tumors. Results of prospective randomized trials in patients with SCLC are not available.

Bisphosphonates are also indicated for hypercalcemia.

6.1.6.2 Brain metastases

The first measure in symptomatic metastatic disease is the administration of corticosteroids to reduce perifocal edema. In symptomatic patients with multiple cerebral lesions, whole-brain irradiation is the therapy of choice. Depending on the setting, chemotherapy may also be used primarily for SCLC, see Figure 6. Stereotactic radiotherapy may also be considered for single metastases or metastases in small numbers and with good demarcation. In individual cases, local surgical therapy or targeted local irradiation (gamma knife, cyber knife, stereotactic radiotherapy) may be discussed for isolated resectable brain metastases persisting or re-progressing after whole brain irradiation.

7 Rehabilitation

Drug therapy, surgery, radiation therapy, and comorbidity can lead to therapy sequelae of varying severity in patients with small cell lung cancer. They can be alleviated by targeted rehabilitative measures in the somatic and psychosocial areas.

Patients should be informed at an early stage about the possibilities of outpatient and inpatient rehabilitation measures as well as other claims arising from social law. With regard to the rehabilitation clinic, the patients' wishes should be taken into account (§9 SGB IX). Nevertheless, a recommendation for a clinic with an oncological focus should be made in order to ensure optimal rehabilitation success.

8 Post-Treatment Control and Follow-up

8.2 Follow-up

The goals of follow-up are early diagnosis of recurrence with the aim of prolonging survival, early diagnosis of secondary neoplasia, detection of side effects of therapy, and preventive care. This concerns patients in the localized stages. Structured follow-up can be guided by the recommendations for NSCLC, see Table 9.

Table 9: Structured follow-up after curative therapy

Procedure	Months 3	6	9	12	18	24	36	48	60
Medical history, Physical examination	X	X	X	X	X	X	X	X	X
CT thorax	X	X	X	X	X	X	X	X	X
Lung function	X	X	X	(X)	(X)	(X)			
Cerebral MRI in LD without PCI	X	X	X	X	X	X	X	(X)	(X)

Legend:
CT = computed tomography, MRI = magnetic resonance imaging, LD = limited disease, PCI = prophylactic cranial irradiation after radiotherapy.
If follow-up examinations reveal a localized recurrence or a recurrence that can be treated locally, the diagnosis should be supplemented by further imaging, including PET-CT if appropriate, and/or methods for histological confirmation.

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14 Links

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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License[4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
Beckmann, Annalen	Universitätsklinikum Münster	**No**	**No**	**No**	**Yes** Alexion, Gilead, Novartis, BMS, Bayer, Servier, Roche, AstraZeneca, Takeda, Merck, BeiGene, MSD, Lilly, ArtTempi, Janssen-Cilag, Amgen, BI	**No**	**No**	**No**
Eberhardt, Wilfried	Conflict of interest declarations pending							
Eichhorn, Martin	Thoraxklinik Heidelberg GmbH	**Yes** Roche, MSD, Intuitive Surgical, AstraZeneca,	**No**	**No**	**Yes** Roche, MSD, Intuitive Surgical, AstraZeneca,	**Yes** MSD, Intuitive Surgical	**No**	**No**
Früh, Martin	Conflict of interest declarations pending							
Gautschi, Oliver	Luzerner Kantonsspital, Luzern, Schweiz	**Yes** Honorare (an die Institution) für Beratertätigkeiten für Amgen 2020-2021	**No**	**No**	**No**	**Yes** Drittmittel (an die Institution) von Firmen und kooperativen Gruppen für die Durchführung von klinischen Studien. Honorare (an die Institution) für die Teilnahme an Advisory Boards von Eli Lilly und Roche.	**No**	**No**
Griesinger, Frank	Pius-Hospital Oldenburg Universitätsmedizin Oldenburg	**Yes** ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Tesaro/GSK, Siemens, Tesaro, Amgen, Sanofi	**No**	**No**	**Yes** ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Tesaro/GSK, Siemens, Tesaro, Amgen, Sanofi	**Yes** ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Siemens, Amgen	**No**	**No**
Hilbe, Wolfgang	Mitarbeiter des Wiener Gesundheitsverbundes	**No**	**No**	**No**	**No**	**No**	**No**	**No**

