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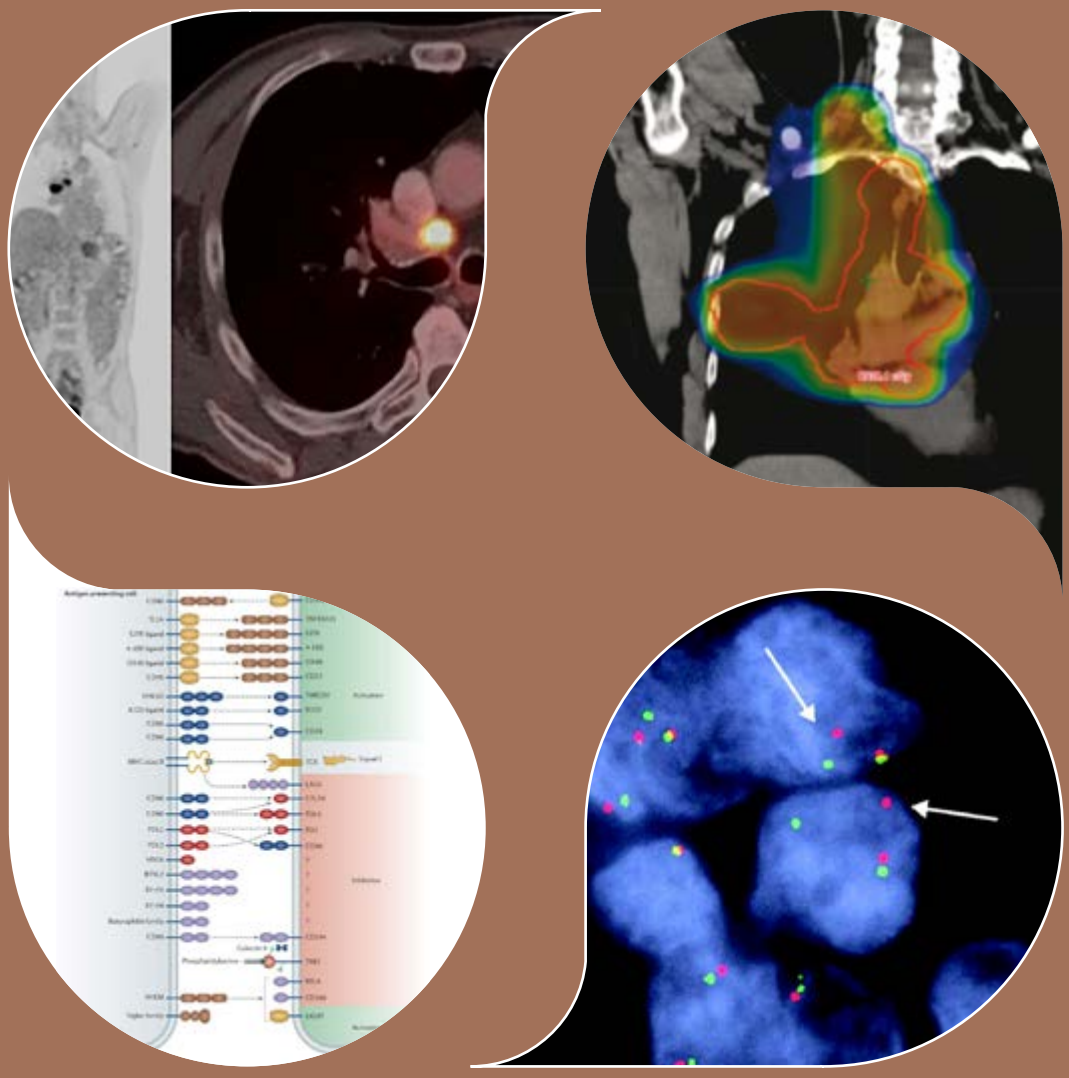
edited by
Rolf A. Stahel
Solange Peters
Marina Garassino

THORACIC TUMOURS

SECOND EDITION

ESSENTIALS *for* CLINICIANS



ESMO Press

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Essentials for Clinicians

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Edited by

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Preface

We are witnessing big improvements in the diagnosis and therapy of thoracic malignancies. This second edition of *Thoracic Tumours: Essentials for Clinicians* encompasses the whole spectrum of current knowledge and provides clinicians with an easily accessible overview as well as a focus on key developments in thoracic malignancies.

Under the editorial supervision of Solange Peters and Marina Garassino, all the chapters have been contributed by experts in thoracic malignancies highly regarded in their field, including epidemiology, pathology, pulmonology, surgery, radiotherapy and medical oncology.

The topics range from pathology to early diagnosis and screening to the current therapeutic options for lung cancer. In addition, essential information on less common forms of thoracic malignancies such as mesothelioma, thymic malignancies and neuroendocrine tumours is included. The short and to the point text together with the many colour illustrations provide the reader with a pleasurable way to acquire information.

Professor Rolf Stahel
Zürich, Switzerland

Editors

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Rolf A. Stahel, MD is Chair of the Comprehensive Cancer Center Zürich, Head of the Center for Lung and Thoracic Oncology and Senior Staff Physician at the Department of Medical Oncology and Hematology, University Hospital of Zürich as well as Titular Professor of Medicine at the University of Zürich, Switzerland.

He is a member of the International Association for the Study of Lung Cancer (IASLC), where he served as Chair of the Fellowship Committee and was a member of the board of directors. In the European Society for Medical Oncology (ESMO) he has chaired several committees, is a member of the ESMO Council and was ESMO President from 2014 to 2015.

Professor Stahel is President of the Foundation Council of the International Breast Cancer Study Group (IBCSG) and President of the European Thoracic Oncology Platform (ETOP). He is Editor-in-Chief of *Lung Cancer*, Editor of *Cancer Treatment Reviews* and Editor of the series *Progress in Tumor Research*.

Solange Peters, MD, PhD

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Solange Peters is Professor and Chair of Medical Oncology as well as the thoracic malignancies programme in the Department of Oncology, University Hospital of Lausanne, Switzerland. Professor Peters' main field of interest is new biomarker discovery and validation in preclinical and clinical settings. She is also strongly involved and interested in multimodality trial building for locally advanced non-small cell lung cancer (NSCLC), as well as cancer immunotherapy.

Professor Peters has authored numerous peer-reviewed manuscripts and book chapters and serves as deputy editor of the *Journal of Thoracic Oncology*. Professor Peters is active in the educational programmes of the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC), notably working as the current editor of the ESMO lung cancer *Clinical Practice Guidelines*. She is the Chair of the ESMO Women for Oncology Committee and the youngest ESMO President-Elect ever, for a mandate in 2020-2021.

Marina Chiara Garassino, MD

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Dr Marina Chiara Garassino is Head of the Thoracic Unit at the Medical Oncology Division of the National Cancer Institute of Milan, Italy, where her main area of research is thoracic oncology.

She graduated in medicine from the University of Milan, and in 1999 she achieved her board specialisation in oncology and trained in various European institutions. From 2005 to 2011, she held a clinical post at the Fatebenefratelli Ophthalmic Hospital in Milan.

Dr Garassino is a member of the European Society for Medical Oncology (ESMO) Lung Cancer Faculty, the EU Policy Committee and Chair of the National Societies Committee. Previously, she was a member of the Publishing Working Group and ESMO National Representative in Italy. She is the President of Women for Oncology Italy. Dr Garassino has published 130 articles in English.

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Abbreviations

ABCP	Atezolizumab/bevacizumab/carboplatin/paclitaxel
AC	Atypical carcinoid
ACP	Atezolizumab/carboplatin/paclitaxel
ACTH	Adrenocorticotropic hormone
ADC	Adenocarcinoma
AE	Adverse event
AIS	Adenocarcinoma *in situ*
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukaemia
APC	Antigen-presenting cell
ASCO	American Society of Clinical Oncology
ATP	Adenosine triphosphate
BCP	Bevacizumab/carboplatin/paclitaxel
BID	Twice daily
BSC	Best supportive care
CAR	Chimeric antigen receptor
ChT	Chemotherapy
CI	Confidence interval
CIS	Carcinoma *in situ*
CISH	Chromogenic *in situ* hybridisation
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CRS	Cytokine release syndrome
CRT	Chemoradiotherapy
CT	Computed tomography
ctDNA	Circulating tumour DNA
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DC	Dendritic cell
DCR	Disease control rate
DFS	Disease-free survival
DoR	Duration of response
EBUS	Endobronchial ultrsound
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMT	Epithelial mesenchymal transition
EORTC	European Organisation for Research and Treatment of Cancer
EPP	Extrapleural pneumonectomy
ERCC1	Excision repair cross-complementation group 1
ES	Extensive stage
ETOP	European Thoracic Oncology Platform
EUS	Endoscopic ultrasound
EvG	Elastica van Gieson
FDA	Food & Drug Administration
FDG	Fluorodeoxyglucose
FGFR	Fibroblast growth factor receptor
FISH	Fluorescent *in situ* hybridisation
FNA	Fine needle aspiration
GGO	Ground glass opacity
GSP	General secretory pathway
HE	Haematoxylin–eosin
HER2	Human epidermal growth factor receptor 2
HIAA	Hydroxyindoleacetic acid
HR	Hazard ratio
IALT	International Adjuvant Lung Cancer Trial
IARC	International Agency for Research on Cancer
IASLC	International Association for the Study of Lung Cancer
ICI	Immune checkpoint inhibitor
IDO	Indoleamine 2,3-dioxygenase
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IMRT	Intensity modulated radiotherapy
IPD	Individual patient data
ISH	*In situ* hybridisation
ITT	Intention to treat
LACE	Lung Adjuvant Cisplatin Evaluation
LAG-3	Lymphocyte-activation gene 3
LAR	Long-acting release
LCNEC	Large cell neuroendocrine carcinoma
LDCT	Low-dose computed tomography
LINAC	Linear accelerator
LN	Lymph node
mAb	Monoclonal antibody
MEN-1	Multiple endocrine neoplasia type 1
MHC	Major histocompatibility complex
MKI	Multikinase inhibitor
MPE	Malignant pleural effusion
MPM	Malignant pleural mesothelioma
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
nAChR	Nicotinic acetylcholine receptor
NET	Neuroendocrine tumour
NGS	Next generation sequencing
NK	Natural killer
NLST	National Lung Screening Trial
NRT	Nicotine replacement therapy
NSCLC	Non-small cell lung cancer
NSE	Neuron-specific enolase
NSQ	Nonsquamous
NTRK	Neurotrophic tyrosine receptor kinase
ORR	Objective response rate / Overall response rate
OS	Overall survival
P/D	Pleurectomy/decortication
PAH	Polycyclic aromatic hydrocarbon
PAS	Periodic acid-Schiff
PCI	Prophylactic cranial irradiation
PCR	Polymerase chain reaction
PD-1/2	Programmed cell death protein 1/2
PDGFR	Platelet-derived growth factor receptor
PD-L1/2	Programmed death-ligand 1/2
PET	Positron emission tomography
PFS	Progression-free survival
PORT	Postoperative radiotherapy
PS	Performance status
QD	Once a day
qPCR	Quantitative polymerase chain reaction
RATS	Robotic-assisted thoracic surgery
RCT	Randomised clinical trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response rate
RT	Radiotherapy
SABR	Stereotactic ablative radiotherapy
SBM	Solitary brain metastasis
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer
SPN	Solitary pulmonary nodule
SQ	Squamous
SR	Sleeve resection
SST	Superior sulcus tumours
TBNA	Transbronchial needle aspiration
TC	Typical carcinoid
TCR	T cell receptor
T-DM1	Ado-trastuzumab emtansine
Teff	Effector T cell
TIM-3	T cell immunoglobulin and mucin domain 3
TKI	Tyrosine kinase inhibitor
TMB	Tumour mutation burden
TMD	Transmembrane domain
TNM	Tumour, Node, Metastasis
TPC	Tunnelled pleural catheter
TRK	Tropomyosin receptor kinase
TTF1	Thyroid transcription factor 1
TTP	Time to progression
UFT	Tegafur-uracil
UICC	Union for International Cancer Control
VATS	Video-assisted thoracoscopic surgery
VDT	Volume doubling time
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBRT	Whole brain radiotherapy
WHO	World Health Organization

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We thank all the contributors who have been patient in seeing their work coming to fruition and have kindly updated their chapters with the most recent data. We also thank Jean-Yves Douillard, who did a thorough review of many chapters, and Arsela Prelaj, for her work on providing the update to the treatment schedules.

A

What every oncologist should know

1 Epidemiology, pathogenesis and risk factors

USA Incidence and mortality

Lung cancer is the leading cause of cancer-related death in both genders worldwide. In 2019, it is expected to account for 228 150 new cases and 142 670 deaths in the USA.

It is the second most common solid tumour type in both genders, after prostate cancer in men and breast cancer in women.

Lung cancer is the cause of 24% and 23% of all male and female cancer-related deaths, respectively, exceeding prostate and breast cancer mortality.

Estimated New Cases

Males			Females		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	8%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All Sites	**870,970**	**100%**	**All Sites**	**891,480**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All Sites	**321,670**	**100%**	**All Sites**	**285,210**	**100%**

Fig. 1.1

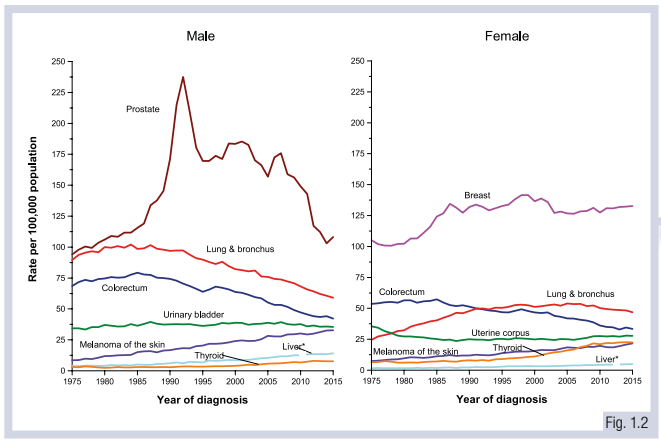

Fig. 1.2

In both genders, USA lung cancer incidence rates increased from the 1970s, until the mid 1980s in men and the late 1990s in women.

Incidence is now beginning to decline, possibly due to the reduction in smoking prevalence. Differences in lung cancer incidence patterns between men and women reflect mainly historical disparities in smoking habits.

Cigarette smoking prevalence peaked about 20 years later in women than in men.

The USA lung cancer death rate rose for most of the 20th century, peaking at the beginning of the 1990s for men, and almost two decades later for women.

Lung cancer death rates have followed the same trend as smoking prevalence and incidence rates, demonstrating the strong correlation between the major risk factor and the disease and the poor prognosis of this malignancy, respectively.

Recently, a steady decline in lung cancer death rates has been observed in both sexes, as a result of combined improvements in primary prevention, control of associated risk factors, and treatment.

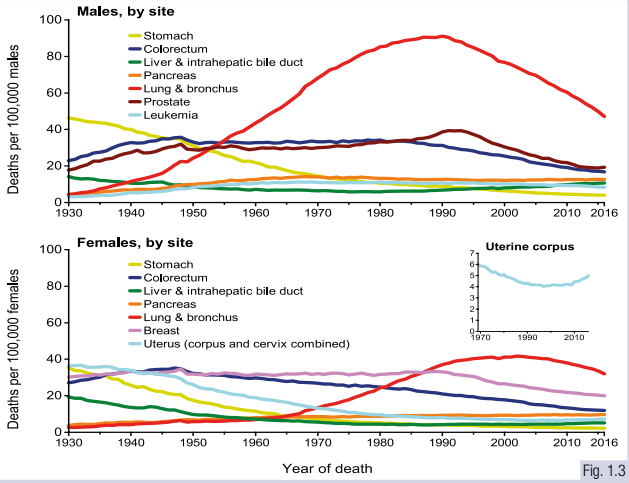

Fig. 1.3

REVISION QUESTIONS

1. What is the lung cancer incidence trend in the USA over the last 20 years?
2. Is there a difference in lung cancer mortality rates between men and women?
3. What is the percentage of deaths due to lung cancer among all cancer-related deaths?

European scenario

European predictions for the year 2018 in men and women, estimated 267 000 and 121 000 lung cancer-related deaths, respectively, corresponding to about 20% of total cancer deaths in both sexes combined.

Lung cancer is the primary cause of cancer-related deaths in men in Europe and is second only to breast cancer in women, with a very slight difference in the number of expected deaths.

European mortality for lung cancer peaked in the late 1980s in men and began declining later, while in women, in contrast to the USA scenario, mortality continues to increase with 26.4 cases/100 000 in 2018. An opposite trend has been observed in breast cancer.

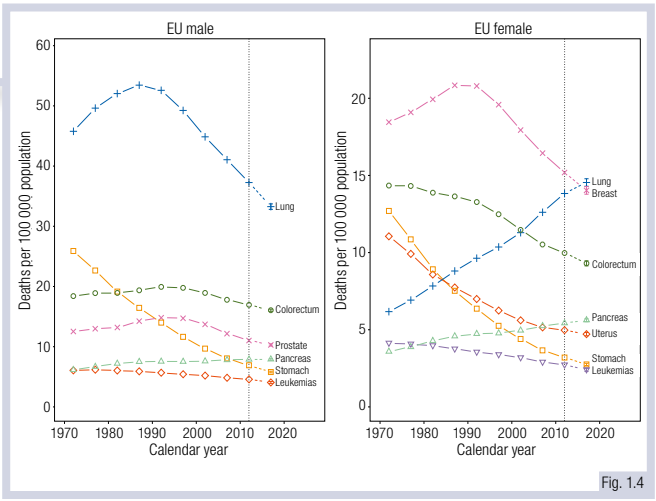

Fig. 1.4

An evaluation performed in 2018 revealed that the lung cancer incidence rate for men was highest in Central and Eastern European countries and lowest in Northern Europe.

On the contrary, with the exception of Hungary, the incidence rate for women was highest in Northern European countries and lowest in Eastern Europe.

Considering both sexes combined, the highest incidence rates were seen in Hungary (incidence rate 111.6 cases/100 000 for men and 58.7 cases/100 000 for women).

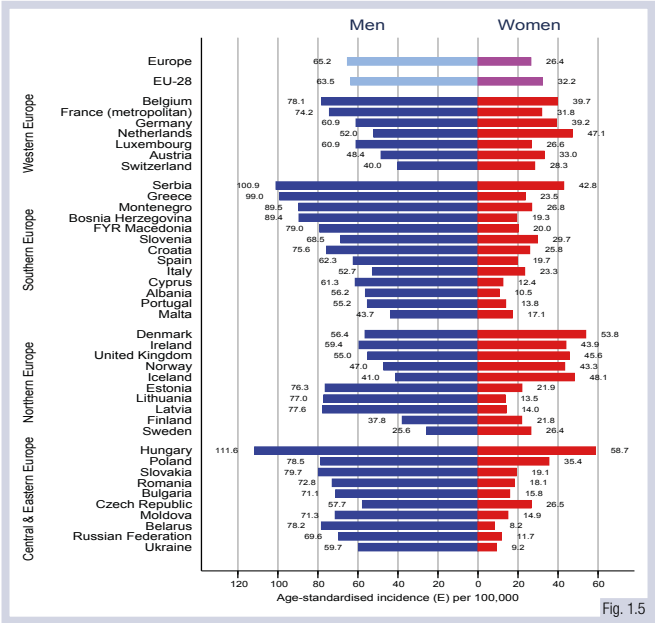

Fig. 1.5

Lung cancer rates in underdeveloped countries are lower than in developed ones, although incidence and mortality are slowly increasing.

The World Health Organization estimates that lung cancer deaths worldwide will continue to rise, largely as a result of an increase in global tobacco consumption (over one billion smokers worldwide).

Worldwide, every year, as many people die from lung cancer as the cumulative number resulting from prostate, breast and colon cancers.

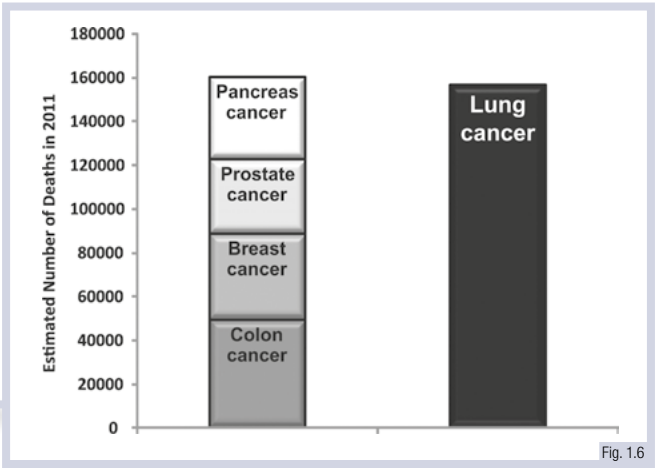

Fig. 1.6

REVISION QUESTIONS

1. Are there differences in the lung cancer mortality rates between the USA and Europe?
2. Is lung cancer incidence homogeneous throughout Europe?
3. What is the mortality rate due to lung cancer compared with other 'big killers'?

Clinical features and survival expectancy

Around only 15% of all lung cancer cases are diagnosed at an early stage, with a 5-year survival rate >50%.

In a large percentage of cases, lung cancer is diagnosed at an advanced stage with distant metastases and a 5-year survival rate of about 5%.

The 5-year survival rate for all lung cancer stages combined is about 18%.

