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Diagnosis and treatment of lung cancer – Non-small cell lung cancer, small cell lung cancer and carcinoids

A. End

Division of Cardiothoracic Surgery, Department of Surgery, Medical University of Vienna, Vienna, Austria

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Bronchuskarzinom und neuroendokrine Tumore – Diagnostik und Therapie

Zusammenfassung. *Grundlagen:* Die Prognose von Lungentumoren hängt von der Histologie und dem Tumorstadium ab. Der häufigste Tumortyp ist das nicht-kleinzellige Bronchuskarzinom (NSCLC) mit einer 5-Jahresüberlebensrate zwischen 67 % (Stadium IA) und < 5 % (Stadium IV).

Methodik: Eine rezente Literaturübersicht zeigt diagnostische und therapeutische Standards des nicht-kleinzelligen Bronchuskarzinoms und der neuroendokrinen Tumore (Leitlinien).

Ergebnisse: Im Stadium I/II ist bei funktioneller Operabilität eine (Bi)Lobektomie bzw. Pneumonektomie mit systematischer mediastinaler Lymphadenektomie durchzuführen. Im Stadium IIIA (IIIB) erfolgt die Resektion nach neoadjuvanter Chemo(radio)therapie. Thorax-CT, PET und Mediastinoskopie (mediastinale Lymphknoten > 1 cm; PET positiv) sind wichtige Staging-Untersuchungen. Adjuvante Chemotherapien werden im Stadium I/II im Rahmen klinischer Studien durchgeführt. Das kleinzellige Bronchuskarzinom (SCLC, hochmaligner neuroendokriner Tumor Grad III) ist die Domäne der Chemotherapie; Resektionen wie beim NSCLC werden in Frühstadien durchgeführt. Bei den neuroendokrinen Tumoren Grad I (typisches Karzinoid) wird eine parenchymsparende bzw. bronchoplastische Resektion durchgeführt; bei den neuroendokrinen Tumoren Grad II (atypisches Karzinoid) wird wie beim NSCLC vorgegangen.

Schlussfolgerungen: Die Inzidenz des Bronchuskarzinoms kann durch Raucherprävention verringert, die Prognose durch Früherkennung und multimodaler Therapie verbessert werden.

Schlüsselwörter: Nicht-/kleinzelliges Bronchuskarzinom, neuroendokrine Tumore, Chirurgie, multimodale Therapie.

Summary. *Background:* The prognosis of lung tumors is determined by histology and staging (nodal status). The most common tumor is non-small cell lung carcinoma (NSCLC) with a 5-year survival rate of 67% (stage IA) to < 5% (stage IV).

Methods: By reviewing the literature guidelines for diagnosis and treatment of non-small cell lung cancer and neurendocrine tumors are presented.

Results: Functional operability provided, (bi)lobectomy or pneumonectomy with mediastinal lymph node dissection are the standard procedures. In case of positive mediastinal lymph nodes (stage IIIA/IIIB) induction chemo(radio)therapy is indicated. Cervical mediastinoscopy is performed in patients with enlarged mediastinal nodes (CT > 1 cm), especially in PET-positive cases. Adjuvant chemotherapy is used in clinical trials. Small-cell lung cancer (SCLC, neuroendocrine tumor grade III) has a poor prognosis, and is treated with chemotherapy; resection may be performed in early stages. Neuroendocrine tumors grade I (typical carcinoid) are resected by segmentectomy, lobectomy, or bronchoplastic resection. Neuroendocrine tumors grade II (atypical carcinoids) are treated like NSCLC.

Conclusions: The incidence of lung cancer is decreased by tobacco control, and the chances of survival are improved by early detection and multimodality regimens.

Key words: Lung cancer, neuroendocrine tumor, surgery, multimodality therapy.