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Hoffmann, Hans	Klinikum rechts der Isar Leiter Sektion Thoraxchirugie Ismaninger Str. 22 81675 München	**No**	**No**	**No**	**Yes** AstraZeneca, BMS, Boehringer, GSL, Pulmonx, Medela	**No**	**No**	**No**
Kraywinkel, Klaus	Robert Koch-Institut	**No**	**No**	**No**	**No**	**No**	**No**	**No**
Loges, Sonja	Universitätsmedizin Mannheim DKFZ Heidelberg	**Yes** S. Loges erhält Referenten- und / oder Beiratshonorare vom Referentenbüro von BerGenBio AS, BMS, Boehringer Ingelheim, Eli Lilly, Roche Pharma, Medac GmbH und Sanofi Aventis, Novartis, AstraZeneca, Pfizer, Takeda, Amgen, Bayer, Janssen, Merck	**No**	**No**	**Yes** S. Loges erhält Referenten- und / oder Beiratshonorare vom Referentenbüro von BerGenBio AS, BMS, Boehringer Ingelheim, Eli Lilly, Roche Pharma, Medac GmbH und Sanofi Aventis, Novartis, AstraZeneca, Pfizer, Takeda, Amgen, Bayer, Janssen, Merck	**Yes** Prof. Loges erhält kommerzielle Forschungsstipendien von BerGenBio AS, BMS, Eli Lilly, Roche Pharma und ADC Therapeutics und hat	**No**	**No**
Pirker, Robert	Conflict of interest declarations pending							
Pöttgen, Christoph	Conflict of interest declarations pending							
Reck, Martin	Lungen-Clinic, Woehrendamm 80, 22927 Grosshansdorf	**Yes** Kompensierte Tätigkeit im Advisory Board von Amgen, AstraZeneca, Boehringer-Ingelheim, Beigene, BMS, Daiichi-Sankyo, Lilly, Merck, MSD, Mirati, Novartis, Pfizer, GSK, Roche, Sanofi, Regeneron.	**No**	**No**	**Yes**	**No**	**Yes**	**No**

Author	Employer[1]	Consulting / Expert opinion[2]	Shares / Funds[3]	Patent / Copyright / License[4]	Fees[5]	Funding of scientific research[6]	Other financial relations[7]	Personal relationship with authorized representatives[8]
					Honorare für Vorträge von Amgen, AstraZeneca, Boehringer-Ingelheim, Beigene, BMS, Daiichi-Sankyo, Lilly, Merck, MSD, Mirati, Novartis, Pfizer, GSK, Roche, Sanofi, Regeneron.		Reisekostenerstattungen für wissenschaftliche Treffen von Amgen, AstraZeneca, Boehringer-Ingelheim, Beigene, BMS, Daiichi-Sankyo, Lilly, Merck, MSD, Mirati, Novartis, Pfizer, GSK, Roche, Sanofi, Regeneron.	
Reinmuth, Niels	Asklepios Fachkliniken München-Gauting Robert-Koch-Allee 2 - 82131 Gauting	**Yes** Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim,Hoffmann-La Roche, MSD, Merck, Pfizer, Takeda	**No**	**No**	**Yes** Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi Sankyo, GSK, Hoffmann-La Roche, Janssen, Lilly, MSD, Merck, Pfizer, Symphogen, Takeda	**No**	**No**	**No**
Sebastian, Martin	Universitätsklinik Frankfurt	**Yes** Astra-Zeneca, Roche, Pfizer, Boehringer-Ingelheim, GSK, Takeda, BMS, Merck, Novartis, Janssen, Sanofi, Amgen	**No**	**No**	**Yes** Astra-Zeneca, Roche, Pfizer, Boehringer-Ingelheim, GSK, Takeda, BMS, Merck, Novartis, Janssen, Sanofi, Amgen, MSD	**Yes** Astra-Zeneca	**Yes** Pfizer, Takeda	**No**
Waller, Cornelius	Universitätsklinikum Freiburg	**Yes** Beratertätigkeit für die Firmen Alvotech, Roche, Mylan.	**No**	**No**	**Yes** Amgen, Astra Zeneca, Boehringer Ingelheim, BMS, Chugai, MSD, Pfizer, Roche, Takeda	**No**	**Yes** Reisekostenerstattungen durch Ipsen, BMS, Lilly, Merck, Janssen	**No**

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Wolf, Jürgen	Universitätsklinikum Köln	**Yes** Amgen, AstraZeneca, Bayer, Blueprint, BMS, Boehringer-Ingelheim, Chugai, Daiichi Sankyo, Janssen, Lilly, Loxo, Merck, MSD, Novartis, Nuvalent, Pfizer, Roche, Seattle Genetics, Takeda, Turning Point	**No**	**No**	**Yes** Amgen, AstraZeneca, Bayer, Blueprint, BMS, Boehringer-Ingelheim, Chugai, Daiichi Sankyo, Janssen, Lilly, Loxo, Merck, MSD, Novartis, Nuvalent, Pfizer, Roche, Seattle Genetics, Takeda, Turning Point	**Yes** BMS, Janssen Pharmaceutica, Novartis, Pfizer (jeweils alle Zahlungen an Institut)	**No**	**No**
Wolf, Martin	Conflict of interest declarations pending							

Legend:

[1] - Current employer, relevant previous employers in the last 3 years (institution/location).

[2] - Activity as a consultant or expert or paid participation in a scientific advisory board of a company in the health care industry (e.g., pharmaceutical industry, medical device industry), a commercially oriented contract research organization, or an insurance company.

[3] - Ownership of business shares, stocks, funds with participation of companies of the health care industry.

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[5] - Honoraria for lecturing and training activities or paid authors or co-authorships on behalf of a company in the health care industry, a commercially oriented contracting institute or an insurance company.

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[7] - Other financial relationships, e.g., gifts, travel reimbursements, or other payments in excess of 100 euros outside of research projects, if paid by an entity that has an investment in, license to, or other commercial interest in the subject matter of the investigation.

[8] - Personal relationship with an authorized representative(s) of a healthcare company.