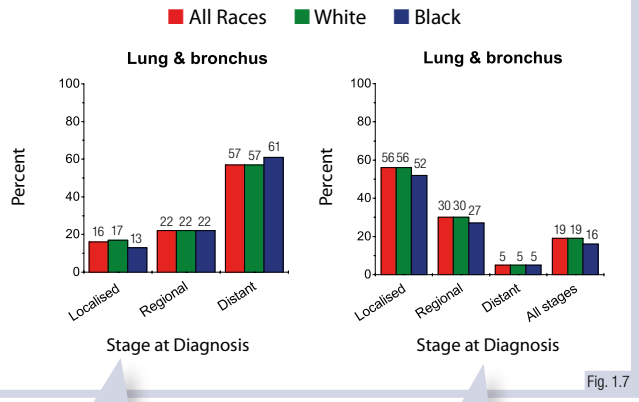

Fig. 1.7

Stage distribution by race, United States, 2008-2014

5-year relative survival rates by race and stage at diagnosis, United States, 2008-2014

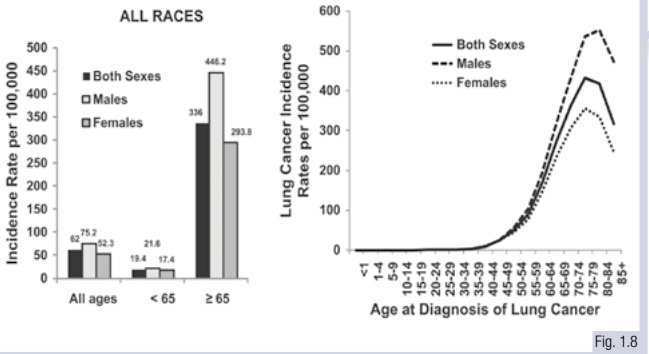

Fig. 1.8

Lung cancer in both sexes is predominantly diagnosed in the elderly population (median age at diagnosis is 71 years).

Compared with men, women are less likely to have a smoking history, are generally younger at the time of diagnosis, and have a better survival expectancy at any stage, independent of the therapeutic approach.

Lung adenocarcinoma is the most common histological subtype among women.

Adenocarcinoma accounts for 38.5% of all lung cancer cases, while squamous cell carcinoma and large cell carcinoma account for 20.0% and 2.9%, respectively.

Over the past decades, adenocarcinoma incidence has progressively increased, and it has now replaced squamous cell carcinoma as the most prevalent non-small cell lung cancer histotype.

Lung adenocarcinoma is also the most represented histotype among never-smokers.

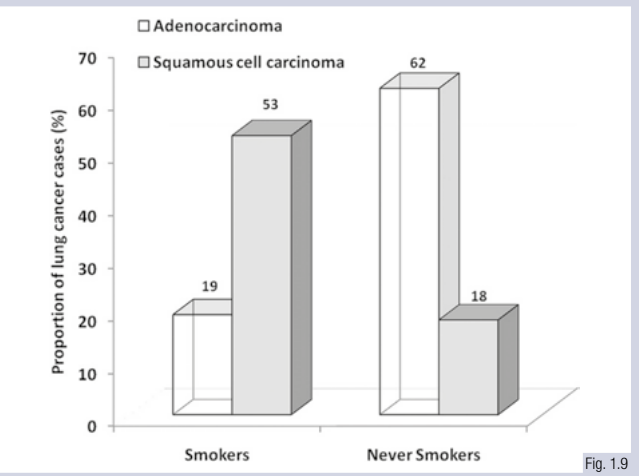

Fig. 1.9

REVISION QUESTIONS

1. What is the proportion of patients with lung cancer diagnosed at early stage of disease?
2. Is there a correlation between a clinical characteristic (such as female gender or smoking attitude) and one specific histotype?
3. Is the subtype histology prevalence the same compared with 30 years ago?

Pathogenesis of lung cancer

The major function of the lungs is respiratory exchange. Inhaled air and potentially dangerous substances are conducted to the alveoli through a network of bronchi and bronchioles.

The putative stem cells of the bronchus are basal cells, which are believed to give rise to the differentiation of ciliated, mucous and neuroendocrine cells.

Lung cancer may arise from all these differentiated and undifferentiated cells, from either the central (small cell lung cancer and squamous cell carcinoma) or the peripheral (adenocarcinoma) airway compartment.

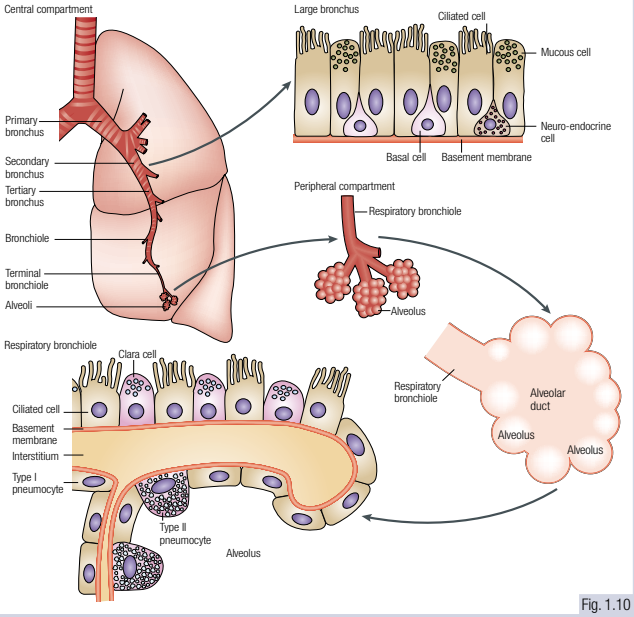

Fig. 1.10

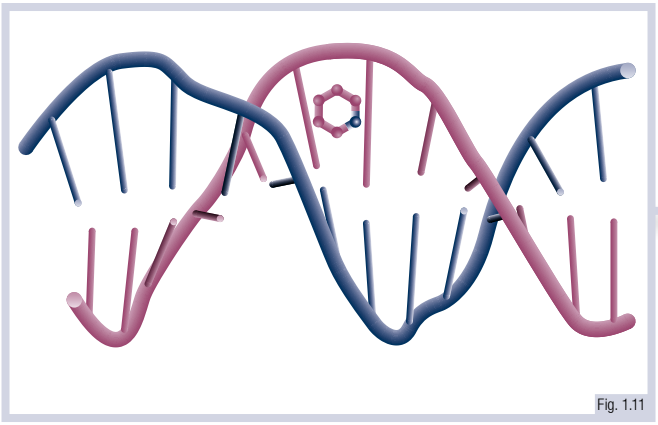
Fig. 1.11

The interaction between inhaled carcinogens and the epithelium of upper and lower airways leads to the formation of DNA adducts: pieces of DNA covalently bound to a cancer-causing chemical.

Repair processes may remove the DNA adducts and restore normal DNA, or alternatively cells with damaged DNA may undergo apoptosis.

If DNA adducts persist or are misrepaired, they result in a mutation and can cause genomic alterations. These are key events in lung cancer pathogenesis, especially if they occur in critical oncogenes and tumour suppressor genes.

Lung cancer pathogenesis is also affected by a genetic component: it relates to the host susceptibility to lung cancer, with or without exposure to carcinogens.

Studies on familial aggregation have supported the hypothesis that a multifactorial hereditary component is possible, even if a clear mechanism of familial transmission is still not described.

The addition of smoking to this genetic inheritance is associated with a three-fold increased lung cancer risk.

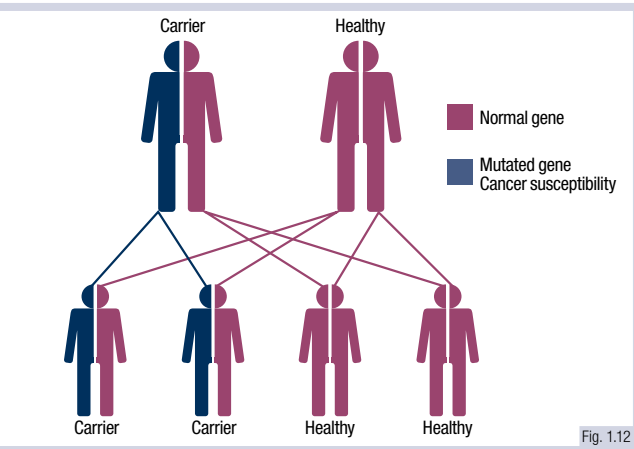

Fig. 1.12

REVISION QUESTIONS

1. Is there a unique and specific component of airway epithelium from which lung cancer can arise?
2. What are the consequences of the action of inhaled carcinogens on the airways' epithelium?
3. Does the hereditary component have a role in lung cancer pathogenesis?

Risk factors

Smoking is considered the principal risk factor in lung cancer patients, causing more than 80% of all cases.

Non-smoking-related risk factors include occupational exposure to asbestos, chromium, arsenic, cadmium, silica and nickel, as well as second-hand smoke, outdoor air pollutants, previous lung diseases, radon exposure and dietary factors.

The main modifiable risk factors for cancer pathogenesis are smoking habit, alcohol consumption, overweight and obesity, and the correct intake of meat, fruit and vegetables in the diet.

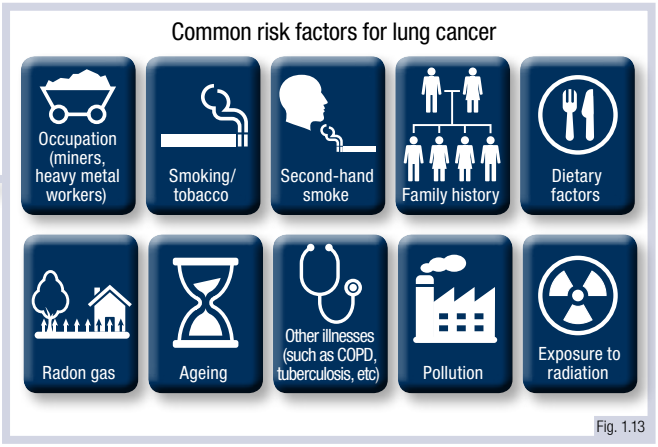

Fig. 1.13

COPD, Chronic obstructive pulmonary disease

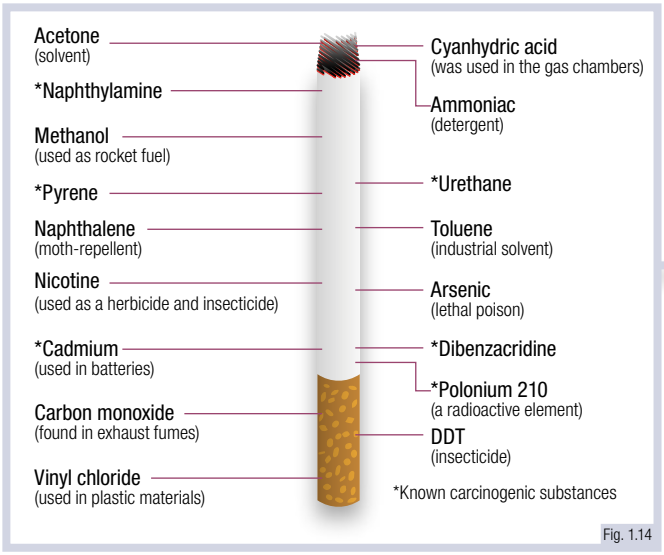

Fig. 1.14

The International Agency for Research on Cancer (IARC) has identified at least 50 carcinogens in tobacco smoke, targeting both central and peripheral airways.

The most potent carcinogens in cigarette smoke are the polycyclic aromatic hydrocarbons (PAHs) and the aromatic amines, N-nitrosamines. It also contains benzene, vinyl chloride, arsenic, chromium, radon, and its decay products, bismuth and polonium.

In the absence of such risk factors, the genetic susceptibility to lung cancer remains the only other parameter predisposing to the onset of the disease.

An estimated 10%–25% of lung cancers worldwide occur in never-smokers, defined as individuals who have smoked less than 100 cigarettes in their lifetime.

Cancers arising in never-smokers predominantly target the distal airways, favouring adenocarcinoma histology and female gender. One of the most relevant risk factors is environmental tobacco smoke exposure.

Lung cancer prevalence in never-smokers is higher in Asian countries, especially in women, probably due to the inhalation of cooking oil vapours and particles emitted by domestic use of coal for cooking and heating.

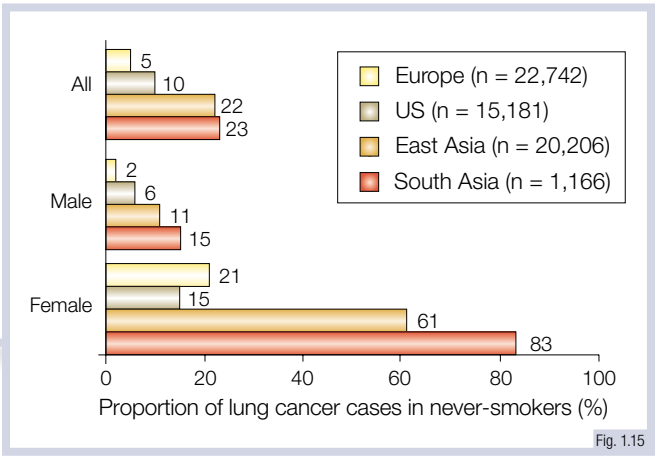

Fig. 1.15

REVISION QUESTIONS

1. What is the definition of 'never-smokers'?
2. Is there a different distribution of lung cancer in never-smokers across the world?
3. Which are the most potent carcinogens of cigarette smoke?

Summary: Epidemiology, pathogenesis, and risk factors

- Lung cancer is the leading cause of cancer-related death worldwide in both genders
- USA incidence rates in both genders increased until the 1990s and began to decline later, similar to the trend in mortality
- In Europe, lung cancer-related deaths in women are secondary only to breast cancer and, in contrast to the USA scenario, the mortality rate continues to increase
- Worldwide, every year, as many people die from lung cancer as from the other 'big killers' (prostate, breast, and colon cancer) combined
- Only 15% of all lung cancer cases are diagnosed at an early stage, while the majority present with distant metastases at diagnosis and a 5-year survival rate of about 5%
- Median age at diagnosis is 71 years and adenocarcinoma is now the most prevalent histotype
- Lung cancer may arise from all the differentiated and undifferentiated cells of the upper and lower airways. The formation of DNA adducts as a consequence of the inhalation of carcinogens plays a central role in lung cancer pathogenesis
- Lung cancer pathogenesis is also affected by a genetic multifactorial susceptibility, which may be further influenced by exposure to certain carcinogens
- Smoking is the principal risk factor for lung cancer, causing more than 80% of all cases
- Non-smoking-related risk factors include occupational exposure to carcinogens, second-hand smoke, pollution, dietary factors, radon exposure and genetic susceptibility

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2 Prevention and screening of lung cancer

Smoking cessation

Nicotine dependence – also called tobacco dependence – is an addiction to tobacco products caused by nicotine products present in tobacco.

Nicotine binds nicotinic acetylcholine receptors (nAChRs), increasing levels of several neurotransmitters which contribute to inducing strong dependence.

Proven treatments fall into two major categories: psychosocial counselling (also called behavioural support) and pharmacotherapy. Combining the two enhances the success rate.

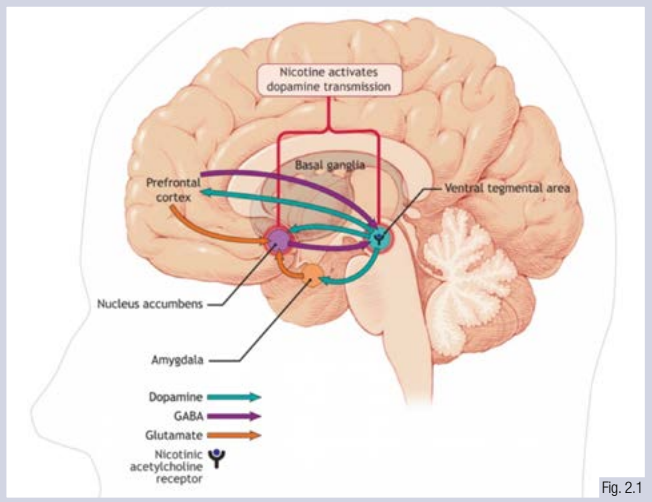


Fig. 2.1

GABA, *Gamma*-aminobutyric acid.

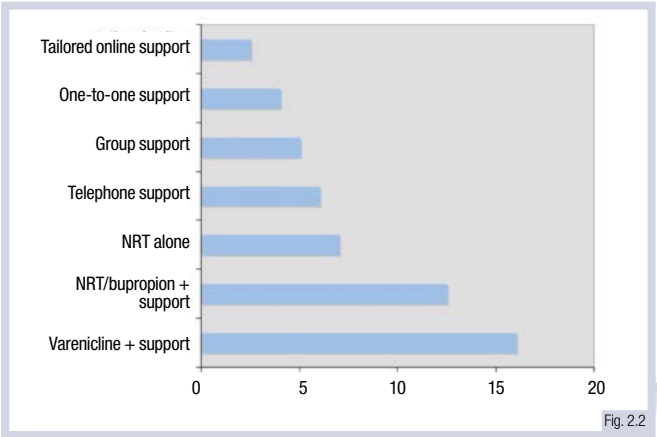


Fig. 2.2

NRT, Nicotine replacement therapy.

Three first-line treatment categories are approved in the USA and many other countries: nicotine replacement therapy (NRT), bupropion (atypical antidepressant), and varenicline or cytisine (selective nicotine receptor partial agonists).

Varenicline, the newest product to market, is effective, but enthusiasm has been tempered by post-marketing concerns about psychiatric side effects and possible increased risk of cardiovascular events. A similar compound is available at lower cost and comparable in efficacy (cytisine).

The figure shows percentage increases in the success rate for smoking cessation at 6 months compared with unaided attempts for each type of cessation support.

Smoking cessation is associated with anger, anxiety, depression, impaired concentration, impatience, insomnia and restlessness. These symptoms peak within the first week and last 2–4 weeks.

The table summarises the immediate and late benefits of smoking cessation.

The risk of cardiovascular events reduces rapidly after cessation, while oncological risks remain higher than those of never smokers for ~15 years.

Within 20 min, blood pressure and heart rate decrease
Within 12 hours, carbon monoxide levels in the blood decrease to normal
Within 48 hours, nerve endings and sense of smell and taste start recovering
Within 3 months, circulation and lung function improve
Within 9 months, coughing and shortness of breath decrease
Within 1 year, the risk of coronary heart disease is cut by half
Within 5 years, the risk of stroke falls to that of a non-smoker, and the risks of developing several cancers (mouth, throat, oesophagus, bladder, uterine cervix) fall significantly
Within 10 years, the risk of dying from lung cancer is cut by half, and the risks of laryngeal and pancreatic cancers also decrease considerably
Within 15 years, the risk of coronary heart disease falls to that of a non-smoker; the risk of developing chronic obstructive pulmonary disease (COPD) also falls considerably

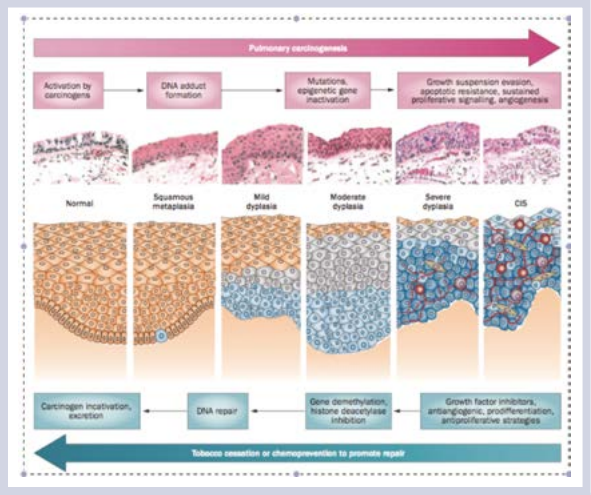
Fig. 2.3

REVISION QUESTIONS

1. What are the two main treatment categories for nicotine dependence?
2. What are the main symptoms that can occur after stopping smoking?
3. What are the early and late benefits of smoking cessation?

Chemoprevention of lung cancer

The figure illustrates the steps in the development of squamous cell lung cancer. Bronchial epithelial cells pass through several altered stages in the progression to carcinoma *in situ* (CIS).



CIS, Carcinoma *in situ*. Fig. 2.4

Adenocarcinoma, on the other hand, seems to be preceded by a premalignant lesion (atypical adenomatous hyperplasia) and preinvasive adenocarcinoma *in situ* (AIS, formerly known as bronchoalveolar carcinoma) which progresses to invasive cancer.

Chemopreventive agents are expected to promote tissue/cell repair and block progression, by suppressing inflammation, interfering with growth stimulation, restoring epithelial differentiation and/or improving immune surveillance.

Intervention	Endpoint	*n*	Outcome
13-cis-retinoic acid	Metaplasia, dysplasia	100	Negative
Fenretinide	Metaplasia	82	Negative
Etretinate	Sputum atypia	150	Negative
Beta-carotene	Sputum atypia	1067	Negative
Vitamin B12/folate	Sputum atypia	73	Negative
Budesonide	Dysplasia	112	Negative for primary endpoint; fewer nodules in treatment group
Budesonide	Nodule size	202	Negative
Fluticasone	Nodule size and number	201	Negative
Anethole dithiolethione	New dysplastic lesions	101	Negative for primary endpoint; rate of worsening lower in treatment group
Iloprost	Dysplasia	152	Positive in former smokers only (improved endobronchial histology)
Celecoxib	Ki-67 Ki-67	204 101	Positive (decreased Ki-67 labelling index in former smokers) Positive (decreased Ki-67 labelling index in former smokers)
Myo-inositol	Dysplasia	26	Promising: a phase I trial with historical control

Fig. 2.5

Phase III lung cancer prevention trials have tested aspirin, retinyl palmitate, 13-cis-retinoic acid, vitamin E, multivitamin supplement, mineral supplement, selenium and beta-carotene. All were ineffective. Beta-carotene was harmful to current smokers.

Phase II cancer prevention trials rely on intermediate biological endpoints as surrogates of cancer incidence and mortality.

The table shows the main published phase II trials, types of agent used, number of cases and results. No trial has shown a clear benefit for a chemopreventive agent compared to placebo.

While in the past most studies had precursors of squamous cell carcinoma as potential pathological target lesions, after the introduction of lung cancer screening, more recent studies have focused on precursors of adenocarcinoma (sub-solid peripheral lesions).