Introduction

Lung cancer is the leading cause of death in patients with cancer in Europe: Out of 1.7 million people who die of cancer each year, 20% have lung cancer, with the rate of women increasing [1]. The overwhelming majority of lung cancer is caused by smoking, and tobacco control is

Correspondence: Adelheid End, M.D., Division of Cardiothoracic Surgery, Department of Surgery, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria.
Fax: ++43-1-40400-6592
E-mail: adelheid.end@meduniwien.ac.at

an important issue with men, and increasingly so with women. Overall prognosis is bad with a 5-yr survival rate up to 15% [2]. Early diagnosis by multislice CT screening in high-risk populations and curative treatment approaches are essential. Each lung cancer patient should be discussed in an interdisciplinary tumor conference, and be offered the best treatment available including multimodality regimens [2, 3]. The short recommendations given here are a summary of current clinical knowledge and take into account different international guidelines [4–12]. They may be valid for the majority of patients, but treatment should always be tailored to the individual patient's needs.

Histology of lung cancer

Histological classification according to the WHO is shown in table 1 [13]. There are two large groups of lung cancer which are treated differently: non-small cell lung cancer (NSCLC) makes up 80% and small cell lung cancer (SCLC) makes up 20% of cases [9, 10]. The most common types of NSCLC are adenocarcinoma and squamous cell carcinoma. Whereas NSCLC is resected with curative intention in early stages, and treated by (neo)neoadjuvant chemo(radio)therapy in advanced stage, SCLC is the domain of chemotherapy [2]. Tumors containing both NSCLC and SCLC are treated like SCLC.

According to neuroendocrine characteristics, small cell lung carcinoma is part of the neuroendocrine tumors (NET), and is classified together with the large cell neuroendocrine carcinoma (LCNEC) as high-grade neuroendocrine tumor (G3). Carcinoids represent 1 to 2% of all lung tumors: the typical carcinoid (low-grade neuroendocrine tumor, G1) has a good prognosis, and is distinguished from the atypical carcinoid (intermediate-grade neuroendocrine tumor, G2) [4].

Table 1. WHO histological classification of tumors of the lung (WHO) [13]

Groups	Subgroups
Non-small cell lung cancer = NSCLC	
Squamous cell carcinoma	Papillary, clear cell, small cell, basaloid
Adenocarcinoma	Bronchioloalveolar carcinoma, solid adenocarcinoma with mucin production
Large cell carcinoma	Large cell neuroenodocrine*, basaloid, lymphoepithelioma-like, clear cell large cell with rhabdoid phenotype
Adenosquamous carcinoma	
Sarcomatoid carcinoma	Pleomorphic, spindle cell, giant cell, carcinosarcoma Pulmonary blastoma
Salivary gland tumors	Mucoepidermoid, adenoid cystic, epithelial-myoepithelial
*Small cell carcinoma = SCLC**	Combined small cell
*Carcinoid tumor**	typical, atypical

* Typical (TC) and atypical carcinoids (AC), small cell carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC) are summarized as "neuroendocrine tumors" (grade I = TC, grade II = AC, grade III = SCLC and LCNEC).

NON-SMALL CELL LUNG CANCER (NSCLC)

NSCLC is classified according to the revised TNM system (Table 2) [14–16]. Staging and 5-yr survival rates

Table 2. Tumor, node, metastasis (TNM)-descriptors [14–16]

Primary Tumor (T)	
TX	Tumor cannot be assessed, or tumor proved by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor = 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T2	Tumor with any of the following features of size or extent: > 3 cm in greatest dimension Involves main bronchus > 2 cm distal to the carina Invades the visceral pleura Associated with atelectasis or obstructive pneumonia that extends to the hilar region but does not involve the entire lung
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with a malignant pleural or pericardial effusion, or with satellite tumor nodule(s) within the ipsilateral primary-tumor lobe
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar nodes, and intrapulmonary nodes involved by direct extension of the primary tumor
N2	Metastasis to ipsilateral mediastinal and/or subcarinal node(s)
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular node(s)
Distant Metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present (separate metastatic tumor nodule(s) in the ipsilateral non-primary tumor lobe(s) are classified M1)

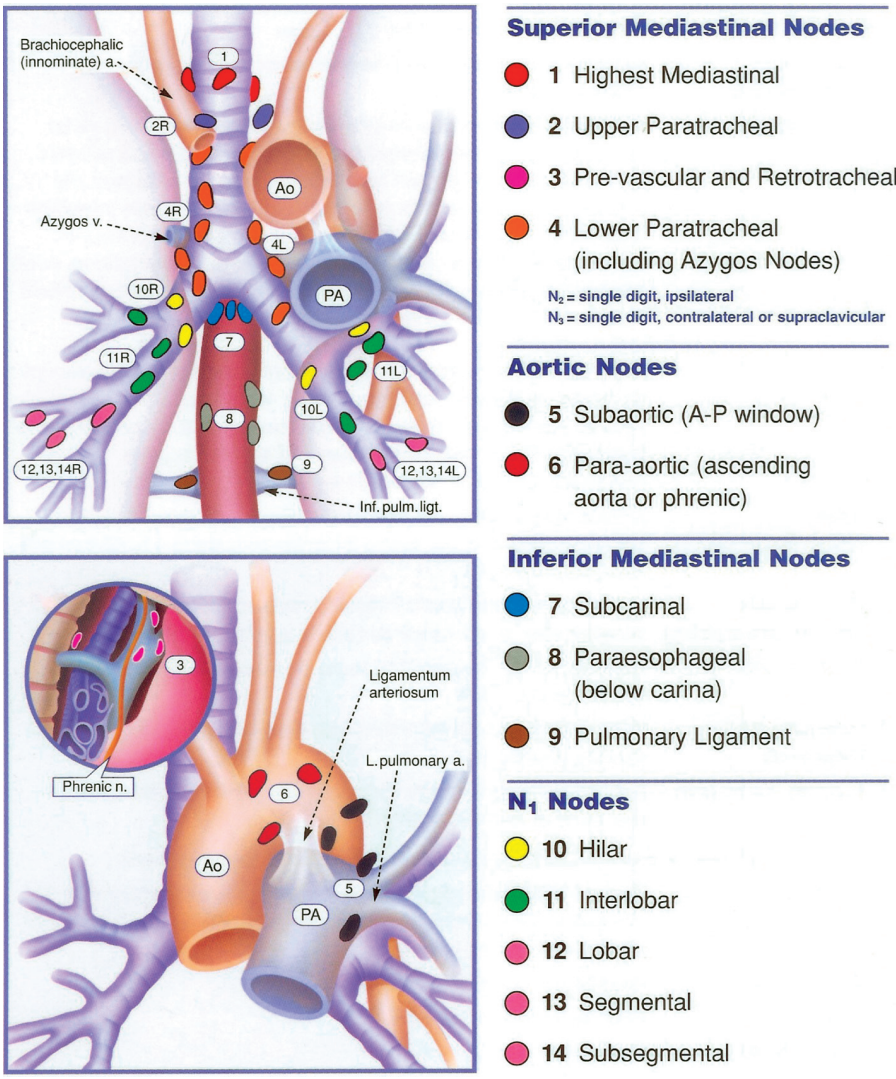

Fig. 1. Regional lymph node stations for lung cancer staging [18]
Reproduced with permission from Mountain and Dresler (Copyright 1996) [18]. Adapted from Naruke [19] and the ATS/North American Lung Cancer Study Group (LCSG) [20].

are given in Table 3 [14–17]. Regional lymph nodes are classified as N1 (ipsilateral hilar, interlobar and lobar), N2 (ipsilateral mediastinal and subcarinal) and N3 (contralateral mediastinal) (figure) [18]. The most common sites of distant metastases are brain, bone, adrenal glands and liver. The incidence of brain metastasis in asymptomatic patients is 4–11% [8].

Staging of NSCLC

Staging consists of *history*, *clinical examination*, *routine laboratory tests*, *chest X-ray*, *chest CT* with contrast-medium including the liver and adrenal glands, and *abdomen sonography* [4, 6, 8, 21]. *Serum tumor markers* such as carcinoembryonic antigen (CEA) and the cytokeratin-derived markers Cyfra 21-1 and tissue polypeptid antigen (TPA) have low sensitivity and specificity and do not play a great role in staging or follow-up [21, 22]. *Histological* diagnosis is made by bronchoscopic, percutaneous or videothoracoscopic biopsy.