Results of meta-analysis on the effect of daily aspirin on long-term risk of cancer death led to aspirin being considered as one of the most promising investigational cancer prevention agents. Aspirin was associated with reduced mortality risk for adenocarcinoma affecting several distinct organs (-40% for lung cancer adenocarcinoma).

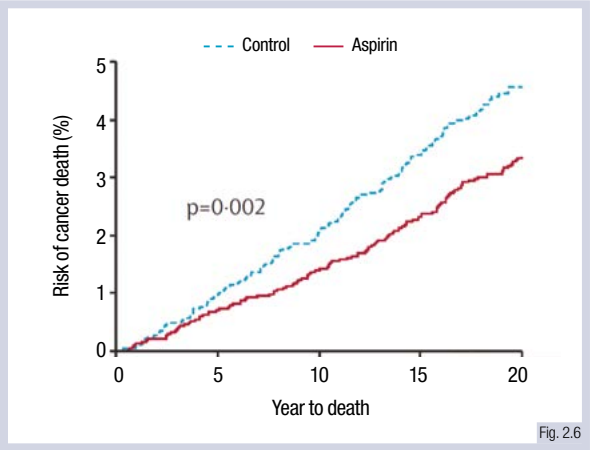


Fig. 2.6

Recent data from a large randomised, placebo-controlled study on canakinumab, an interleukin-1 beta inhibitor given for cardiovascular prevention in CRP (C-reactive protein)-positive patients, showed a significant reduction in lung cancer incidence and mortality.

REVISION QUESTIONS

1. By what mechanisms do chemopreventive agents promote cell repair and block tumour progression?
2. Have chemopreventive agents against lung cancer proven effective when tested in phase III trials?
3. What are the main endpoints of phase II trials on lung cancer prevention?

Chest X-ray and low-dose computed tomography

The aim of screening is to detect lung cancer at a stage when it is not causing symptoms and when treatment is most successful.

Screening should: (a) improve outcomes; (b) be scientifically validated in terms of sensitivity and specificity; and (c) be low risk, reproducible, accessible and cost effective.

In the 1970s chest X-ray and sputum screening trials showed no mortality reduction in the screening arm compared with the no-screening arm. The results of the Mayo Lung Project, from over 10 000 high-risk men, are shown in the figure.

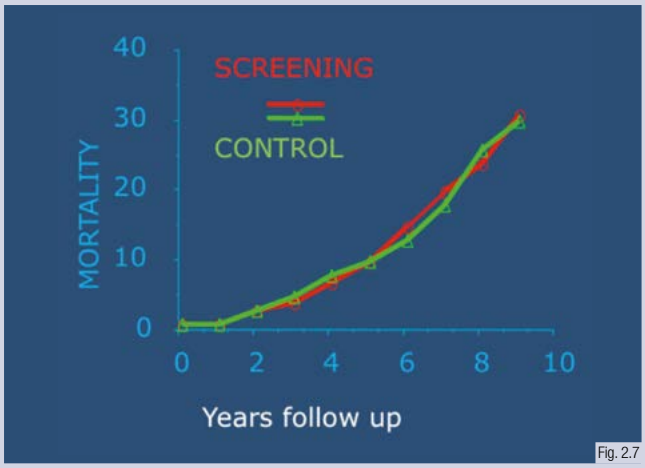


Fig. 2.7

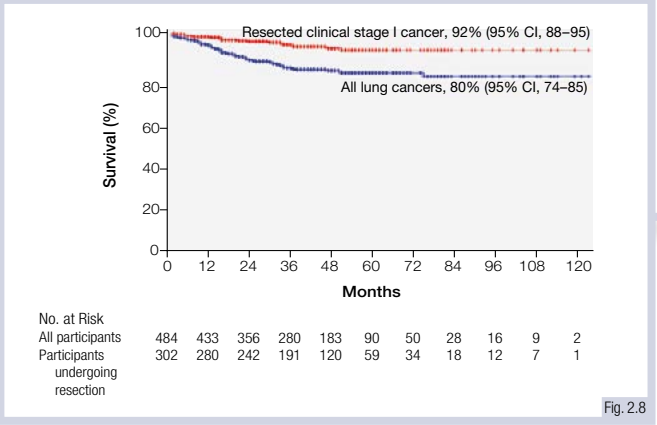


Fig. 2.8

CI, Confidence interval.

The introduction of spiral multi-detector computed tomography (CT) of the chest has made it possible to reduce the radiation dose to 10%–20% of that of standard CT, maintaining high sensitivity for small nodules.

The single arm I-ELCAP study used low-dose CT (LDCT) screening to detect 484 lung cancer cases among 31 000 participants. Overall cancer-specific survival was very high at 80% in a publication from 2006.

Other single-arm studies have shown similarly high survival, as well as favourable stage distribution and small mean size of diagnosed cancers.

Lung nodules detected at CT are divided into: solid, partially solid and non-solid. Volume doubling time (VDT) has been introduced to distinguish malignant from benign nodules and define the aggressiveness of malignant nodules.

No-contrast LDCT has limited resolution in centrally located cancers. The figures show a right lower lobe cancer diagnosed only at the 4th scan in one year. LDCT has much higher resolution in peripheral nodules. In fact, most cancers diagnosed by LDCT screening are peripheral stage I adenocarcinomas.

LCDT screening also gives useful information on collateral smoking-related diseases such as cardiovascular risk (with calcium score) and emphysema.

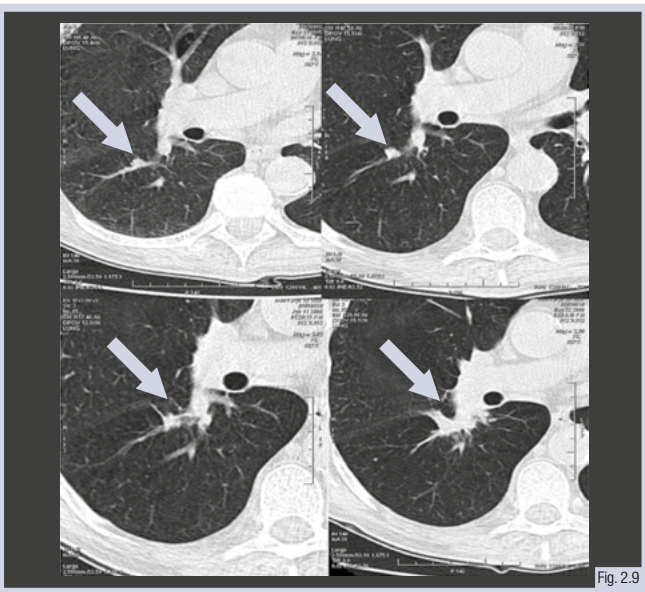


Fig. 2.9

REVISION QUESTIONS

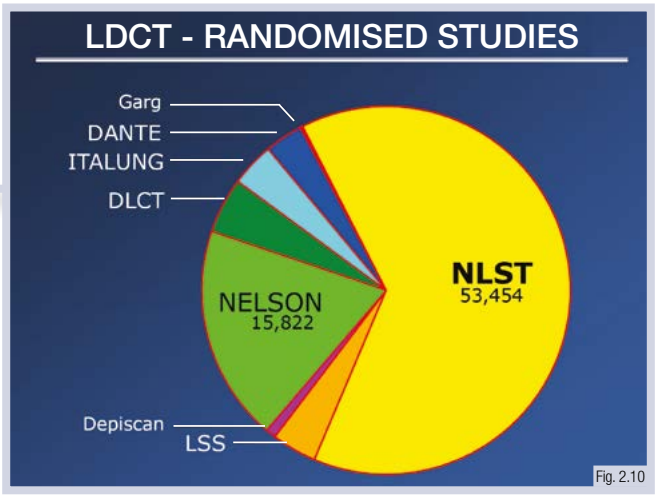
1. Did trials on chest X-ray screening show reduced lung cancer mortality in the screened arm?
2. What was the main result of the I-ELCAP study on LDCT screening for lung cancer?
3. What is the most common type of lung cancer diagnosed by LDCT screening?

LDCT screening for lung cancer: results of randomised studies and guidelines

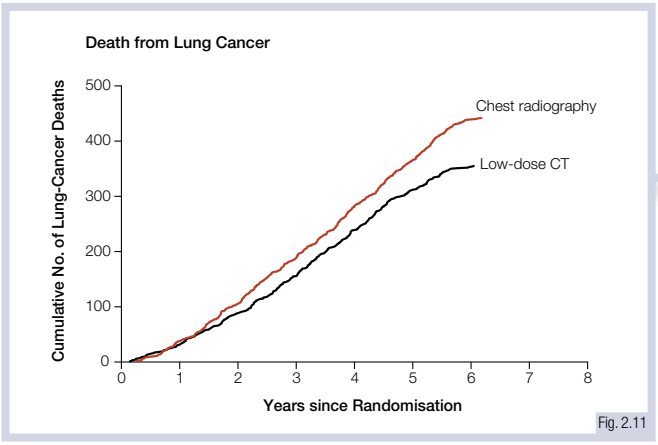
Over-diagnosis and lead-time bias may contribute to improved survival and stage shift found for screening-detected lung cancers compared with historical controls.

To overcome these biases and determine mortality reduction in LDCT-screened populations compared with controls, a number of randomised trials were started in Europe and the USA.

The USA National Lung Screening Trial (NLST) was a prospective, randomised lung cancer screening trial comparing annual LDCT scan with annual chest X-ray for 3 years.



DLCT, Danish Lung Cancer Screening Trial; LDCT, low-dose computed tomography; LSS, Lung Screening Study; NLST, USA National Lung Screening Trial.



CT, Computed tomography.

The NLST enrolled 53 454 high-risk participants aged 55–74 years who had at least a 30-pack-year smoking history.

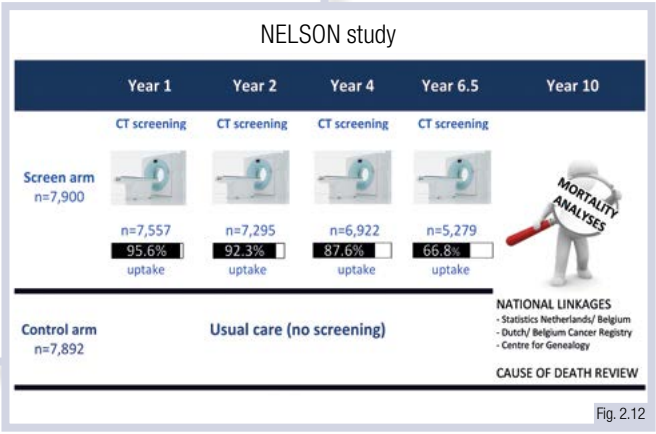
The NLST found a 20% reduction in lung cancer-specific mortality and a 7% reduction in all-cause mortality in the screened arm after 5 years.

Most published European studies did not find a significant reduction in mortality; however, recent data from the NELSON study showed a significant reduction in lung cancer mortality in the CT arm compared with the control (hazard ratio [HR] 0.84 in men, 0.58 in women).

As a consequence of the NLST and NELSON findings, most scientific organisations have recommended LDCT lung cancer screening implementation in high-risk individuals.

High-risk populations are defined according to the NLST (age >55 years, at least 30 pack-years). Those enrolled in LDCT screening should also adhere to smoking cessation programmes.

Most authorities agree that LDCT screening should take place only within a programme run by a centre with experience in CT screening, a dedicated multidisciplinary team to manage findings, and with quality and effectiveness control procedures in place.



CT, Computed tomography.

REVISION QUESTIONS

1. What are the potential biases of single-arm screening studies with LDCT?
2. Was the NLST able to demonstrate a reduction in lung cancer mortality in the screened arm?
3. What are the recommendations of several scientific societies to heavy smokers regarding the possibility to be screened?

Performance of LDCT screening and risk modelling

The figure shows the distribution according to VDT of lung cancers diagnosed over 5 years in a screening study; 10% of cases had VDT ≥600 days and were considered indolent or 'over-diagnosed'.

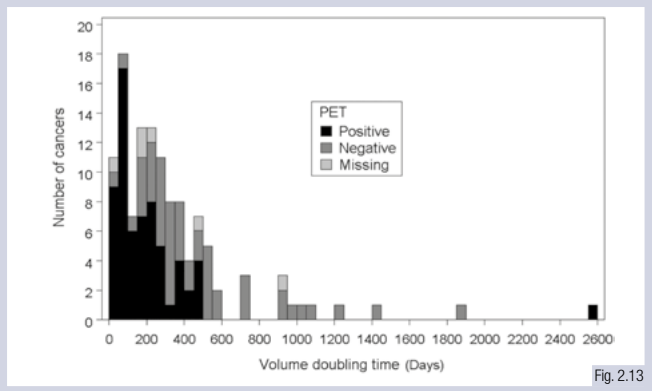


Fig. 2.13

PET, Positron emission tomography.

Another risk of screening is that invasive procedures are often performed for what is benign disease: 0%–25% of 'positive' nodules are diagnosed as benign in published studies.

Eight to nine percent of screening-detected lung cancers are estimated as diagnosed with delay, due to central position or fast-growing disease.

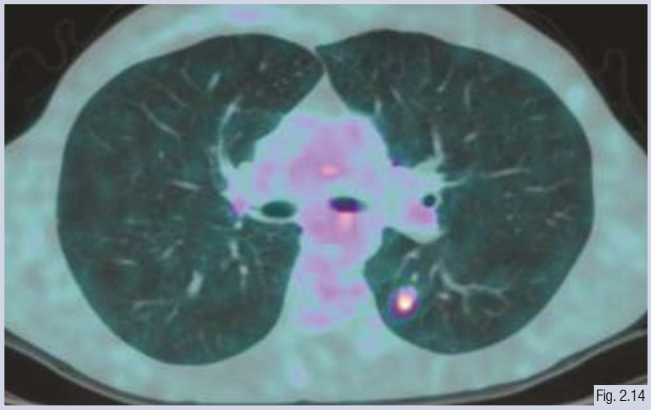


Fig. 2.14

To reduce the proportion of false-positives and false-negatives, diagnostic protocols have been developed to manage the high number of indeterminate nodules detected by CT screening.

A 'further investigation' threshold of 5 mm was recently amended to 6 mm; smaller nodules are investigated at the next annual scan. Positron emission tomography (PET) can be useful in reducing invasive investigations for differential diagnosis. PET-CT can reduce the use of more invasive procedures to diagnose benign disease.

The NELSON study introduced software-calculated VDT into the nodule management algorithm.

Models have been developed to estimate the risk of individuals developing lung cancer: to reduce both costs and the number of potentially harmful screening CT scans. PLCO12 has been validated in large screening cohorts.

The table summarises efficacy (area under ROC curve) of published risk models. Most models use epidemiological variables to estimate risk; some combine epidemiological risk factors with DNA repair assays.

The COSMOS risk model incorporated epidemiological variables with first screening CT findings. Validation is ongoing. Low-risk individuals identified by this model may benefit from an increased interval between screenings.

Author, publication year	Country	Lung cancer cases	Variables included in lung cancer risk prediction model	Model prediction accuracy: area under the ROC curve
Bach et al, 2003	USA	1070	Age, sex, asbestos exposure history, smoking history	0.72
Spitz et al, 2008	USA	725	Smoking history, emphysema, dust exposure, family history of cancer, asbestos exposure history, hayfever, DNA repair capacity, bleomycin treatment	Former smokers: 0.70 Current smokers: 0.73
Cassidy et al, 2008	UK	579	Smoking history, pneumonia, asbestos exposure history, previous cancer, family history of cancer	0.70
Young et al, 2009	New Zealand	239	Panel of 20 single nucleotide polymorphisms, age, family history of lung cancer	0.77
Calabro et al, 2010	Italy	57	FEV1%pred	0.70
Raji et al, 2010	UK	200	Smoking history, pneumonia, asbestos exposure history, previous cancer, family history of cancer + *SEZ6L* genotype	0.75
Maisonneuve et al, 2011	Italy	55	Model 1: Age, sex, asbestos exposure history, and smoking history Model 2: As model 1 + CT findings	Model 1: 0.62 Model 2: 0.76
Tammemagi et al, 2011	Multinational 10 sites	1040	Age, education, body mass index, family history of lung cancer, COPD, recent chest X-ray, smoking history	Model 1: 0.78 Model 2: 0.84
Hoggart et al, 2012	Multinational Europe	1250	Smoking history	Former smokers: 0.83 Current smokers: 0.82 Ever smokers: 0.84
Lin et al, 2012	China	633	Sex, lung disease history, occupational exposure, family history, smoking history	0.71
Li et al, 2012	China	2283	Smoking status + genetic score based on 5 single nucleotide polymorphisms (rs2736100, rs402710, rs1051730, rs4083914, rs4488809)	0.64
Park et al, 2013	Korea	10 007	Smoking history, body mass index, physical activity, fasting glucose levels	0.87

Fig. 2.15

COPD, Chronic pulmonary obstructive disease; CT, computed tomography; FEV1%pred, forced expiratory volume in 1 second % predicted.

REVISION QUESTIONS

1. What is the estimated rate of indolent cancers (potentially over-diagnosed cases) in LDCT screening?
2. Are the risks of false-positive cases and useless interventions limitations of LDCT screening as currently practised?
3. What are the objectives of risk modelling in the screening context?

Future perspectives in diagnosis and treatment

Lung cancer biomarkers could gain a potential role in risk stratification and early-stage disease detection. A simple blood test providing a reliable risk estimate might encourage widespread implementation and uptake of screening and refine its specificity.

Potential biomarkers for lung cancer screening include: serum autoantibodies, DNA hyper-methylation in sputum, volatile compounds in breath, proteomic methods and serum-micro RNAs.

More recently, mutation panel tests of cell-free circulating tumour DNA have emerged as promising potential screening markers.

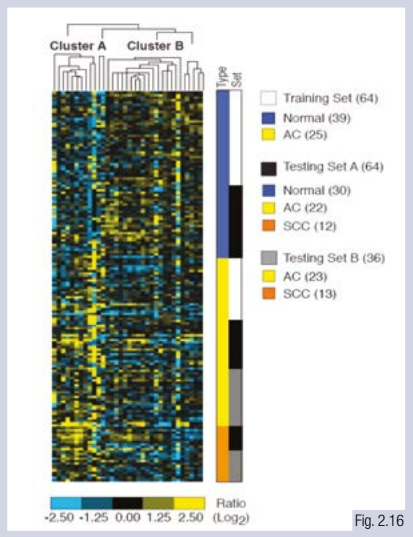


Fig. 2.16

AC, Adenocarcinoma; SCC, squamous cell carcinoma.

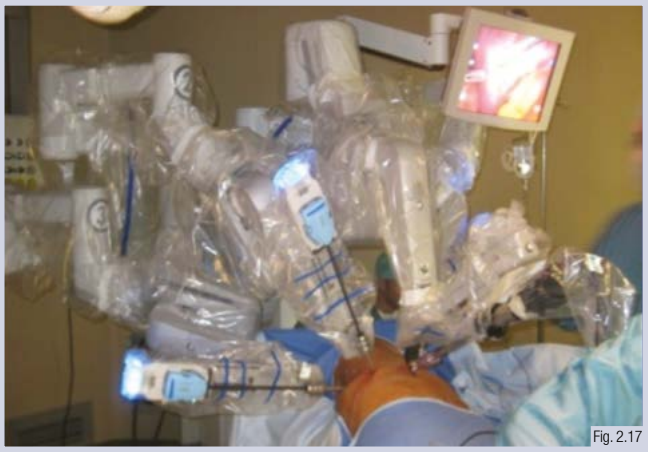


Fig. 2.17

Screening detects more cancers at an earlier stage, where less invasive surgery is justified – this is associated with less postoperative pain and fewer complications when compared with traditional open thoracotomy.

A meta-analysis found that the video-thoracoscopic approach seems to be associated with improved oncological outcomes, compared with open thoracotomy.

Robotic surgery is a fast-growing development of the video-thoracoscopic approach to lung cancer resection. Advantages are: high-definition 3D view, 7 degrees of movement, hand tremor filtration, and better ergonomics; although costs are higher.

Less extensive lung resections might also be justified in selected patients. Large retrospective studies show that oncological outcomes after sublobar resection in patients with cT1N0M0 non-small cell lung cancer (NSCLC) of 2 cm or smaller are equivalent to those for standard lobectomy. Randomised trials are ongoing.

Also for small (<1 cm) or PET-negative nodules, hilar and mediastinal lymph node dissection may not be essential as risk of nodal involvement is limited.

Pilot studies indicate that stereotactic ablative radiotherapy (SABR) is a promising alternative to surgical resection of very early cancers, as shown mainly in inoperable patients to date.

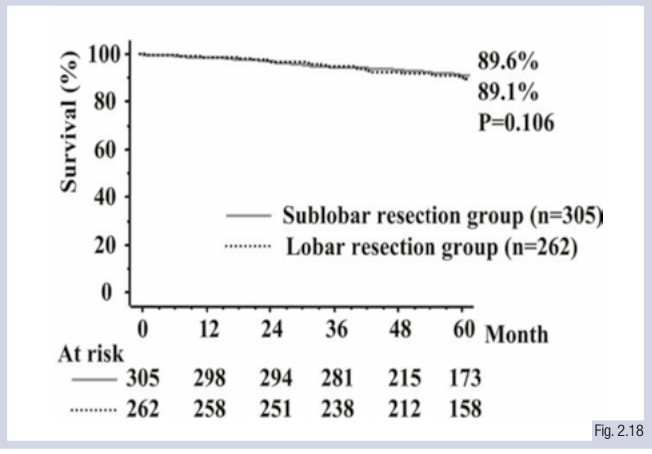


Fig. 2.18

REVISION QUESTIONS

1. Why are molecular markers likely to become important in the early detection of lung cancer?
2. What reduced-invasiveness surgical treatments are currently being used and tested for early-stage lung cancers?
3. Is minimally invasive surgery indicated for screening-detected lung cancers?

Summary: Prevention and screening of lung cancer

- Smoking is a chronic disease-promoting condition due to nicotine addiction
- Treatment with varenicline, cytisine, nicotine replacement therapy or bupropion is more effective than counselling alone in inducing people to stop smoking
- None of the chemopreventive agents tested in large phase III lung trials demonstrated a protective effect against lung cancer
- Recent phase II trials of chemopreventive agents adopted intermediate endpoints (adenocarcinoma precursors) as surrogates for cancer incidence and mortality
- Screening with chest X-ray is not effective in reducing lung cancer mortality, as demonstrated by several trials conducted in the 1970s
- Studies show that LDCT is highly sensitive for very early cancers. The results of the I-ELCAP study indicate that screening can diagnose lung cancer at an early stage and improve survival
- The USA NLST and the European NELSON study showed that LDCT screening significantly reduces lung cancer mortality in a defined high-risk population
- Most scientific societies recommend annual LDCT screening in smokers (>30 pack-years) over 55 years of age but risk models are emerging as new tools to select target population
- Diagnostic algorithms should be used to manage indeterminate nodules and reduce false positives
- Assessment of calcium score to prevent cardiovascular events is considered a collateral benefit of LDCT screening
- Persons undergoing LDCT screening should be actively encouraged to stop smoking

Further Reading

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Diagnosing lung cancer

Clinical presentation

Lung cancer may be found incidentally on chest imaging, within a screening programme, or may present with symptoms.

Symptoms as a result of the location of the primary tumour: cough, haemoptysis, dyspnoea, wheezing.

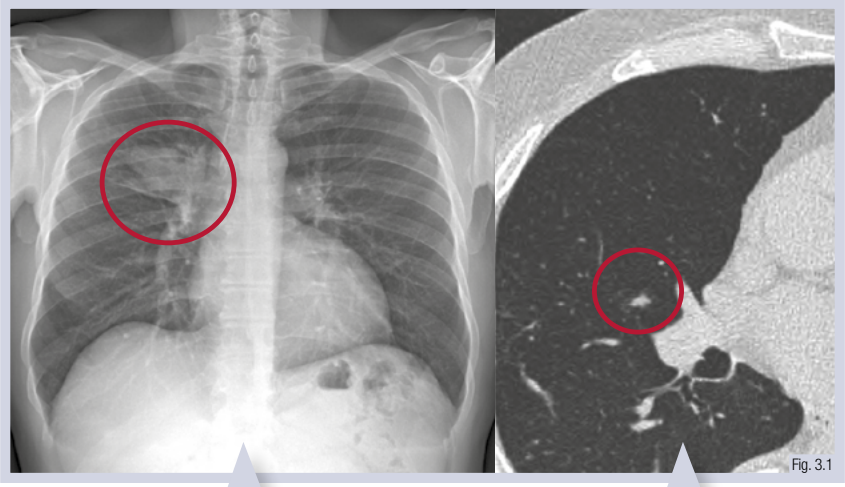

Fig. 3.1

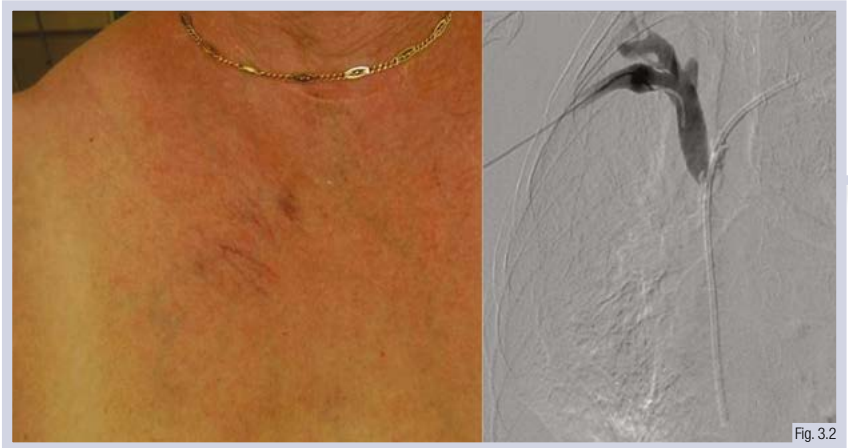

Fig. 3.2

Symptoms as a result of local invasion or compression of adjacent structures: chest pain (pleural, chest wall or mediastinal invasion), stridor, hoarseness (left recurrent laryngeal nerve), dysphagia, diaphragmatic paralysis (phrenic nerve), superior vena cava syndrome, Pancoast syndrome (shoulder pain, Horner upper extremity muscle wasting).

Symptoms as a result of distant metastasis: brain, bone, liver, adrenal gland; constitutional symptoms (loss of appetite, weight loss, fatigue, malaise).

Symptoms of paraneoplastic syndrome in 10% of lung cancer patients.

Endocrine	SIADH/hyponatraemia; PTH/hypercalcaemia; ACTH/Cushing; β-hCG/gynaecomastia; insulin-like factor/hypoglycaemia; growth hormone/acromegaly; TSH/hyperthyroidism; prolactin/galactorrhoea
Musculoskeletal	Hypertrophic osteoarthropathy; clubbing; polymyositis; dermatomyositis; myopathy
Neurological	Lambert-Eaton myasthenia; cerebellar degeneration; peripheral, encephalitis, or autonomic neuropathy
Other	Haematological (anaemia, thrombocytosis, leucocytosis, non-bacterial thrombotic endocarditis); skin (pruritus, erythema multiforme, acanthosis nigricans)

Fig. 3.3

ACTH, Adrenocorticotropic hormone; β-hCG, human chorionic gonadotropin; PTH, parathyroid hormone; SIADH, syndrome of inappropriate antidiuretic hormone; TSH, thyroid stimulating hormone.

REVISION QUESTIONS

1. How may a patient with lung cancer present?
2. What are the typical symptoms of locoregional lung cancer invasion?
3. What are the paraneoplastic syndromes seen in lung cancer?

Clinical presentation (continued)

An asymptomatic pulmonary lesion found incidentally on chest imaging is often a non-calcified solitary pulmonary nodule (SPN), which is defined as a solitary radiographic opacity ≤3 cm in diameter on a computed tomography (CT) scan with at least two thirds of its margins surrounded by normal lung parenchyma and not associated with intrathoracic lymph nodes (LNs) or a pleural effusion.

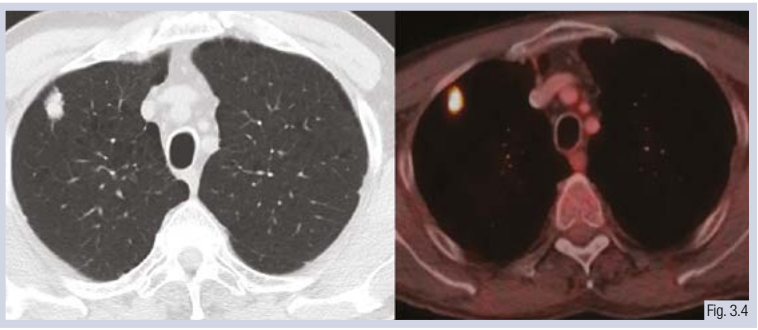

Fig. 3.4

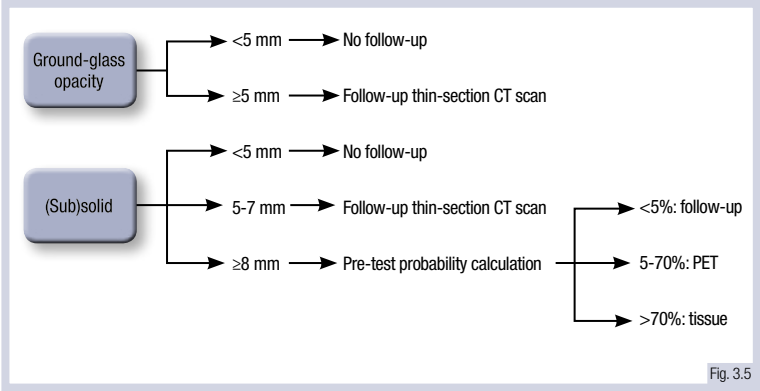

Fig. 3.5

CT, Computed tomography; PET, positron emission tomography.

Clinical evaluation of an SPN is dependent on:

1. Appearance and size on thin-section CT scan
2. Calculation of pretest probability of malignancy: consider the Brock model, the Mayo model, the Herder model.

Staging of lung cancer

Tumour, Node, Metastasis (TNM) staging is a multidisciplinary process involving physical examination and endoscopic, imaging and surgical techniques to establish the TNM category and stage group.

The TNM 8th edition paradigm is based solely on anatomy. Different types of TNM categories are used dependent on the time point of evaluation: c, clinical before any therapy; y, restaging after systemic therapy; p, pathological after surgical resection; r, at disease relapse.

The disease stage is the most important prognostic factor in lung cancer to date.

Stage group	T	N	M
Occult Ca	Tx	N0	M0
0	Tis	N0	M0
IA1	T1a(mi) T1a	N0 N0	M0 M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a T1b T1c T2a T2b T3	N1 N1 N1 N1 N1 N0	M0 M0 M0 M0 M0 M0
IVA	Any T Any T	Any N Any N	M1a M1b

Stage group	T	N	M
IIIA	T1a T1b T1c T2a T2b T3 T4 T4	N2 N2 N2 N2 N2 N1 N0 N1	M0 M0 M0 M0 M0 M0 M0 M0
IIIB	T1a T1b T1c T2a T2b T3 T4	N3 N3 N3 N3 N3 N2 N2	M0 M0 M0 M0 M0 M0 M0
IIIC	T3 T4	N3 N3	M0 M0
IVB	Any T	Any N	M1c

Fig. 3.6

Ca, Carcinoma; M, metastasis; N, node; T, tumour.

REVISION QUESTIONS

1. What is the definition of an SPN?
2. How is an SPN clinically evaluated?
3. What is clinical TNM staging?

Staging of lung cancer (continued)

Standard white light video bronchoscopy and autofluorescence bronchoscopy: in addition to pathological confirmation, it also permits endobronchial staging, i.e. detection of synchronous radio-occult endobronchial lesions or extension of the primary tumour.

T-descriptor:

- eT1: tumour ≤3 cm not extending into main bronchus (see Fig. 3.7)
- eT2: tumour involving main bronchus distal to main carina
- eT4: tumour involving main carina and/or distal trachea

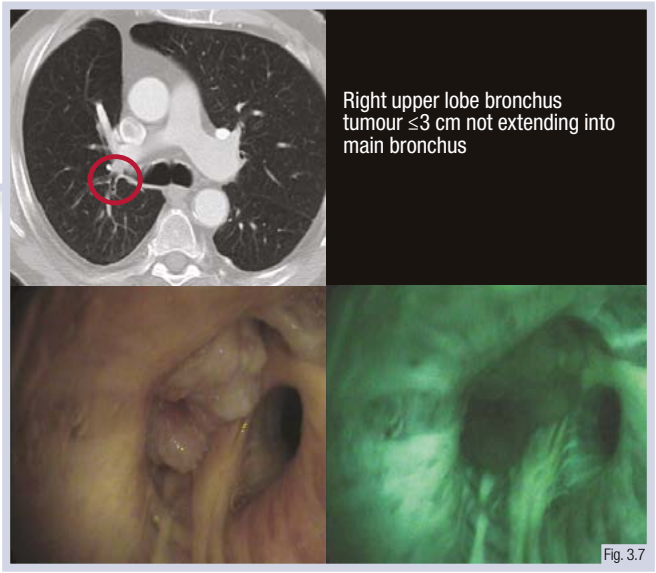

Fig. 3.7

CT scan of chest and upper abdomen are done in all patients to detect nodal and extranodal disease. Cranial magnetic resonance imaging (MRI) is required for patients with stage IB-III lung cancer.

Modern spiral contrast-enhanced multi-detector CT with multiplanar reconstruction offers great anatomical detail and is the standard to assess resectability, type of resection, and T-descriptor (e.g. relation to fissures, mediastinum or chest wall).

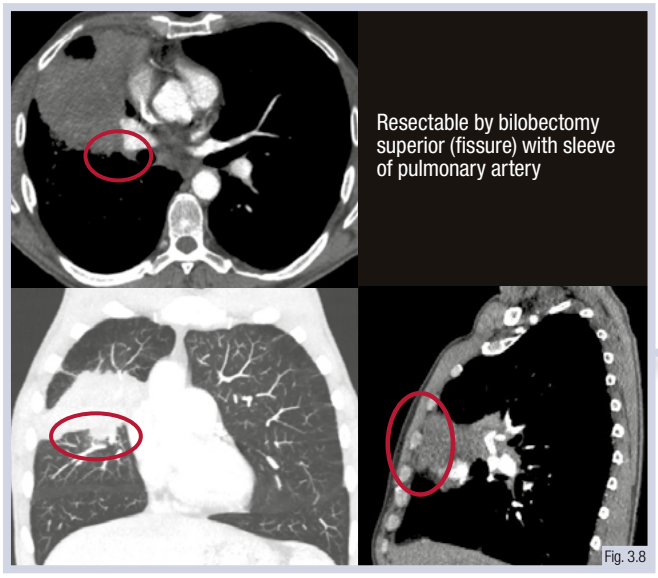

Fig. 3.8

Positron emission tomography (PET) has a complementary role to CT for two reasons:

- Detection of unexpected LN involvement or distant metastatic organ spread in 4%–12% of stage I-III lung cancer. The overall evidence points to significantly more accurate TNM staging with PET-CT.
- Determination of the nature of some equivocal lesions on conventional CT imaging.

Randomised trials demonstrated the utility of integrated PET-CT to significantly reduce futile thoracotomy rate or futile (chemo)radiotherapy rate.

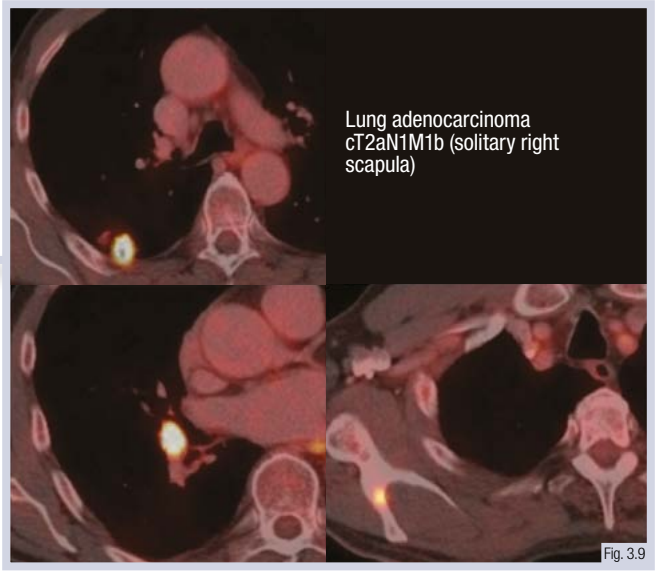

Fig. 3.9

REVISION QUESTIONS

1. How does bronchoscopy impact on the T-stage?
2. What is the value of a multi-detector CT scan of the chest?
3. What is the clinical impact of PET-CT?

Staging of lung cancer (continued)

For the N-descriptor, contrast-enhanced CT is accurate in delineating LN enlargement (defined as ≥10 mm short axis) and helps to allocate the nodal stations as defined in the International Association for the Study of Lung Cancer (IASLC) lymph node map (Rusch 2009).

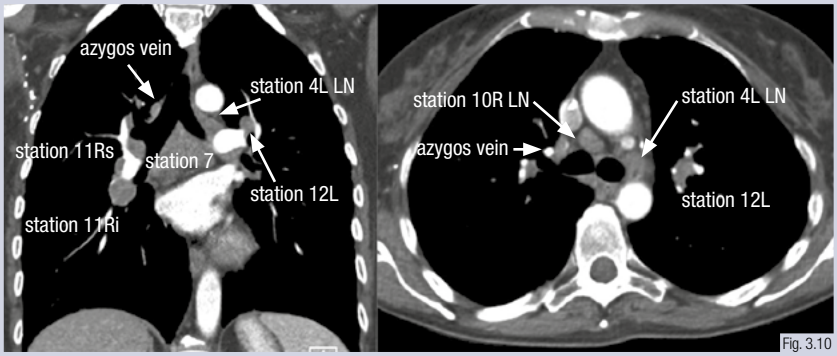

Fig. 3.10

LN, Lymph node.

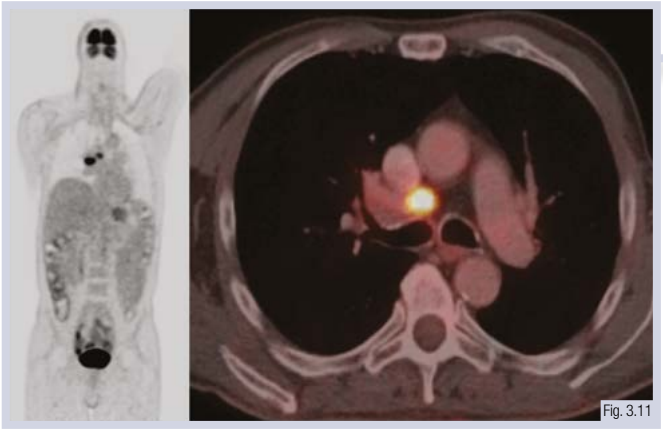
Fig. 3.11

For the N-descriptor, integrated PET-CT has a pooled weighted sensitivity of 0.76 (95% confidence interval [CI] 0.65–0.84) and specificity of 0.88 (95% CI 0.82–0.92).

False-negative PET findings in mediastinal LN staging occur in presence of:

- a central tumour
- N1 nodes
- tumour >3 cm
- enlarged LNs on CT

False-positive PET findings in mediastinal LNs are due to the fact that fluorodeoxyglucose (FDG) uptake is not tumour specific.

Invasive mediastinal nodal staging starting with endosonography (endobronchial ultrasound [EBUS] and endoscopic ultrasound [EUS]) and – if negative – surgical staging has been proven to detect significantly more mediastinal nodal disease compared with mediastinoscopy alone.

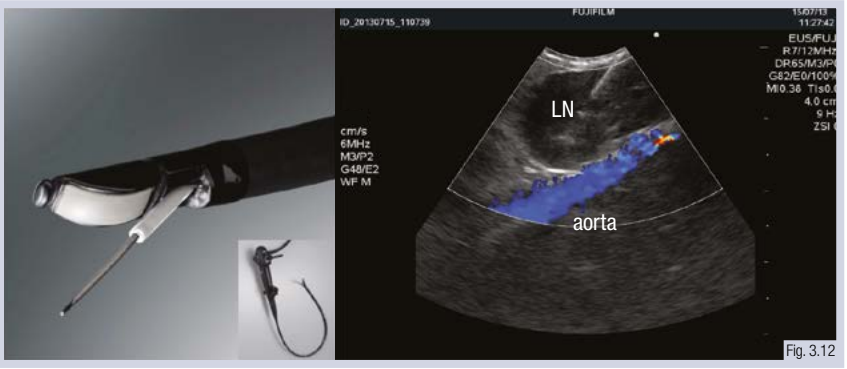

Fig. 3.12

LN, Lymph node.

The negative likelihood ratio of endosonography alone is 0.13–0.15. Therefore, in routine practice a preoperative surgical staging procedure (videomediastinoscopy or video-assisted thoracic surgery [VATS]) is indicated in case of a negative endosonography.

The implementation of endosonography for baseline mediastinal nodal staging clearly reduces the need for surgical mediastinoscopy.

REVISION QUESTIONS

1. What is the value of a chest CT scan for N-staging?
2. Which situations make mediastinal nodal staging by FDG-PET unreliable?
3. Discuss the post-test probability of combined endosonography.

Techniques for achieving histological diagnosis

Clinicians must obtain tissue from an appropriate tumour site in sufficient quantity and of appropriate quality for accurate pathological testing.

Factors to be considered in choosing the optimal technique:

- anticipated diagnostic yield and diagnostic accuracy
- invasiveness and risk of a procedure
- efficiency: accessible site, also relevant for staging
- local expertise available

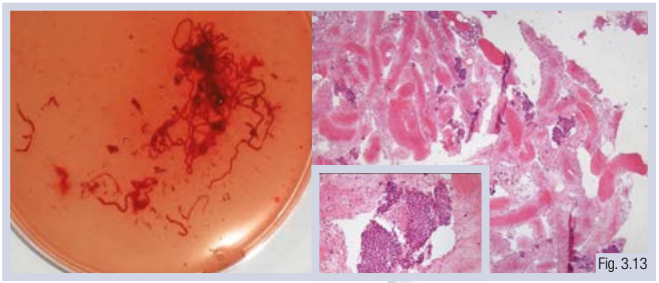
Fig. 3.13

Endoscopic biopsy:

- endobronchial biopsy (forceps biopsy or cryobiopsy)
- transbronchial lung biopsy: guidance by radial EBUS miniprobe
- **EBUS-controlled transbronchial needle aspiration (EBUS-TBNA)**
- **EUS-guided fine needle aspiration (EUS-FNA)**
- thoracocentesis or medical pleuroscopy

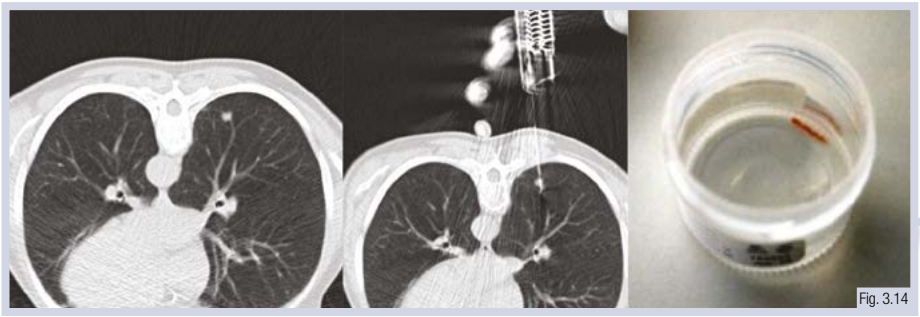
Fig. 3.14

Image-guided percutaneous core needle biopsy:

= CT-guided biopsy or ultrasound-guided biopsy of

- supraclavicular LN
- **pulmonary lesion: parenchymal or pleural node/mass**
- liver or adrenal metastasis

Surgical biopsy:

- **VATS for diagnostic wedge resection**
- VATS for sampling of nodal station 5/6 LNs
- cervical mediastinoscopy
- parasternotomy
- (solitary) bone, adrenal, or skin lesion

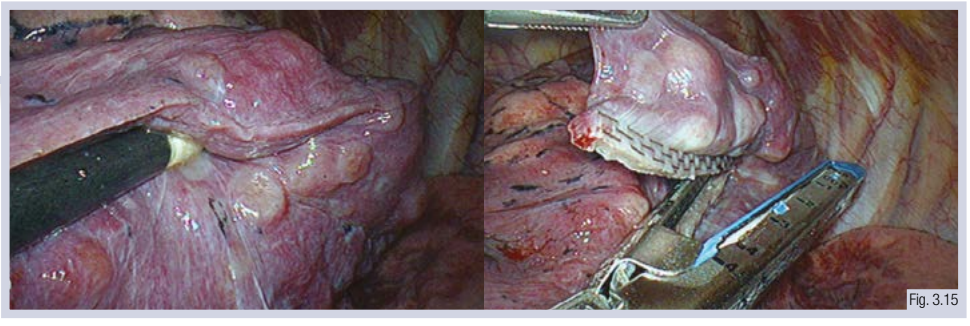
Fig. 3.15

REVISION QUESTIONS

1. Which factors determine the invasive test chosen?
2. Discuss the different types of endoscopic biopsy techniques.
3. How can mediastinal nodal stations 5 and 6 be staged?