MRI may help to assess infiltration of the thoracic wall, neurovascular structures (pancoast tumor = tumors of the sulcus superior), and suspicious adrenal findings.

Cytology, pleural biopsy and thoracoscopy are used to diagnose pleural effusions.

Fluorodeoxyglucose *positron emission tomography* (FDG-PET) offers high sensitivity to detect glucose-active lesions; it has a high negative predictive value (87%) [8, 23]. As inflammatory lymph nodes may be PET positive, further examinations are required. CT-PET-fusion techniques combine the advantages of both techniques [23].

Cervical mediastinoscopy should be performed if mediastinal lymph nodes are greater than 1 cm in CT, especially with positive PET-scans [4, 6, 8, 9, 24]. Positive N2/3 lymph nodes (stage IIIA/B) are an indication for induction chemotherapy. A refinement of the conventional method is the video-assisted mediastinoscopic lymphadenectomy (VAMLA) which allows an excellent exposure

Table 3. Stage grouping of TNM-subsets and 5-yr survival rates of lung cancer [14–17]

Stage	T	N	M	5-yr Survival (%) Clinical Stage	Pathological Stage
Non-small cell lung cancer (NSCLC)					
IA	T1	N0	M0	61	67
IB	T2	N0	M0	38	57
IIA	T1	N1	M0	34	55
IIB	T2	N1	M0	24	39
	T3	N0	M0	22	38
IIIA	T3	N1	M0	9	25
	T1-3	N2	M0	13	23
IIIB	T4	N0-N2	M0	7	N/A
	T1-4	N3	M0	3	N/A
IV	Any T	Any N	M1	<1	N/A
Small cell lung cancer (SCLC)					
Limited disease (LD): Tumor confined to ipsilateral hemithorax; can be encompassed by one radiation port				20	
Extensive disease (ED): All other disease, including metastatic disease				2	

Revisions in the TNM system and 5-yr survival rates are given according to Mountain [14]; T denotes tumor, N node, and M metastasis. N/A: not applicable. The staging system was developed by the American Joint Commission on Cancer, it is also applied in SCLC. The simple two-stage system of SCLC was developed by the Veteran's Administration Lung Cancer Study Group; 5-yr survival rates are given according to [17].

of the mediastinum and should be performed prior to video-assisted thoracoscopic lobectomy [25].

Symptomatic patients undergo *brain CT/MRI* and/or *bone scan*. Brain CT should always be performed in patients with locally advanced tumor stages who are considered for curative resection.

Lung function testing

Derived by spirometry, the forced expiratory volume in one second (FEV1), the forced vital capacity (FVC), and the ratio between the two, are the most important values of judging functional operability. Further studies include blood gas analysis, total body plethysmography and diffusing capacity for carbon monoxide (DLCO). In high risk patients lung perfusion scintigraphy and spiroergometry are performed [6, 12, 21].

Treatment according to stage [2, 4, 6, 9, 12]

Stage I – Surgical resection

Surgery is the treatment of choice: lobectomy, bilobectomy or pneumonectomy if the tumor goes beyond the fissure, or bronchovascular sleeve resections of small centrally located tumors, to avoid pneumonectomy in patients with impaired lung function. In patients with good lung function lobectomy is the standard procedure for peripheral T1N0. In patients with contraindications to resection (functional or multimorbidity, high age), limited resections of peripheral tumors (segment or wegde) can be performed [6, 12, 26–28].

Stage II – Surgical resection

Standard therapy is resection like in stage I [12]. If the mediastinum is negative, frozen sections should be done in suspicious interlobar nodes and the bronchial resection margin. In patients with good lung function, pneumonectomy – and not bronchial sleeve resections – should be performed if N1 are positive. If the tumor is located centrally, involves the hilum or is located in the lobar fissure, or in cases of positive interlobar lymph nodes, pneumonectomy has to be performed.