Summary: Diagnosing lung cancer

- Clinical presentation: incidentally – symptoms – screening programme
- Multidisciplinary tumour board evaluation: thoracic surgeon, radiotherapist, oncologist, thoracic radiologist and nuclear clinician, pulmonologist
- Staging of (suspected) lung cancer:
  - TNM 8 is the staging system currently used
  - Imaging required: contrast-enhanced CT of chest and upper abdomen in all patients; integrated PET-CT in stage I-III; brain MRI in stage IB-III
  - Pathological mediastinal LN evaluation in stage I-III patients, except for a peripherally located stage IA lung cancer
  - Additional investigations required for specific situations (e.g. solitary metastasis)
  - Disease stage based on TNM group is currently the best prognostic factor
- Techniques for achieving histological diagnosis: thoracic endoscopy, imaging-guided percutaneous core needle biopsy, or surgical biopsy

Further Reading

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Histopathological and molecular characterisation of lung cancer

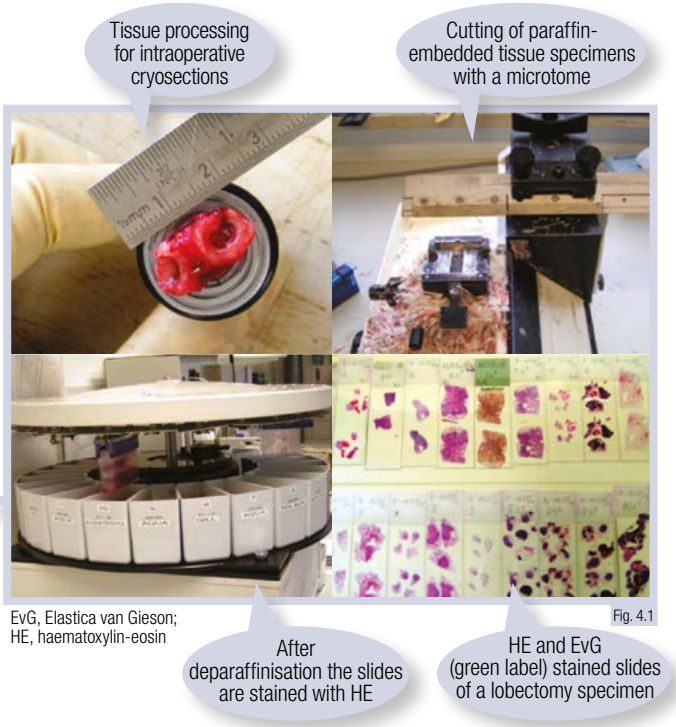
4

Introduction – cytology and histology

Pathology (derived from *logos*, 'study', and *pathos*, 'suffering') is a discipline devoted to studying histomorphological and molecular changes associated with disease in cells, tissues and organs.

When lung cancer diagnosis is suspected, the material obtained is examined macroscopically, microscopically, and with the aid of immunophenotypic and genetic studies (diagnostic and predictive biomarkers).

Cryosections are required for intraoperative diagnosis, while most specimens are paraffin-embedded, sectioned in 2–5 µm slides, and stained with haematoxylin–eosin (HE) or other useful stains (e.g. periodic acid-Schiff [PAS], Elastica van Gieson [EvG]).



EvG, Elastica van Gieson; HE, haematoxylin-eosin

Fig. 4.1

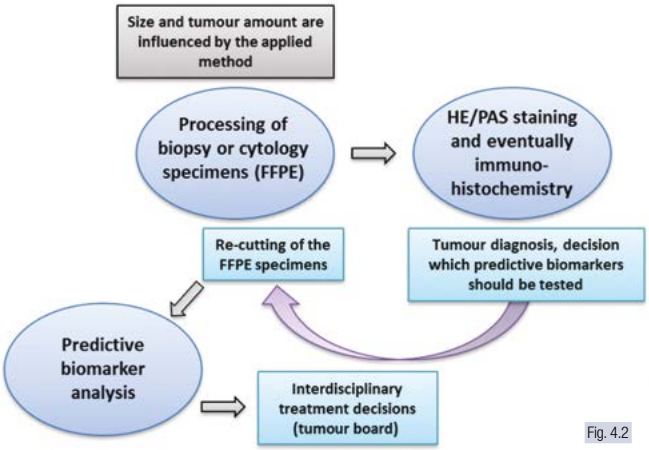


Fig. 4.2

FFPE, Formalin-fixed, paraffin-embedded; HE, haematoxylin-eosin; PAS, periodic acid-Schiff.

Lung cancer is usually diagnosed in advanced stages.

Thus, in the majority of cases, only cytology or small biopsy material are available for both precise morphological and immunohistochemical subtyping, and predictive molecular analyses.

Therefore, rational tissue processing is essential. In order not to waste sparse tumour tissue, frequent re-cutting of the paraffin blocks must be avoided.

The amount of tumour material available is influenced by the biopsy or resection strategy.

About 200 tumour cells are sufficient for diagnosis and predictive biomarker analyses. For cytological specimens, the preparation of cell blocks is recommended.

Cryobiopsies and transthoracic needle core biopsies are usually superior to forceps biopsies with respect to tumour quantity.

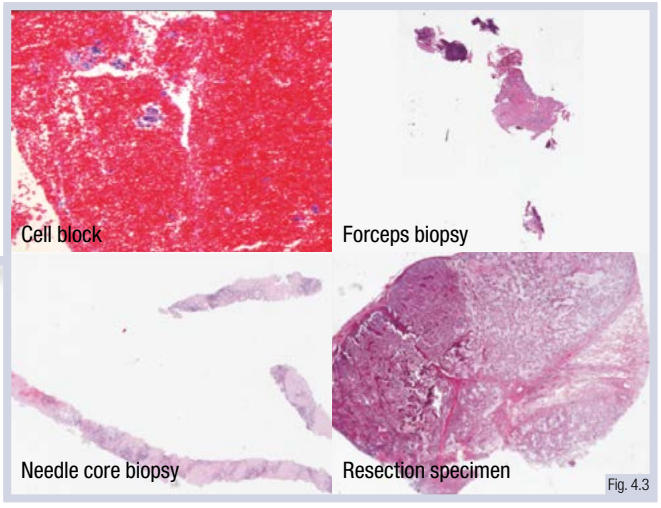


Fig. 4.3

REVISION QUESTIONS

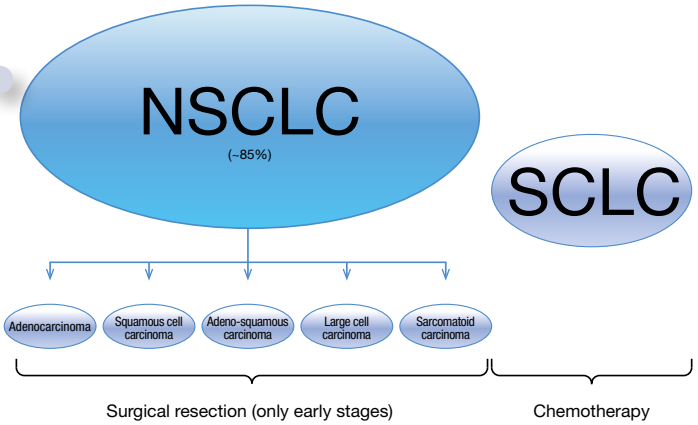
1. How is pathology defined?
2. How are lung cancer specimens processed?
3. How are diagnostic and predictive analyses influenced by different sampling methods?

Histopathology of lung cancer

Historically, and based on therapeutic options, lung cancer is classified as small cell lung cancer (SCLC; approx. 15%) and non-small cell lung cancer (NSCLC).

Furthermore, carcinoids, salivary gland tumours and other rare entities need to be considered.

NSCLC is further categorised into adenocarcinomas (ADCs), squamous cell carcinomas (SCCs), adenosquamous carcinomas, large cell carcinomas and sarcomatoid carcinomas. Lung tumours can show a combination of different histotypes.



NSCLC, Non-small cell lung cancer; SCLC, small cell lung cancer. Fig. 4.4

A: Squamous cell carcinoma B: Small cell carcinoma

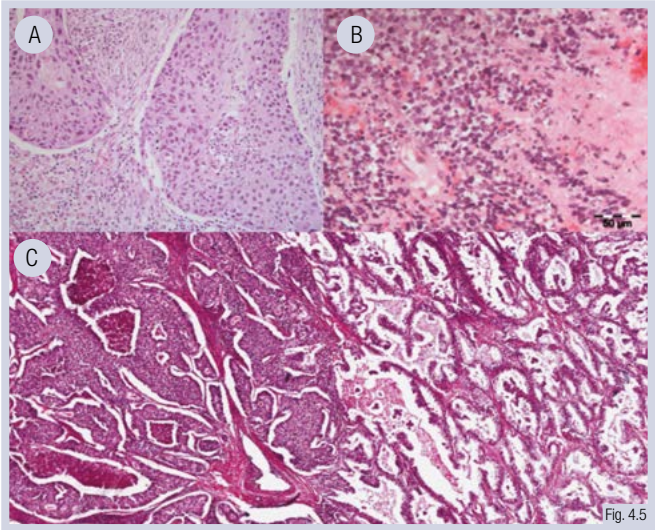


Fig. 4.5

C: Combined large cell neuroendocrine (left) and adenocarcinoma (right)

ADCs seem to have different precursors. Centrally located ADCs are thought to arise from the surface or glandular epithelium of bronchi, in contrast to the terminal respiratory unit ADCs, for which the stem cells are likely to be exocrine bronchiolar cells and type II pneumocytes.

SCCs occur after squamous metaplasia of the respiratory epithelium with subsequent dysplasia, usually as a consequence of chronic, smoking-related inflammation of the airways.

In smokers, the occurrence of multiple synchronous NSCLC is common due to an effect designated as field cancerisation.

ADCs are characterised by various histomorphological growth patterns. Semi-quantitative assessment (subtyping) of these patterns provides relevant clues for optimised treatment decisions.

The predominant ADC growth pattern is associated with the patient's prognosis and has been demonstrated to be a stage-independent predictor of survival.

Specific ADC growth patterns are associated with a distinct tumour biological behaviour, prevalence of predictive biomarkers and lymph node metastasis.

Lymph node metastasis based on predominant pattern of pulmonary adenocarcinomas	
Lepidic:	7%
Acinar:	46%
Papillary:	43%
Solid:	51%
Micropapillary:	76%

Fig. 4.6

REVISION QUESTIONS

1. How is lung cancer classified? What is the rationale behind this classification?
2. How do SCCs arise in the respiratory epithelium?
3. What is the clinical impact of morphological ADC subtyping?

Histochemistry and immunohistochemistry

Histochemistry is the aspect of histology concerned with the identification of chemical components in cells and tissues. Besides HE, additional histochemical stains are used to improve the diagnostic accuracy of histomorphological diagnoses.

PAS staining is essential for the diagnosis of solid ADC (PAS-positive intracytoplasmic mucin droplets).

EvG staining is used to identify elastic fibres (dark black) and is recommended to specifically assess tumour infiltration of the visceral and parietal pleura.

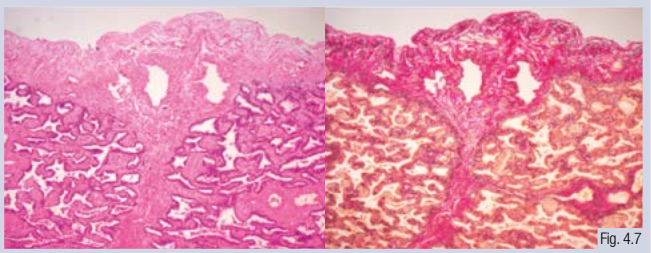


Fig. 4.7

Haematoxylin-eosin staining (left) and Elastica van Gieson staining (right) of a pulmonary adenocarcinoma. The elastic layers of the pleura are delineated in black and thus allow optimised tumour staging.

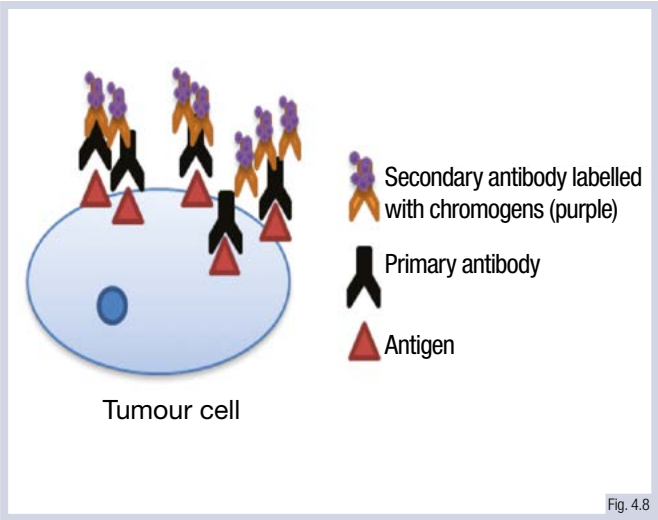


Fig. 4.8

Immunohistochemistry (IHC) refers to the process of detecting antigens in cells. By exploiting the principle of antibodies binding specifically to antigens, IHC represents the most important method for immunophenotyping of morphologically unclear cancers.

IHC allows the visualisation of an antigen by means of primary monoclonal or polyclonal antibodies and a detection system.

A primary (direct method) or secondary antibody (indirect method; more sensitive) is therefore labelled with a chromogen. Counterstains are used to provide contrast that helps the primary stain stand out.

For reliable tumour diagnoses, lineage-specific antibodies are required. Thyroid transcription factor 1 (TTF1) and napsin A are frequently used to confirm pulmonary ADC; p63 (p40) and cytokeratin 5/6 are used as markers for SCC.

A neuroendocrine differentiation is confirmed with antibodies against chromogranin A, synaptophysin, or CD56.

IHC staining requires a careful correlation with the morphological findings to define lineage and immunophenotype of the neoplastic cells.

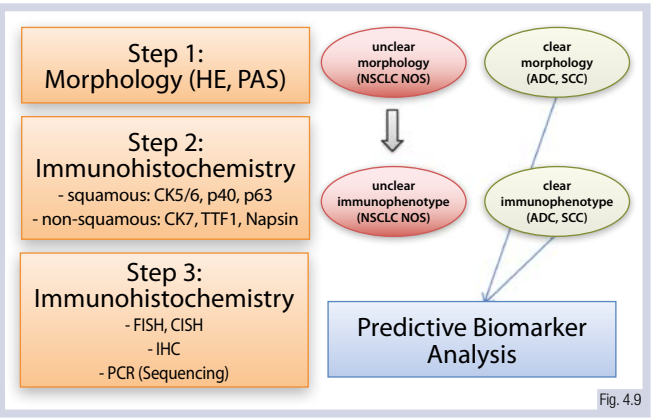


Fig. 4.9

ADC, Adenocarcinoma; CISH, Chromogenic *in situ* hybridisation; FISH, fluorescent *in situ* hybridisation; HE, haematoxylin-eosin; IHC, immunohistochemistry; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PAS, periodic acid-Schiff; PCR, polymerase chain reaction; SCC, squamous cell carcinoma; TTF1, thyroid transcription factor 1.

REVISION QUESTIONS

1. Which stains are commonly used in cytology and histology?
2. What is the difference between histochemical and immunohistochemical stains?
3. Which markers are used to separate SCC and ADC?

Molecular diagnostics – polymerase chain reaction (PCR) and sequencing

PCR is a very sensitive method to detect mutations but also DNA or RNA of bacteria or viruses. It can also be used to detect specific chromosomal rearrangements.

For DNA extraction, tumour areas with high tumour cell content are identified by a pathologist.

Subsequent microdissection is essential in order to minimise the amount of contaminating non-neoplastic cells.

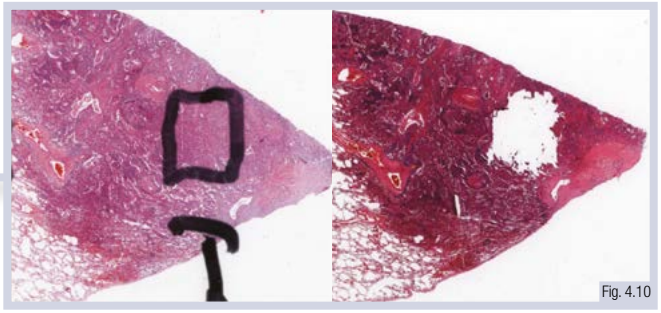


Fig. 4.10

Identification of areas with high tumour cell content after haematoxylin-eosin staining (left) and the same slide after microdissection (right)

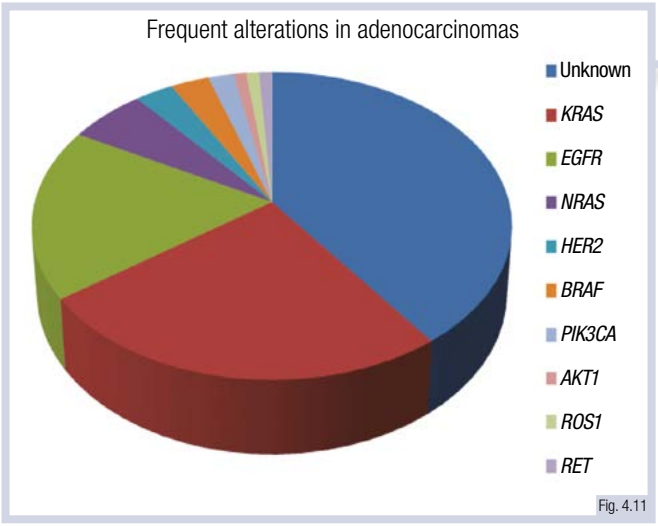


Fig. 4.11

EGFR, Epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2.

In NSCLC, especially in ADC, a still-increasing number of potentially druggable mutations and amplifications have been identified.

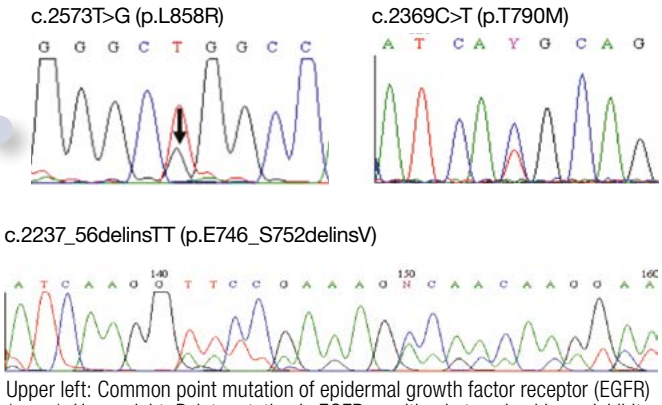
For each biomarker, reliable diagnostic methods (e.g. IHC, PCR-based mutation analysis, *in situ* hybridisation [ISH]) and respective cutoff values for clinical decisions need to be established.

Various methods for PCR-based mutation analyses are available. Targeted detection PCR, Sanger sequencing, pyrosequencing, or next generation sequencing approaches are used in pathological institutions.

Sanger sequencing is based on the selective incorporation of modified, labelled chain-terminating dideoxynucleotides by DNA polymerase during *in vitro* DNA replication, resulting in interruption of DNA extension. After electrophoretic separation, the DNA sequence of the analysed amplicon can be read.

For reliable Sanger sequencing a tumour cell concentration of 30% is required to detect all types of mutations.

Pyrosequencing and next generation sequencing have a higher sensitivity when only sparse tumour material is available.



Upper left: Common point mutation of epidermal growth factor receptor (EGFR) (arrow). Upper right: Point mutation in EGFR resulting in tyrosine kinase inhibitor resistance. The lower sequence demonstrates a complex EGFR deletion/ insertion mutation. Note the sequence shift of the mutated allele compared to the wild-type allele

Fig. 4.12

REVISION QUESTIONS

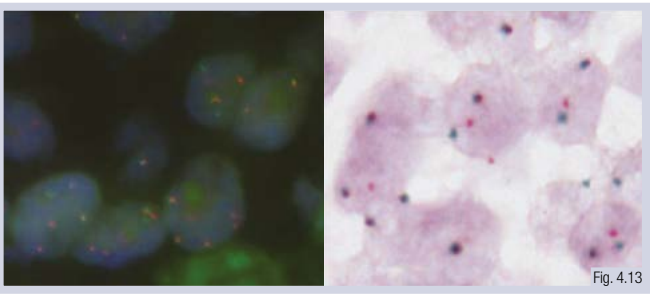
1. Why is PCR used in pathological tissues?
2. Which molecular methods are used to analyse predictive biomarkers?
3. What is a major limitation of Sanger sequencing?

Molecular diagnostics – *in situ* hybridisation

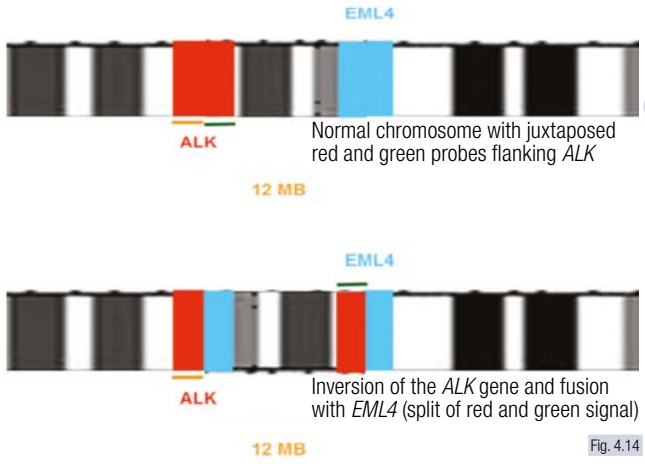
ISH uses labelled probes (complementary DNA or RNA strands) which are hybridised to specific DNA or RNA sequences in interphase nuclei of tissue or cytology specimens.

The probes for specific gene loci are labelled with different colours. In case of a fusion strategy, juxtaposed probes indicate a reciprocal translocation. In break-apart (or split-signal) probes, split signals (single red and green signals) indicate a translocation.

ISH analyses require high tissue quality and tailored handling procedures. Interpretation of the results should be performed by specifically trained personnel.



Fluorescent (FISH; left) and chromogenic *in situ* hybridisation (CISH; right) demonstrating a translocation of the *ALK* (anaplastic lymphoma kinase) gene locus with juxtaposed probes of the normal chromosome (yellow in FISH, brown in CISH) and rearranged probes (single red or green signals)



ALK, Anaplastic lymphoma kinase.

ISH with break-apart strategy is used to detect rearrangements of the investigated gene, without knowing the partner involved in the translocation.

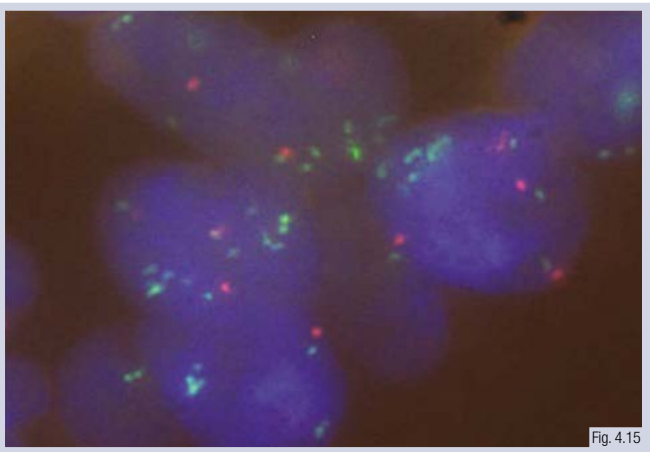
For ISH fusion strategies, the fusion partners must be known.

Since even clinically relevant chromosomal rearrangements in NSCLC (for example, translocations of anaplastic lymphoma kinase *[ALK] or ROS1*) involve multiple fusion partners, break-apart probes are more commonly used in daily practice.

Amplification of a specific gene is another relevant finding to be analysed by ISH. For example, in 20%–25% of SCCs, fibroblast growth factor receptor 1 (*FGFR1*) has been found amplified, which is currently exploited by usage of FGFR1 inhibitors in clinical trials.

For amplification analyses, the ISH probe for the gene of interest is labelled with one colour and for internal reference a centromere probe is labelled with a different colour.

By counting the signals per cell, the amplification of the relevant gene is determined.



Amplification of the *FGFR1* gene locus (green) in relation to the centromere probe (red) in a SCC

FGFR1, Fibroblast growth factor receptor 1; SCC, squamous cell carcinoma.

REVISION QUESTIONS

1. What is the difference between CISH and FISH?
2. What are the different ISH strategies to test for chromosomal rearrangements?
3. How is an amplification determined by ISH?

Summary: Histopathological and molecular characterisation of lung cancer

- Pathology is a discipline devoted to studying histomorphological and molecular changes associated with disease in cells, tissues and organs
- Historically, lung cancer is classified as NSCLC or SCLC based on cytological and histomorphological criteria
- NSCLC is further categorised into ADCs, SCCs, adenosquamous carcinomas, large cell carcinomas and sarcomatoid carcinomas
- Whereas cryosections are required for intraoperative diagnosis, most biopsy and resection specimens are formalin-fixed, embedded in paraffin, and subsequently stained histochemically and/or immunohistochemically
- Histochemical and immunohistochemical stains are important for subtyping of NSCLC, especially in small biopsy or cytology specimens
- The amount of available tumour material is critical to facilitate all required diagnostic and predictive analyses. The tumour cell concentration is significantly influenced by the biopsy or resection strategy
- After microdissection and DNA extraction from tumour-containing samples, PCR and sequencing are used to detect specific mutations relevant for targeted antitumour therapies
- FISH and CISH allow visualisation of chromosomal translocations or amplifications important for targeted antitumour therapies

Further Reading

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Principles of surgery of non-small cell lung cancer

5

Stage I and II non-small cell lung cancer (NSCLC)

Principles of surgery in stage I and II disease without mediastinal lymph node involvement: complete radical resection of the primary tumour.

In order to obtain full surgical staging, a systematic mediastinal lymphadenectomy should be performed in every case.

Depending on functional status of the patient, radical resection can be achieved by: sublobar resection (anatomical segmentectomy, wedge resection), lobectomy, bilobectomy or pneumonectomy.

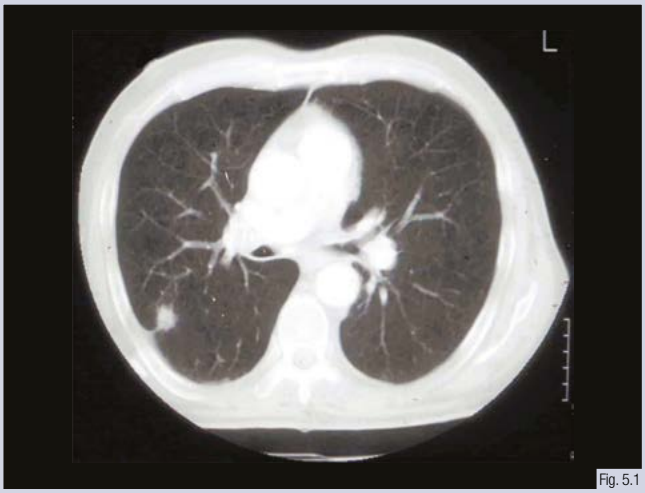


Fig. 5.1

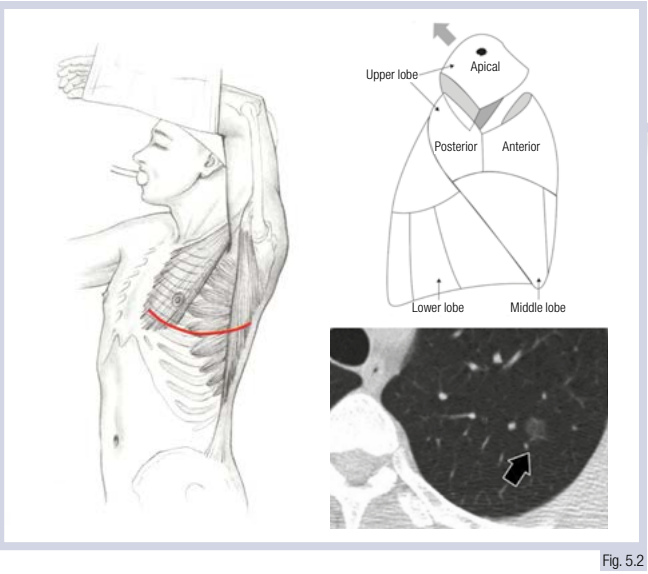


Fig. 5.2

A muscle-sparing anterolateral thoracotomy is the most common approach for open surgery. However, a posterolateral or muscle-sparing posterior thoracotomy is also commonly used.

The role of sublobar resection (anatomical segmentectomy, or wide-wedge resection) is being reconsidered for very early lung cancer (cT1N0) presenting as ground glass opacities (GGOs). Evidence exists from retrospective studies and this approach is being evaluated in prospective clinical trials.

Well-selected use of sublobar resection, especially for pure adenocarcinoma *in situ* (AIS) of <2 cm, yields comparable survival and recurrence rates to lobectomy.

Lobectomy with mediastinal lymph node dissection is considered the standard surgical treatment for all tumours >2 cm and tumours <2 cm that have a solid appearance on chest computed tomography (CT).

In experienced hands, mediastinal lymph node dissection does not increase morbidity, while intraoperative staging becomes more precise.

Morbidity rates after lobectomy vary from 3% to 6%. Typical complications are prolonged air leak, bleeding, chylothorax and recurrent nerve palsy.

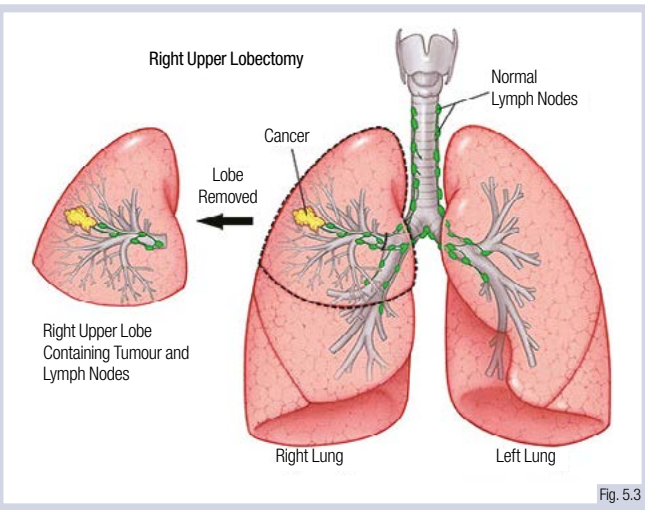


Fig. 5.3

REVISION QUESTIONS

1. What is the most common surgical approach?
2. What is the standard surgical treatment for tumours <2 cm that have a solid appearance on chest CT?
3. Is there a role for sublobar resection?

Minimal invasive thoracic surgery and parenchyma-sparing resections

The current evidence indicates that lobectomy performed with minimal invasive thoracic surgery techniques like video-assisted thoracic surgery (VATS) and robotic-assisted thoracic surgery (RATS) for early-stage NSCLC is associated with fewer postoperative complications than open lobectomy.

Current data also strongly suggest oncological equivalence of minimal invasive versus open lobectomy for patients with early-stage NSCLC.

Minimal invasive lobectomy should be performed at experienced centres. Patients should undergo an accurate preoperative work-up to exclude locally advanced disease.

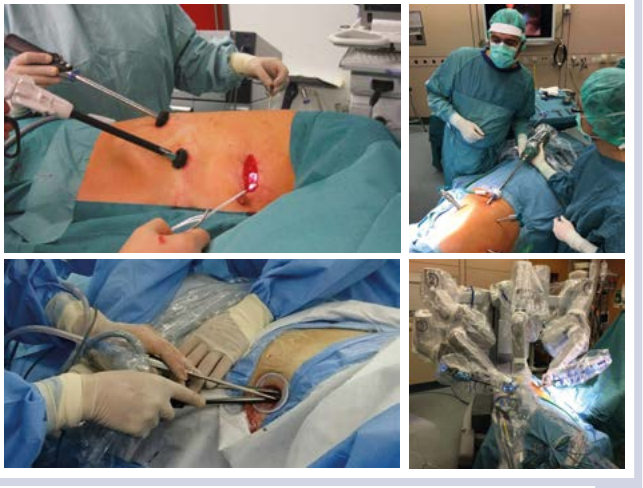


Fig. 5.4

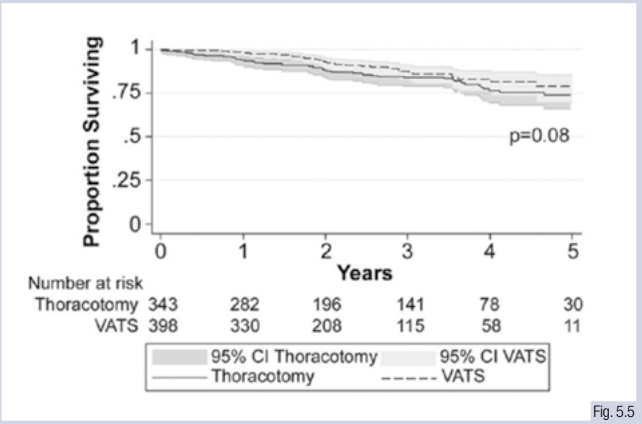


Fig. 5.5

CI, Confidence interval; VATS, video-assisted thoracoscopic surgery.

In recent reports, the 5-year survival for minimal invasive lobectomy in stage IA NSCLC is close to 80%, similar to that for open lobectomy.

Minimal invasive lobectomy for early-stage NSCLC might be associated with less negative biological impact than open lobectomy.

Postoperative pain and length of hospital stay might be decreased. Patients can be mobilised earlier and may be more compliant to receive adjuvant therapies compared with patients undergoing open procedures.

In case of a centrally located tumour, a parenchyma-sparing sleeve resection (SR) can be performed in order to avoid a pneumonectomy.

Sleeve lobectomy can be performed with low morbidity and mortality and a favourable oncological outcome comparable to standard lobectomy or pneumonectomy.

Evidence in the literature indicates that parenchyma-sparing SR can even be safely performed after induction treatment.

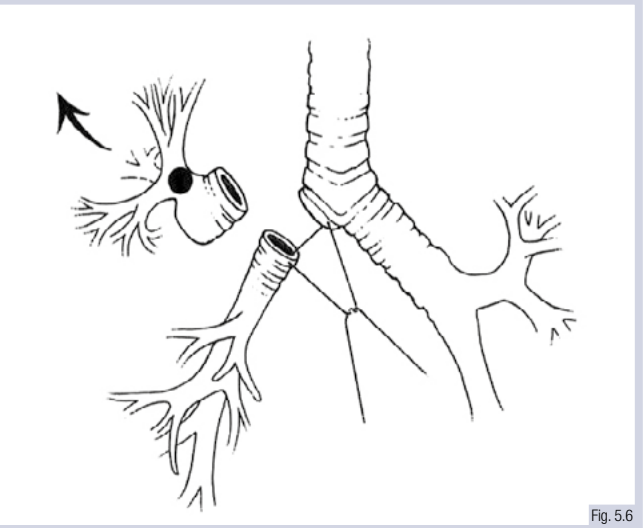


Fig. 5.6

REVISION QUESTIONS

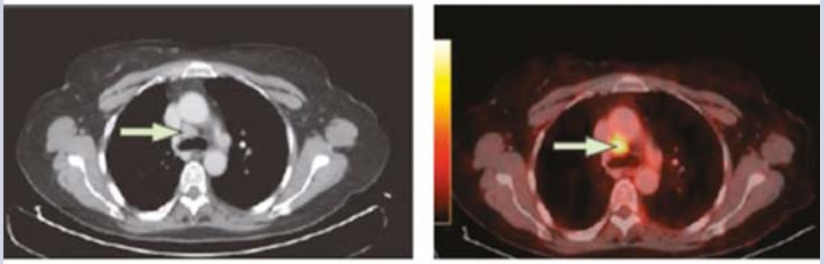
1. Is minimal invasive lobectomy associated with fewer postoperative complications?
2. Is the long-term outcome of minimal invasive lobectomy comparable to standard lobectomy?
3. In centrally located tumours, what is the alternative to pneumonectomy?

Stage III non-small cell lung cancer

Stage III NSCLC is a heterogeneous disease, which can be subclassified into locally advanced primary tumours (T3N1, T4N0-1) and N2-positive NSCLC.

In case of locally advanced lung cancer (T3N1, T4N0-1), radical resection can be achieved with or without neoadjuvant treatment.

Patients with limited mediastinal lymph node involvement undergoing neoadjuvant treatment can be eligible for radical resection after down-staging.



CT, Computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography

Fig. 5.7

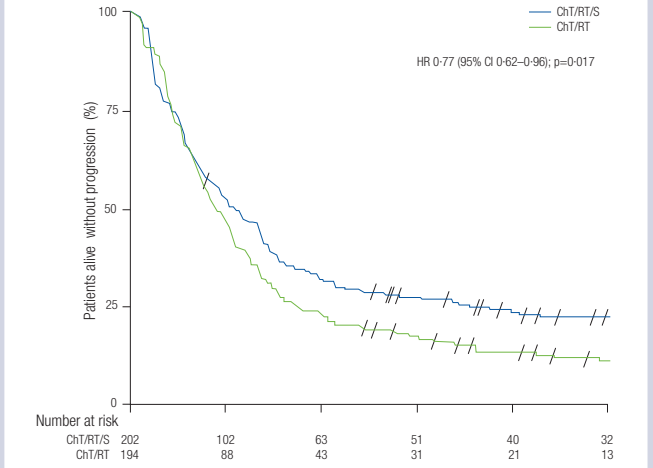


Fig. 5.8

Patients with N2 disease undergoing surgery after neoadjuvant treatment had a significantly longer progression-free survival compared with those receiving chemoradiotherapy (CRT) alone.

Patients undergoing induction CRT and lobectomy had an improved overall survival compared with patients with CRT alone.

This result could not be confirmed for patients undergoing pneumonectomy due to unusually high mortality.

ChT, Chemotherapy; CI, Confidence interval; HR, hazard ratio; RT, radiotherapy; S, surgery.

However, pneumonectomy after induction CRT can obtain favourable outcomes when performed at experienced centres.

Patients must be selected very carefully with regard to their performance status and must be staged accurately in order to exclude more advanced disease. Current published evidence suggests that there is no difference in outcomes in the choice of neoadjuvant treatment protocols (chemotherapy vs CRT).

However, clear evidence-based treatment protocols for patients with N2-positive NSCLC cannot be defined on the basis of the current literature.

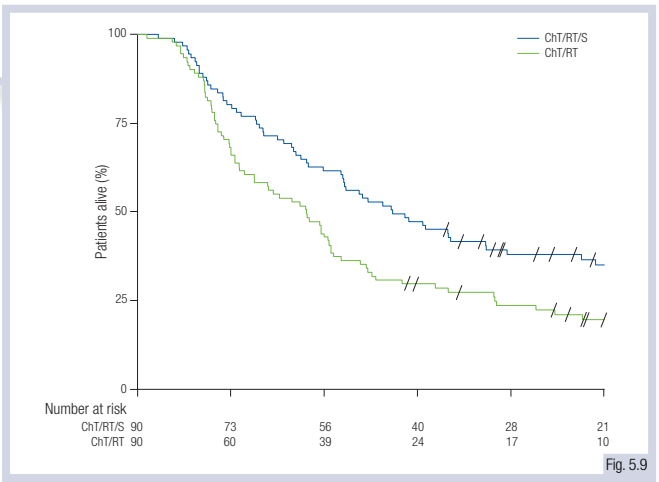


Fig. 5.9

ChT, Chemotherapy; RT, radiotherapy; S, surgery.

REVISION QUESTIONS

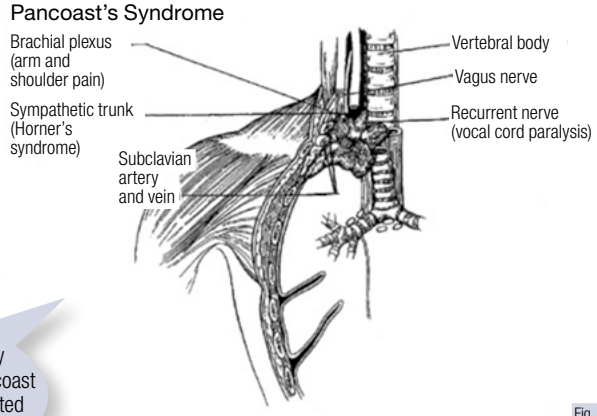
1. Does surgery play a role in patients with proven N2 disease?
2. Does every patient with T4N0 NSCLC need to undergo neoadjuvant treatment?
3. Should pneumonectomy be avoided in N2-positive patients even after neoadjuvant treatment?

Pancoast tumours

Pancoast or superior pulmonary sulcus tumours (SSTs) are a rare subset of NSCLC, occurring with an incidence of less than 5% of all lung cancers.

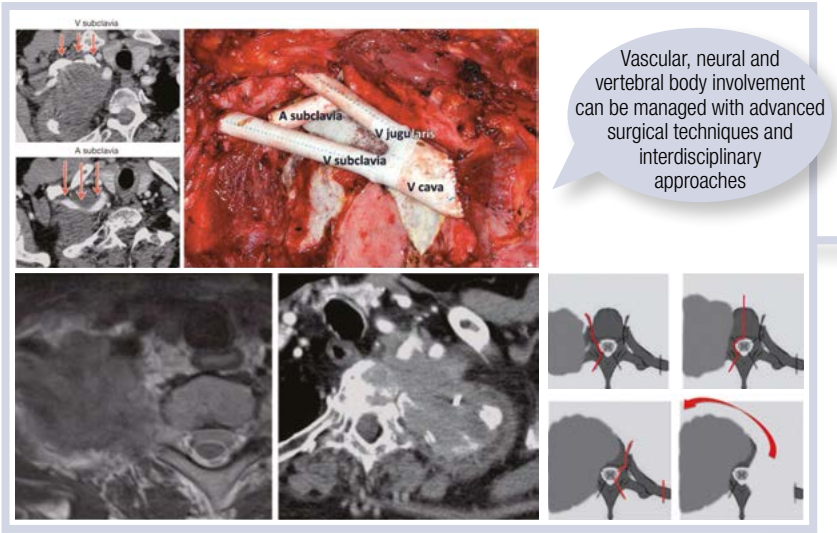
The clinical picture consists of typical symptoms (pain down the arm, Horner's syndrome) and radiographic evidence of first rib and/or vertebral body destruction.