In T3N0-tumors with infiltrating the parietal pleura, chest wall, diaphragm, mediastinal pleura, pericardium, an en bloc resection of the primary tumor and the thoracic wall (or the involved structures) has to be performed with tumor-free resection margins (superior sulcus tumor see below). If R0-resection is achieved, no adjuvant local radiotherapy is needed.

In T3-tumors with involving the main bronchus less than 2 cm distally from the carina, a bronchoplastic resection of the upper lobe, a pneumonectomy or sleeve pneumonectomy with a resection of the carina is performed [6, 26, 28, 29].

Stage IIIA – Induction chemotherapy

Potential prognostic factors are microscopic involvement of one/two versus multilevel lymph node involvement [22].

If N2-nodes are known to be positive, induction chemotherapy is done first. If there is a response, resection is performed. If there is no clinical suspicion of mediastinal metastases (N2), resection is followed by postoperative chemotherapy (+/– mediastinal radiation).

Extended resections may be performed in selected cases with curative intent. These cases include peripheral lesions infiltrating the thoracic wall, tumors of the superior sulcus (see below), central lesions invading the mediastinum, and focal infiltration of the pericardium or phrenic nerve [26].

Stage IIIB – Potentially resectable

Some *locally advanced*, initially unresectable tumors can become operable after induction chemoradiotherapy. 5-yr survival rate is reported to be 42% in patients with complete tumor resection and without nodal involvement at the time of surgery [30, 31].

In *potentially resectable T4* (invasion of superior vena cava, carina, lower trachea, left atrium, vertebrae, limited infiltration of the esophagus, satellite nodule in the same lobe) with N0, resection may be performed [11, 30–32].

Tumors of the superior sulcus (Pancoast tumor)

They are classified as T3, or T4 if they infiltrate nerves or bones (Pancoast-syndrome). Preoperative radio-therapy (40–60 Gy) and/or chemotherapy with subsequent resection is recommended, followed by adjuvant radiation (–60 Gy) if necessary [4, 6, 11, 12, 26]. Posterolateral, anterior cervical, or hemi-clamshell incisions

(thoracotomy with partial median sternotomy) are used but depend on the structures involved [33, 34].

Stage IIIB – Definitely not resectable

These are T4 with malignant pleural or pericardial effusion, major infiltration of esophagus, and vertebrae [31]. Superior vena cava syndrome should be managed with radiation with or without chemotherapy [4, 8]. In some cases of malignant pleural effusion extrapleural pleuropneumonectomy is performed in nodal negative patients. If chemoradiotherapy fails in bulky mediastinal involvement (i.e. visible on chest radiograph), surgery is not indicated [4].

Stage IV – Palliative chemotherapy

In stage IV palliative chemo(radio)therapy is performed. Surgery of the primary tumor might be considered in patients with solitary brain (or adrenal) lesions (if N2/N3 nodes are negative) [8]. If the brain lesion can be totally resected by radiosurgery, the primary lung tumor is operated sequentially. Isolated lesions in the adrenals or the contralateral lung are treated on an individualized basis [6, 8, 11, 12].

General comments on surgery

If resection with curative intent is feasible, surgery should always be performed; complete dissection of regional lymph nodes is mandatory. The *standard access* is a muscle-sparing anterolateral thoracotomy.

In stage I and II primary radiotherapy is no alternative to surgery, and should only be performed in cases of inoperability [4, 6, 9].

In cases of functional inoperability, multimorbidity, reduced performance status or refusal of operation or chemotherapy, stereotactic radiotherapy (or radiofrequency ablation) of a potentially resectable tumor may be performed. In multimorbid or old-age patients palliative limited resection can be performed.

Video-assisted thoracoscopic surgery (VATS) is used to resect undefined peripheral pulmonary nodules; if they are primary malignant, the minimal access is converted to thoracotomy. VATS is also be used for palliative resections of peripheral carcinomas, or for staging (i.e. biopsies of enlarged lymph nodes in the aorto-pulmonary window) [21]. *Video-assisted thoracoscopic lobectomy* is performed in stage I by experienced surgeons [12, 35, 36]. A utility thoracocotomy of about 5–7 cm is necessary to remove the resected lobe. There is controversy if systematic mediastinal lymphadenectomy can be performed as adequately as with open procedures.

Adjuvant radio-/chemotherapy

Postoperative radiotherapy (PORT) reduces the local recurrence rate in stage II and IIIA, but has no influence on survival. It is indicated in R1/R2-resection (bronchus, chest wall), multiple N1- and N2-disease [3, 6]. A metaanalysis showed an adverse effect on survival in stage I/II, whereas for stage III, N2 patients the role of PORT is not yet clear [37].

Adjuvant *chemotherapy* after complete resection in stage I–IIIA has been proposed based on the fact that distant metastatic disease is the most frequent form of recurrence and that micrometastatic spread is present at the time of diagnosis in a considerable number of patients [2]. In a metaanalysis a favourable effect of platin-based chemotherapy was found in all comparisons, i.e. adjuvant chemotherapy vs. surgery alone, radiochemotherapy vs. radiotherapy, and supportive care plus chemotherapy vs. supportive care alone [38].

The International Adjuvant Lung Cancer Trial of adjuvant chemotherapy in stage I–III found a 5-yr survival benefit of 4 % and an advantage of 5 % for disease-free survival for platin-based regimens [39]. In a recent multi-center study of 482 randomized patients with completely resected NSCLC stage IB and II, adjuvant chemotherapy with vinorelbine and cisplatin was superior to observation alone (5-yr survival, 69% vs. 64%) [40]. In stage IB/II/IIIA adjuvant platinum-based doublet chemotherapy (3–4 cycles) should be offered to patients with good postoperative recovery and good performance status [2, 4]. Predictive factors to more precisely identify candidates for adjuvant treatment have to be found.

Multimodal regimens in stage III NSCLC

Neoadjuvant chemotherapy aims to downstage the tumor as well as regional lymph nodes in stage IIIA/B, and to reduce the risk of distant tumor spread [2, 3]. Reports claim a 17% 5-yr survival rate with chemoradiotherapy, whereas radiotherapy alone had a 5-yr survival of 6% in stage III; however, most patients develop local recurrence and/or distant metastases [41].

Trimodal regimes in stage IIIA/B included surgical evaluation after induction chemoradiotherapy (cisplatin/-etoposide plus concurrent chest radiotherapy to 45 Gy), and resulted in a 3-yr survival rate of 26% [42]. *Concurrent chemoradiotherapy* seems to offer better results than sequential chemoradiotherapy [2, 43].

Benefits in disease-free survival and overall survival have been shown, although they are not always significant in *randomized* trials that compare neoadjuvant therapy with surgery alone in stage I–IIIA [44].

First-line chemotherapy schemes are platinum-based with 3rd generation drugs (gemcitabine, vinorelbine, docetaxel, paclitaxel) [2, 4].

Surgery after neoadjuvant therapy

Morbidity but not overall mortality is slightly increased with multimodality treatment [26]. Bronchovascular sleeve resections after induction chemotherapy do not bear a higher risk of surgical complications [45]. After trimodality treatment morbidity rose up to 46% with an in-hospital mortality rate of 4.6% [46]. As the wound healing is disturbed after induction therapy, the bronchial stump should be covered with vital autologous material, especially after right-sided pneumonectomy to decrease the risk of bronchial stump insufficiency. There are several options of pedicled flaps to reinforce the suture or staple line: epipericardial fat pad flap, pericardial flap, intermuscle flap, diaphragm, and serratus anterior flap.

Palliative therapy

Palliative therapy in stage IV (IIIB) comprises chemo/radiotherapy and best supportive care. Chemotherapy improves survival in patients with good performance status compared to best supportive care alone. Firstline protocols contain cisplatin (or carboplatin) and one of the newer cytostatic agents (3–4 cycles) (see above). Single-agent therapy is used in patients with reduced performance status [4, 8, 9, 12].