Neoadjuvant CRT followed by surgical resection (multimodality approach) has become the treatment of choice for Pancoast tumour patients.



Originally described by the radiologist Henry Pancoast in 1932 as tumours located in the superior sulcus

Fig. 5.10



Vascular, neural and vertebral body involvement can be managed with advanced surgical techniques and interdisciplinary approaches

Fig. 5.11

Surgery requires expertise and should be performed only in specialised centres by an experienced team, including also a neurosurgeon or orthopaedic surgeon.

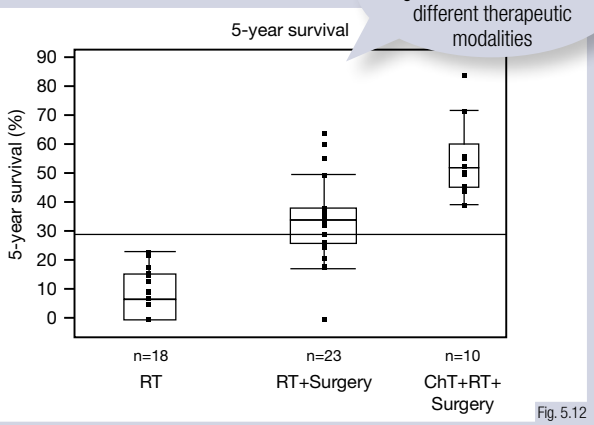
The distinct anatomical location of SSTs has necessitated the development of special surgical approaches for adequate resection of the tumour and involved adherent structures.

Differentiation into anterior (infiltration of great vessels and ribs) and posterior (infiltration of vertebral body and plexus) SST type is important for planning adequate surgery.

Combined treatment schedules have led to improvements in completeness of resection and clinical and pathological response rates, resulting in improved long-term survival.

The three most important prognostic factors for tumour recurrence are completeness of resection, T status, and N status of the tumour.

For SSTs, the expected incidence of brain metastasis as a first site of recurrence has been described as high as 24%, but occurrence of brain metastasis did not impact on survival.



Data pooled from different publications reporting long-term survival rates after different therapeutic modalities

Fig. 5.12

ChT, Chemotherapy; RT, radiotherapy.

REVISION QUESTIONS

1. Which therapy modality has become the modern treatment standard for SSTs?
2. Is infiltration in the adjacent anatomical structures a contraindication for surgical treatment?
3. Which factors are the most important prognosticators in the treatment of Pancoast tumours?

Surgery in the palliative setting and stage IV NSCLC

Carefully selected patients with oligometastatic disease may benefit from resection of both the primary and metastatic sites in a multimodality treatment approach.

Isolated adrenal and solitary brain metastasis (SBM): if the primary is resectable, adrenalectomy or resection of SBM can be considered in combination with chemotherapy in selected patients.

Good survival results can be expected in those patients in whom a complete resection of the primary tumour and radical control of the distant disease are accomplished.

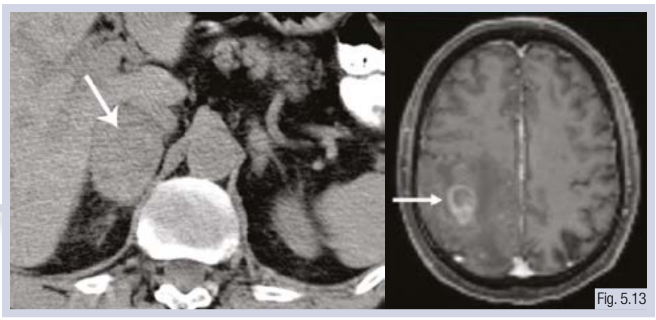


Fig. 5.13

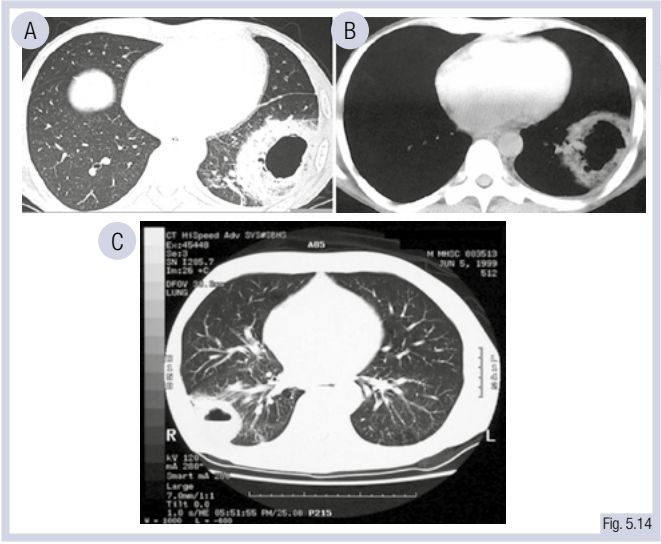


Fig. 5.14

Salvage resections can be indicated in patients with intratumoural cavitation and superinfection, for whom no other treatment modality is appropriate.

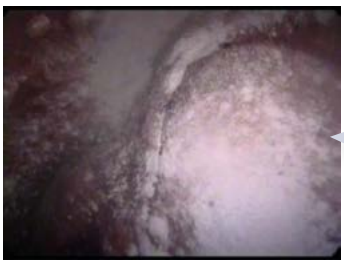
Salvage resection can also be performed for recurrent lung cancer following definitive CRT, with acceptable morbidity and mortality rates.

For both patient groups, careful selection and preoperative assessment as well as postoperative care can result in overall survival up to 30 months.

In NSCLC, malignant pleural effusion (MPE) is a terminal condition diminishing quality of life and requiring multiple hospital admissions and interventions.

MPE can be treated surgically with talc pleurodesis or tunnelled pleural catheters (TPCs). TPCs became popular as a less invasive, outpatient modality in MPE management in NSCLC.

TPCs are particularly preferred for patients with trapped lung or those who are not considered candidates for pleurodesis because of short life-expectancy.



Talc pleurodesis performed by minimal invasive thoracic surgery in a patient with right-sided MPE, white powder = talc

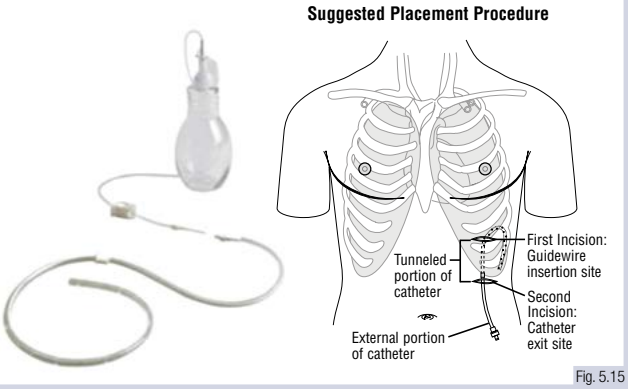


Fig. 5.15

MPE, Malignant pleural effusion.

REVISION QUESTIONS

1. Are all lung cancer patients with metastasis eligible for curative resection within multimodality protocols?
2. Which is the treatment of choice for superinfected tumour cavitation after CRT?
3. Do NSCLC patients need any surgical intervention for recurrent MPE?

Summary: Principles of surgery of non-small cell lung cancer

- Stage I and II NSCLC: primary resection and systematic mediastinal lymph node dissection
  - Anterolateral thoracotomy is the most common approach
  - Minimal invasive lobectomy may be oncologically equivalent to open lobectomy
  - Parenchyma-sparing sleeve lobectomies are considered a safe alternative to pneumonectomy in centrally located tumours
- Stage III NSCLC is a heterogeneous disease with different surgical/multimodal treatment concepts
  - N2-positive NSCLC: patients can benefit from radical resection after responding to neoadjuvant treatment
- Pancoast tumours: induction CRT followed by surgery is the treatment of choice
- Patients with isolated adrenal and/or brain metastasis can benefit from resection with a multimodality protocol
- Salvage resections are indicated for infected cavitated tumours or patients with recurrence after definitive CRT
- Talc pleurodesis and tunnelled pleural catheters are an effective palliative surgical treatment for recurrent pleural effusions

Further Reading

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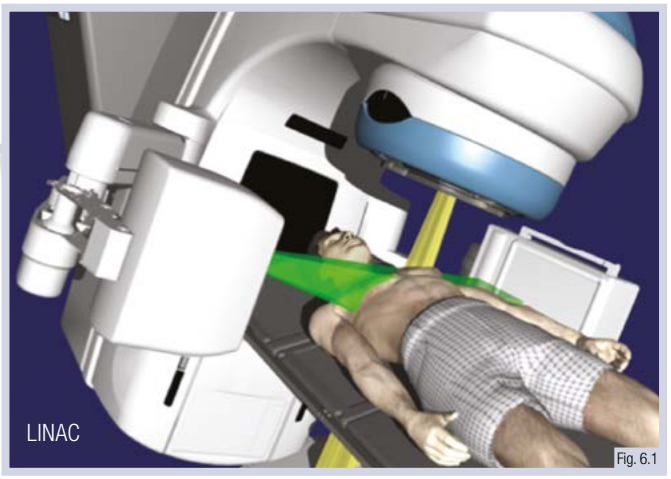
Principles of radiotherapy of thoracic tumours

Background

External beam radiotherapy (RT) is a key modality in both the curative and palliative treatment of lung cancer.

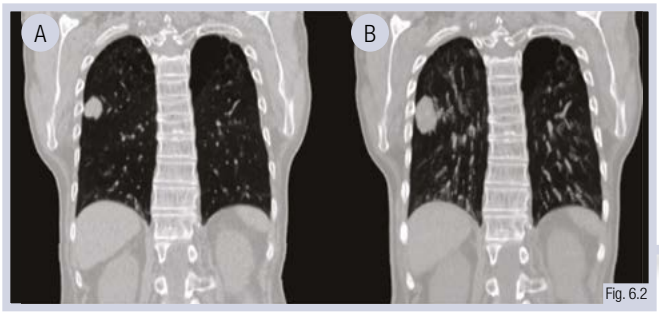
Radiation is usually delivered using a linear accelerator (LINAC), a device used to generate high-energy X-rays that destroy tumour cells.

Patients are positioned on a moveable treatment couch, where imaging using X-rays and computed tomography (CT) scan allows for more accurate delivery.



LINAC – yellow simulates the radiation beam, while green simulates the X-rays used for imaging patient anatomy

Example of 3D imaging (A) and 4D imaging (B) for the same tumour. (A) Position of tumour in right upper lobe in a single conventional scan; however, (B) shows all positions occupied by tumour during respiratory cycle, illustrated in a maximum intensity projection image



A planning CT scan is performed before high-dose RT, to generate a treatment plan.

Treatment plans are optimised to ensure dose coverage of the 'target volume', while limiting doses to surrounding organs.

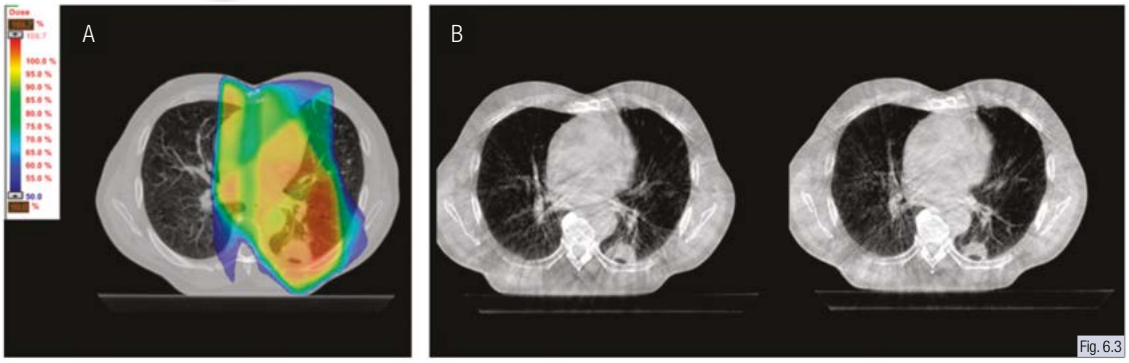
A 4-dimensional (or respiration-correlated) CT scan is the preferred technique for planning curative radiation, as it allows for motion to be visualised for tailored delivery.

Target coverage can be improved by performing on-table cone-beam CT scans with the patient on the LINAC couch.

Any changes in tumour position can be accounted for by 'adapting' the initial plan in order to ensure dose coverage.

Repeated imaging during treatment delivery is a component of modern image-guided RT.

Planning CT (A) and cone-beam CT (B) for a stage III non-small cell lung cancer



CT, Computed tomography.

REVISION QUESTIONS

1. Can radiation cure patients with lung cancer?
2. How is RT delivered to patients?
3. What is image-guided RT?

Dose-fractionation schemes

The radiation dose delivered at each session is measured in units called Grays (Gy).

Palliation involves the use of doses ranging from 4 Gy to 8 Gy, delivered in 1–5 fractions. High response rates are seen for painful lesions and bleeding.

If required, palliative RT can be repeated.

Palliative RT for vertebral metastases, using either simple 2D field (left) or CT planning (right)

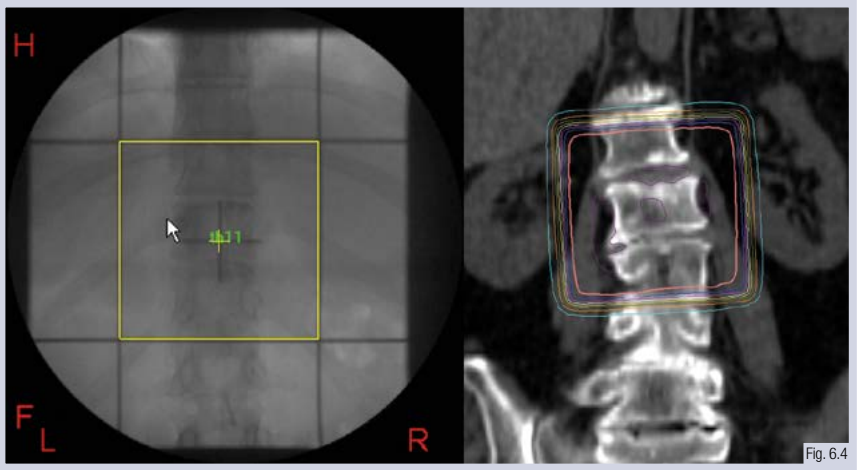
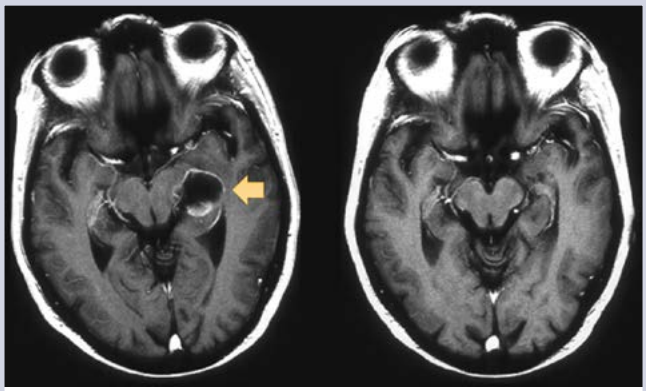


Fig. 6.4

CT, Computed tomography; RT, radiotherapy.

Pre- and post-treatment imaging of a cystic brain metastasis (arrow)



Pre-treatment Post-treatment Fig. 6.5

Stereotactic ablative radiotherapy (SABR) is a form of high-dose, high-precision delivery, resulting in high local control rates.

In patients with 1–3 brain metastases, superior local control is obtained using single doses of stereotactic RT rather than conventional whole-brain RT.

Stereotactic RT is an established treatment of early-stage non-small cell lung cancer (NSCLC). Local control rates of 90% are reported following delivery in a total of 1-8 fractions.

Large radiation field for a locally advanced lung cancer

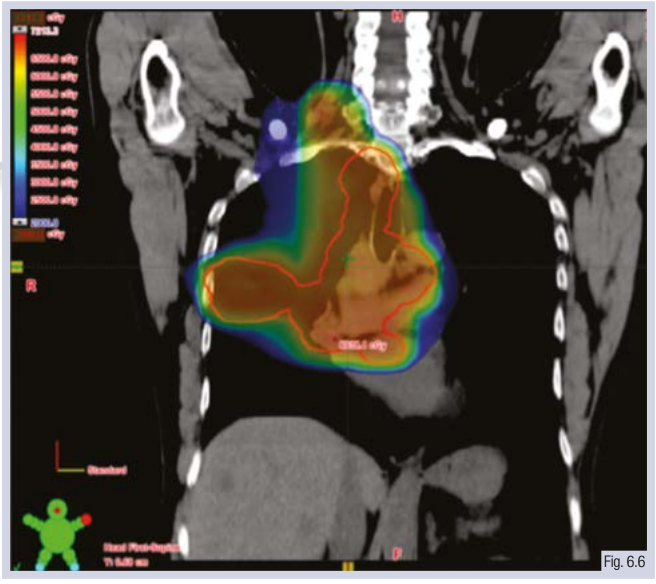


Fig. 6.6

In locally advanced NSCLC, 30 once-daily fractions of 2 Gy are typically delivered concurrently with chemotherapy (ChT).

For limited-stage small cell lung cancer (SCLC), ChT with concurrent thoracic RT (30 twice-daily fractions of 1.5 Gy, or 30-33 once-daily fractions of 2 Gy) is the standard of care.

If RT follows ChT, e.g. in less fit patients, higher daily doses (e.g. 2.6–3 Gy) are used to shorten treatment times and improve survival.

REVISION QUESTIONS

1. How many treatment fractions are used to deliver palliative RT?
2. What are the features of SABR?
3. How frequently are patients irradiated for locally advanced lung tumours?

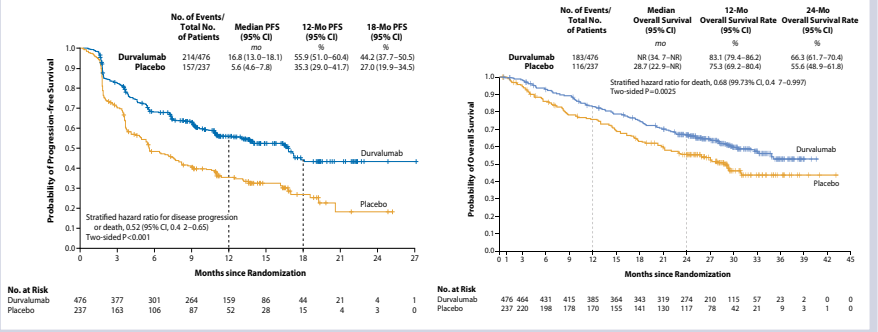
Locally advanced non-small cell lung cancer (NSCLC)

In fit patients, platinum-based concurrent chemoradiotherapy (CRT) is the standard of care, followed by consolidative treatment with the immune checkpoint inhibitor durvalumab.

The ChT schemes recommended for concurrent CRT include cisplatin or carboplatin doublets with etoposide, vinorelbine, pemetrexed and paclitaxel.

The recommended RT dose is 60 Gy, delivered in once-daily doses of 2 Gy.

Durvalumab, a PD-L1 inhibitor, improved PFS (left) and OS (right) when administered for up to 12 months in patients who completed CRT



CI, Confidence interval; CRT, chemoradiotherapy; NR, not reached; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival. Fig. 6.7

Radiation plan showing large fields. High-dose regions in mediastinum and left lung

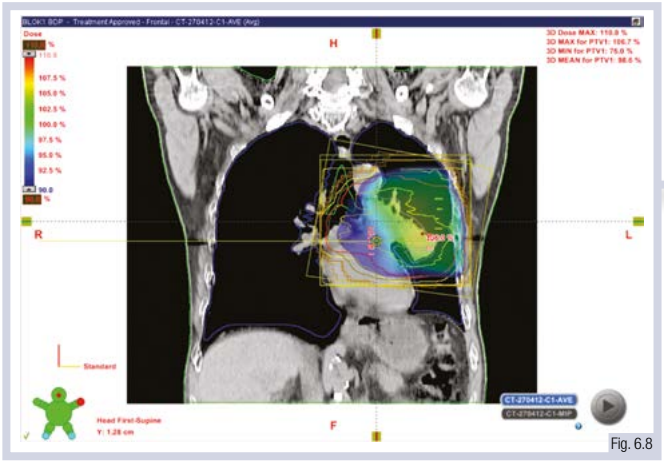


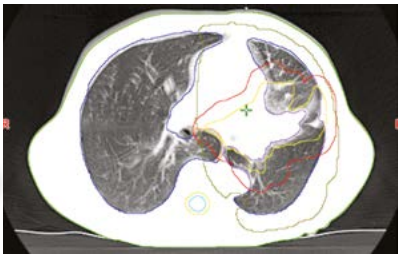
Fig. 6.8

Treatment toxicities include pain with swallowing (oesophagitis), haematological toxicity and radiation pneumonitis.

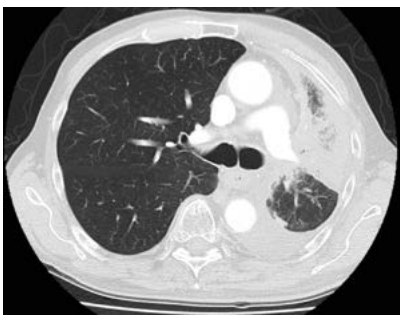
Dietary advice and painkillers can mitigate symptoms of oesophagitis, but severe reactions occur in up to 20% of cases, and a feeding tube may be required.