Endobronchial therapies such as laser (Nd-YAG), argon plasma coagulation, cryocoagulation, stenting, brachytherapy and photodynamic treatment are palliative options in malignant airway obstruction [4, 6]. Endoscopic photodynamic therapy may also be used in early cancer restricted to the bronchial wall (Tis) if limited pulmonary reserve prohibits surgery [4]. For malignant pleural effusion video-assisted thoracoscopic talcum pleurodesis is performed [12].

SMALL CELL LUNG CANCER (SCLC)

Without treatment, small cell lung cancer has the most aggressive clinical course of any type of lung tumor. It tends to metastasize early in supraclavicular nodes, the liver, adrenals, bone, and brain, but it is more sensitive to chemo- and radiotherapy [5, 10].

Staging examinations are similar to those in NSCLC, in addition cranial CT and bone scintigraphy in asymptomatic patients are performed. Serum tumor markers – such as NSE (neuron specific enolase) may play a certain role in follow-up [21]. Biopsies of bone marrow are not performed routinely.

Tumor extent at the beginning of therapy and response to therapy are important prognostic factors. Besides the TNM classification, a simple 2-stage system is more commonly used: limited-stage (LD) and extensive-stage disease (ED). 5-yr survival is poor [2, 5, 7, 10, 12] (Table 3).

Limited-stage Disease (LD) (stage I–IIIB, UICC)

The tumor extension is limited to the ipsilateral hemithorax, the mediastinum, and the supraclavicular nodes. There is no universally accepted definition of this term which is used differently by various groups [5]. Median survival time is 15–24 months [2, 5, 17].

Standard treatment should be a combination of cisplatin/etoposide (4–6 cycles) plus chest radiation therapy (45 Gy) administered during the first or second cycle of chemotherapy. In 80 to 90% remission (50–60% complete) is achieved. In stage I disease (T1–2 N0) – primary surgical resection followed by chemotherapy or chemoradiotherapy is performed. Phase II trials with postoperative adjuvant therapy in stage I–IIIA had an overall 3-yr survival rate of 61% (13% in stage IIIA), with distant failure in 34% [47].

If there is no response after chemo(radio)therapy, salvage surgery should be considered as these patients may have a mixed tumor type (NSCLC/SCLC) and may profit from resection. As the risk of brain metastases is up to 60%, a prophylactic brain irradiation (PCI) is performed in cases with complete remission [2, 5, 7, 12].

Extensive-stage Disease (ED) (stage IV, UICC)

Patients with distant metastases are always considered to have ED. Median survival time is 6–12 months [5, 17]. Primary treatment is chemotherapy with a reponse rate of about 70%; complete remissions are found in 20–30% [5, 7]. Many patients develop a recurrence despite good initial response. Palliative radiotherapy is performed for bone and brain metastases, salvage surgery for tumor bleeding or septic complications [7].

Standard protocols for firstline chemotherapy are cisplatin/etoposide and adriamycine/cyclophosphamide/-vincristin (ACO); for recurrence, topotecan is an alternative [2].

NEUROENDOCRINE TUMORS (NET)

Typcial carcinoids (TC; low-grade malignancy) have a good prognosis, if they are resected with free resection margins (i.e.segmental or wedge resection, bronchial sleeve resection) [6]. No adjuvant therapy is necessary.

Atypical carcinoids (AC; intermediate-grade) are treated like NSCLC because of their metastatic potential; the tumor size correlates with lymphovascular metastasis (positive mediastinal lymph nodes are found in more than 15%, if the tumor is > 2 cm). 5-yr survival is about 60% which lies between the rates of TC and SCLC/LCNEC (large-cell neuroendocrine carcinoma) [5]. Standard resection procedures such as lobectomy with systematic mediastinal lymph node dissection are mandatory [6]. Opinions vary on the appropriate adjuvant chemo/radiotherapy [48–50].

High-grade neuroendocrine tumors – SCLC and LCNEC – have the worst prognosis with an overall 5-yr survival of less than 10% [7, 48–50].

Follow-up care after surgery for lung cancer

The guidelines disagree on the follow-up intervals and the kind of examinations that should be done [4, 6, 8, 9, 12]. Some authors doubt the benefit of systematic follow-up [8, 10], others argue that patients may be cured or that their chance of survival may be increased if local recurrencies are detected early [6].

Follow-up intervals may be: every 3 months in the first and second postoperative year, every 6 months thereafter through year 5, then once a year [6]. Follow-up examinations are chest X-ray, chest CT (including adrenals), upper abdomen sonography, bronchoscopy if there is a pathological CT, and laboratory tests. Serum markers are of minor importance.

Take-Home-Messages

1. Histologie und klinisches Stadium (mediastinaler Lymphknotenstatus) bestimmen die Prognose.

Die Therapie des nicht-kleinzelligen Bronchuskarzinoms (NSCLC) ist zunehmend eine multimodale, und sollte interdisziplinär in einer Tumorkonferenz festgelegt werden.

2. Die Standardtherapie des Stadiums I/II ist die (Bi)Lobektomie bzw. Pneumonektomie mit mediastinaler Lymphadenektomie. Im Stadium IIIA (IIIB) ist eine neoadjuvante Chemo(radio)therapie indiziert, im Stadium IV (IIIB) eine palliative Chemo(radio)therapie. Adjuvante

Chemotherapien im Stadium I/II werden derzeit in klinischen Studien durchgeführt.

3. Bei suspekten mediastinalen Lymphknoten (CT > 1 cm; PET positiv) ist eine Mediastinoskopie durchzuführen. Sind ipsi (N2)- und/oder kontralaterale (N3) mediastinale Lymphknoten positiv, erfolgt eine Induktionschemotherapie.

4. Singuläre Hirn- oder Nebennierenmetastasen sind keine Kontraindikation für die Resektion des Primärtumors. T4-Tumore (Infiltration resektabler Organe und der Hauptcarina) können – mit akzeptabler Prognose bei negativem Lymphknotenstatus – reseziert werden.

5. Domäne des hochmalignen kleinzelligen Lungenkarzinoms (SCLC; neuroendokriner Tumor Grad III) ist die Chemo(radio)therapie. Bei den neuroendokrinen Tumoren Grad II (atypisches Karzinoid) wird chirurgisch wie beim NSCLC vorgegangen, bei den prognostisch günstigen neuroendokrinen Tumoren Grad I (typisches Karzinoid) wird eine parenchymsparende Resektion durchgeführt.

Take-Home-Messages

1. Therapy of lung cancer should be based on a multimodality approach and interdisciplinary teamwork. Histology and clinical stage (mediastinal lymph node status) are of prognostic significance.

2. Standard procedures in stage I/II are (bi)lobectomy and pneumonectomy in combination with systematic mediastinal nodal staging. In stage IIIA (IIIB) induction chemotherapy is indicated; in stage IV (IIIB) palliative chemo(radio)therapy is performed. Adjuvant chemotherapy in stage I/II is administered in clinical trials.

3. Staging mediastinoscopy is performed if lymph nodes are > 1 cm in CT, especially if PET scan is positive. If mediastinal nodes (N2/3) are positive, induction chemotherapy is performed.

4. Singular cerebral or adrenal gland metastases do not represent a contraindication to resection of the primary tumor. Tumors with infiltration of the carina or other resectable organs can be surgically removed with an acceptable prognosis if mediastinal lymph nodes are negative.

5. In small cell lung cancer (SCLC; neuroendocrine tumor grade III) chemo(radio)therapy is mandatory. In early stages surgery may be performed in addition to chemotherapy. Neuroendocrine tumors grade II (atypical carcinoid) are treated as NSCLC. Neuroendocrine tumors grade I (typcial carcinoid) have a good prognosis and undergo parenchyma saving resections.

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