Severe radiation pneumonitis rates are below 5%–10% in trials, in which RT is focused on areas with proven or suspected disease.

Pre- and post-treatment images showing radiation fibrosis



Pre-treatment



6 months post-treatment Fig. 6.9

Post-treatment response evaluation can be difficult due to fibrosis, but up to 30% of patients may develop a local recurrence vs 50% with distant failures.

The routine addition of surgery has not improved overall survival vs use of CRT only.

All patients should undergo long-term follow-up to identify and treat any complications, co-existing disease such as chronic obstructive pulmonary disease (COPD) and second tumours.

REVISION QUESTIONS

1. What is the common ChT of choice with concurrent RT?
2. Name two common toxicities of concurrent thoracic RT.
3. What proportion of patients develop distant disease failures after CRT?

Stereotactic ablative radiotherapy (SABR)

SABR is the non-surgical treatment of choice for early-stage NSCLC and local control rates in excess of 90% are obtained.

So-called 'risk-adapted' dosing schemes are used to deliver a biologically equivalent tumour dose of ≥100 Gy, in 1–8 fractions.

SABR is associated with low toxicity in patients with COPD and the elderly, and improves population-based survival in elderly patients.

USA population changes in types of RT use for inoperable early-stage NSCLC

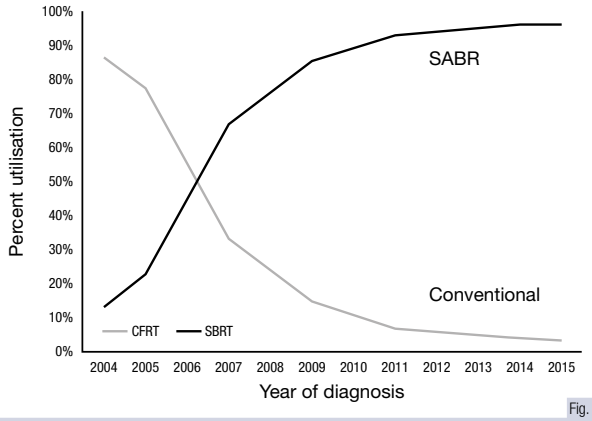
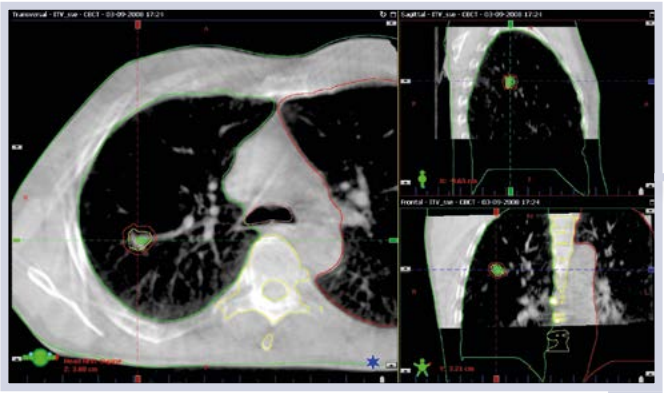


Fig. 6.10

CFRT, Conventionally fractionated radiotherapy; NSCLC, non-small cell lung cancer; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiotherapy; RT, radiotherapy.

On-table cone-beam CT of a patient undergoing SABR for a right-sided lung tumour



CT, Computed tomography; SABR, stereotactic ablative radiotherapy.

Fig. 6.11

Patients are treated on LINACs in an outpatient setting, and each session can take as little as 20 minutes in total. A variety of different treatment machines are in use.

Pre-treatment, on-table image guidance utilises cone-beam CT scans on the treatment table and, less commonly, tracking of implanted fiducial markers.

SABR is an effective treatment for metastases. Use of SABR in so called oligometastatic disease (patients with up to five lesions) can improve progression-free and overall survival.

Radiological follow-up is required after SABR in order to distinguish benign fibrosis, which is common, from local tumour recurrence.

Most recurrences after SABR for early-stage NSCLC are distant or regional metastases.

Long-term follow-up can identify both locoregional failures and new primary tumours, both of which are suitable for curative therapies.

Post-SABR fibrosis

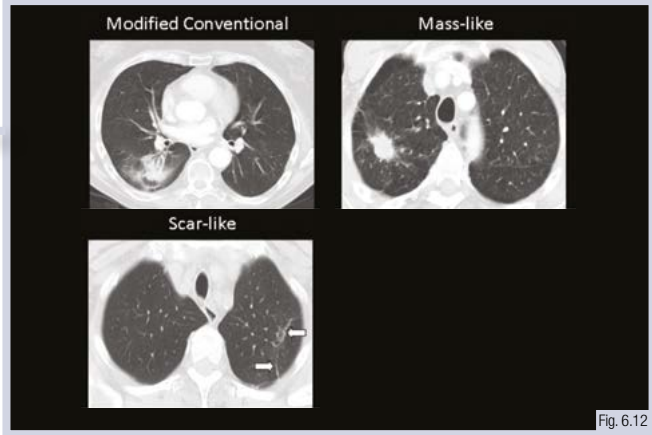


Fig. 6.12

SABR, Stereotactic ablative radiotherapy.

REVISION QUESTIONS

1. What is the local control rate after SABR for early-stage lung tumours?
2. What is the predominant pattern of disease recurrence after SABR?
3. What is the aim of follow-up after treatment of early-stage lung cancer?

Small cell lung cancer (SCLC)

Both ChT and RT are essential in the treatment of both early-stage and advanced SCLC.

In fit patients with limited-stage SCLC, the standard treatment is CRT to the thorax using a platinum-based scheme, and prophylactic cranial irradiation (PCI).

Thoracic RT is delivered twice-daily over 3 weeks, or once daily over 6–6½ weeks. Results are comparable, with 5-year survival of up to ~30% in recent trials.

Comparable survival in patients with limited-stage SCLC after CRT with twice-daily (3 weeks) and once-daily (6.5 weeks) RT

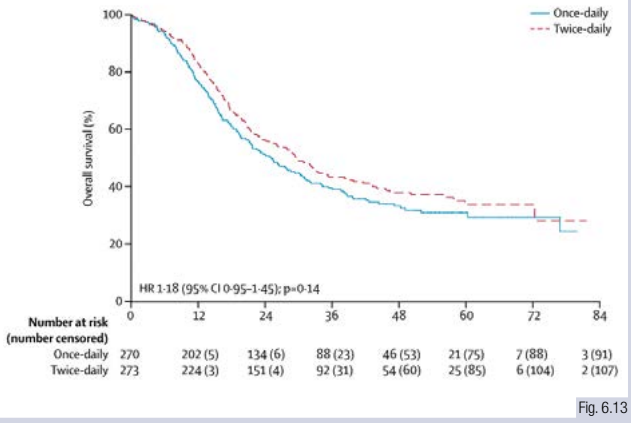
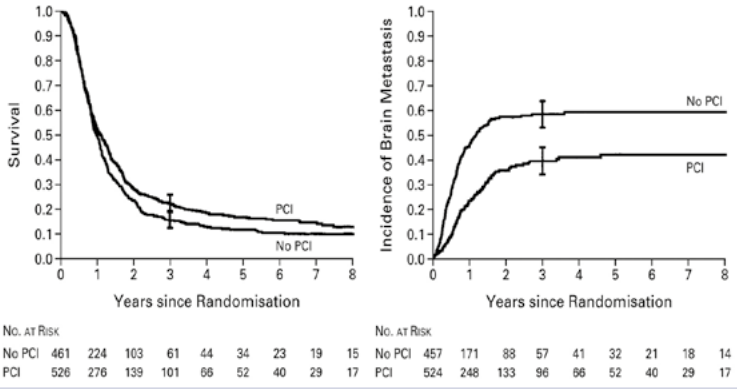


Fig. 6.13

CI, Confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; RT, radiotherapy; SCLC, small cell lung cancer.

Administration of PCI in limited-disease SCLC improved overall survival and reduced the risk for brain relapses



PCI, Prophylactic cranial irradiation; SCLC, small cell lung cancer.

Fig. 6.14

PCI reduces the risk of brain metastases, and increases absolute survival rates by 5% in limited-stage SCLC.

PCI is delivered in 10 fractions of 2.5 Gy, and is associated with alopecia and a short-term decrease in quality of life.

Concurrent CRT to the thorax is associated with oesophagitis, bone-marrow depression and a risk of radiation pneumonitis.

In extensive-disease SCLC, ChT is the mainstay of treatment. RT is used for palliation, and PCI can improve survival in patients who respond to ChT.

In patients with extensive-disease SCLC who do not undergo PCI, periodic brain MRI (magnetic resonance imaging) during follow-up can be considered as an alternative.

Long-term survivors of limited-stage SCLC are at risk for a second lung cancer, and should be counselled on smoking cessation.

Immobilisation mask and simulation radiograph for delivery of conventional brain irradiation

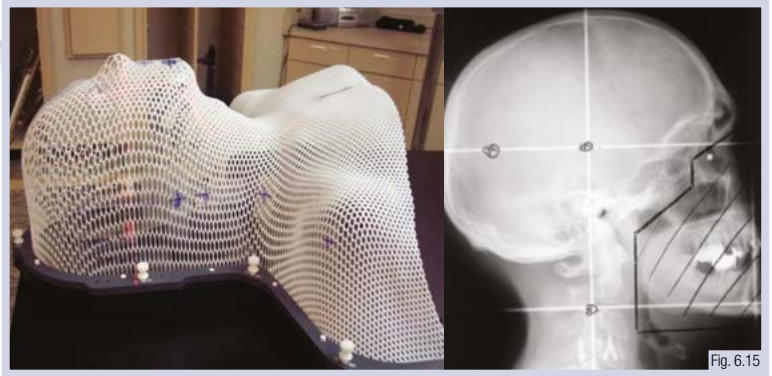


Fig. 6.15

REVISION QUESTIONS

1. Can use of prophylactic brain RT improve survival in SCLC?
2. What are common side effects of PCI?
3. Are survivors of SCLC at risk of developing other lung tumours?

Summary: Principles of radiotherapy of thoracic tumours

- RT is used in both the curative and palliative treatment of thoracic tumours
- In patients with early-stage NSCLC who are unfit or unwilling to undergo surgery, SABR is a curative treatment option
- In both limited-stage SCLC and locally advanced NSCLC, concurrent CRT offers the best chance of cure
- Prophylactic brain irradiation improves the survival of patients with SCLC whose disease does not progress following ChT
- Precise targeting of tumours using image-guided RT can minimise the risk of normal tissue damage

Further Reading

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Adjuvant and neoadjuvant therapy

Perioperative therapy

Five-year survival rates for resected non-small cell lung cancer (NSCLC) range between 73% for pathological stage IA and 25% for pathological stage IIIA (American Joint Committee on Cancer/Union for International Cancer Control [AJCC/UICC] TNM [Tumour, Node, Metastasis] 7th edition).

The International Adjuvant Lung Cancer Trial (IALT) was the first randomised study to show a benefit for a cisplatin-based chemotherapy (ChT) regimen after complete surgical resection in patients with stage I to III NSCLC.

The 5-year survival rate was 45% in the ChT arm vs 40% in the control arm (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.76–0.98; $p < 0.03$).

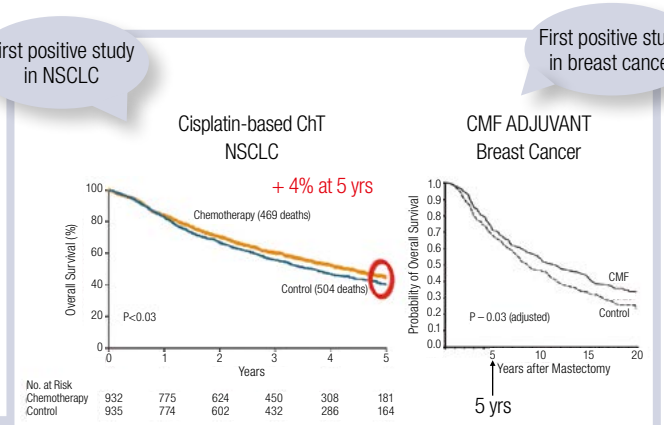


Fig. 7.1

ChT, Chemotherapy; CMF, cyclophosphamide/methotrexate/fluorouracil; NSCLC, non-small cell lung cancer.

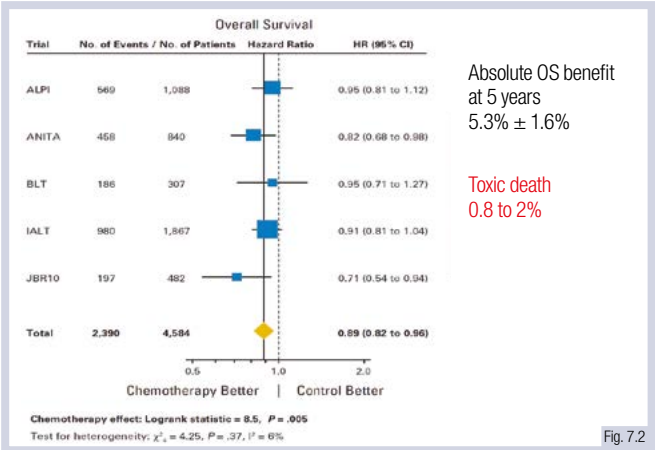


Fig. 7.2

Absolute OS benefit at 5 years 5.3% ± 1.6%

Toxic death 0.8 to 2%

CI, Confidence interval; HR, hazard ratio; OS, overall survival.

The Lung Adjuvant Cisplatin Evaluation (LACE) pooled analysis included 4584 patients accrued in five large cisplatin-based adjuvant trials. Adjuvant ChT showed a 5.3% improvement in overall survival (OS) and 5.2% improvement in disease-free survival (DFS) at 5 years.

The treatment should ideally begin within 2 months after surgery in Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 patients without postoperative complications and who are <75 years of age.

Three to four cycles of ChT should be offered, although the duration of ChT is still challenging.

Vinorelbine is the most frequently used compound in combination with cisplatin in the adjuvant setting. Other third-generation cytotoxics have not been formally compared with vinorelbine-containing regimens but can be used based on LACE.

Three out of five studies included in LACE offered 4 cycles of high-dose cisplatin (100 mg/m² every 4 weeks) and vinorelbine (25–30 mg/m² every week, up to 16 weeks) in the experimental arm.

However, in the metastatic setting the high dose is similar to an alternative lower dose regimen: 75–80 mg/m², which is more frequently prescribed in the adjuvant setting although it has not been prospectively evaluated.

Trial name	Inclusion criteria	Chemotherapy (No. of cycles, dose of cisplatin by cycle, daily dose × No. of doses for other drugs)	Radiotherapy	Inclusion period	No. of patients included
JBR.10	pT2pN0 or pT1-2pN1	4 cycles, cisplatin (50 × 2) mg/m² Vinorelbine 25 mg/m² × 16	No radiotherapy	1994–2001	482
Adjuvant Lung Cancer Project Italy	Stage I, II, IIIA	3 cycles, cisplatin 100 mg/m² Mitomycin 8 mg/m² × 3, vindesine 3 mg/m² × 6	Optional after chemotherapy	1994–1999	1088
Adjuvant Navelbine International Trialist Association 01	Stage I, II, IIIA	4 cycles, cisplatin 100 mg/m² Vinorelbine 30 mg/m² × 16	Optional for pN+ after chemotherapy	1994–2000	840
International Adjuvant Lung Trial	Stage I, II, III	3 cycles, cisplatin 100 or 120 mg/m² or 4 cycles, cisplatin 80 or 100 mg/m² Vindesine 3 mg/m² × 6-8, or Vinblastine 4 mg/m² × 6-8, or Vinorelbine 30 mg/m² weekly × 13, or Etoposide 100 mg/m² × 9-12	Optional according to pN after chemotherapy	1995–2001	1867
Big Lung Trial	Stage I, II, III	3 cycles, cisplatin 80 mg/m² (bitherapies) or 50 mg/m² (tritherapies) Vindesine 3 mg/m² × 6, or Vinorelbine 30 mg/m² × 6, or Mitomycin 6 mg/m² × 3 and ifosfamide 3 g/m² × 3, or Mitomycin 6 mg/m² × 3 and vinblastine 6 g/m² × 3	Optional after chemotherapy	1995–2001	307

Fig. 7.3

pN, Pathological node; pN+, pathological node positive.

REVISION QUESTIONS

1. What is the 5-year benefit of adjuvant ChT?
2. What are the characteristics of patients eligible for adjuvant ChT?
3. How many cycles should be given in the adjuvant setting?

Perioperative therapy (continued)

In LACE, histology is not a predictive factor for the benefit of adjuvant ChT.

Stage II and III NSCLC patients are candidates for adjuvant ChT: the risk reduction is 17%.

There was a negative effect of adjuvant ChT for stage IA. The risk reduction was 8% for stage IB, in which adjuvant ChT is still debated.

Most adjuvant studies used the 6th TNM classification, where stage IB was defined as tumours ≥3 cm. Five-year survival benefit rates cannot be applied to the 8th TNM classification but specific trial criteria can be used for treatment decisions.

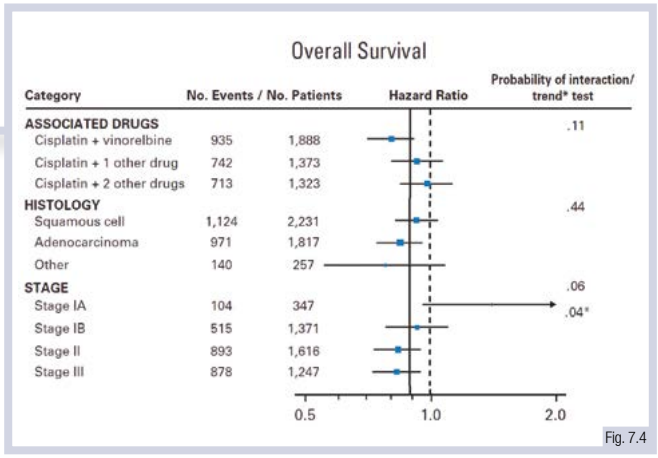


Fig. 7.4

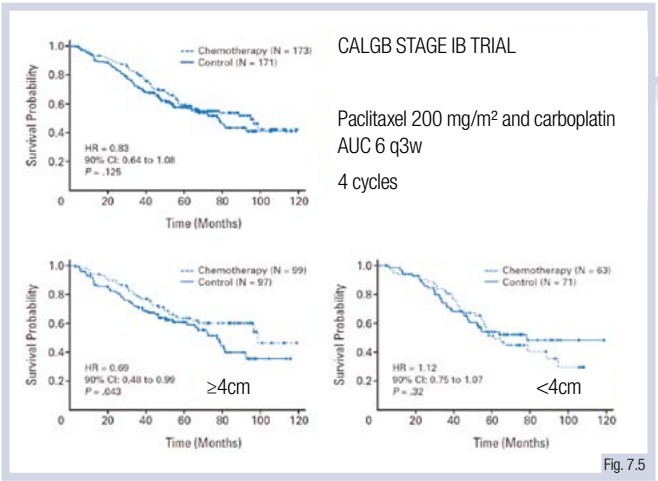


Fig. 7.5

AUC, Area under the curve; CI; confidence interval; HR, hazard ratio; q3W, every 3 weeks.

The CALGB study, which was terminated prematurely, compared 4 cycles of paclitaxel/carboplatin in patients with resected stage IB NSCLC. There was a significant benefit for tumours ≥4 cm.

In the JBR.10 study, patients with tumours ≥4 cm derived clinically meaningful benefit from ChT (HR 0.66, 95% CI 0.39–1.14; $p = 0.13$) as opposed to those with tumours <4 cm (HR 1.73, 95% CI 0.98–3.04; $p = 0.06$).

Most of the ongoing adjuvant trials include patients with stage IB ≥4 cm, stage II and stage III NSCLC. According to the 8th TNM definition, pathological stage II and stage III are eligible for adjuvant ChT.

Three large adjuvant ChT trials have been updated. The CALGB 9633 was initially reported as a positive trial for OS and DFS after 2.8 years of median follow-up and as a negative trial after 4.5 and 6.1 years of follow-up.

In both IALT and JBR.10 updated results, a smaller benefit was seen than in first reports.

Late effects of cisplatin-containing ChT regimens, particularly for vascular disease, could explain this fading effect.

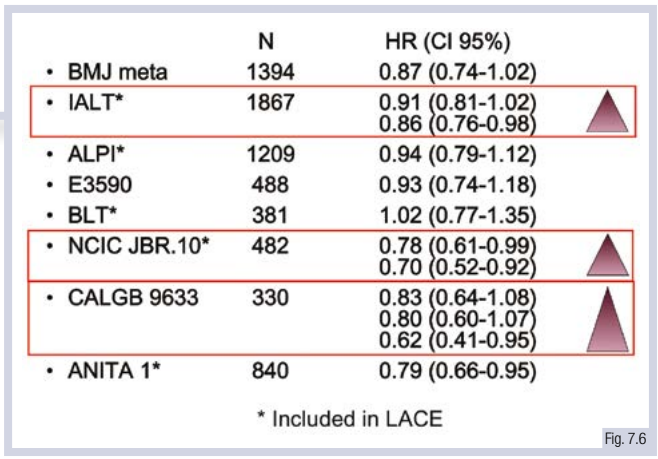


Fig. 7.6

CI, Confidence interval; HR, hazard ratio; IALT, International Adjuvant Lung Cancer Trial; LACE, Lung Adjuvant Cisplatin Evaluation; N, number.

REVISION QUESTIONS

1. When can adjuvant ChT be offered after resection of stage IB NSCLC?
2. Is carboplatin a standard treatment in the adjuvant setting?
3. Is the long-term toxicity of ChT a concern?

Adjuvant and neoadjuvant therapy

A 2-year adjuvant treatment with tegafur-uracil (UFT) vs surgery alone, showed benefit in Japanese patients with stage I disease.

A meta-analysis of 2003 eligible patients showed an increase in survival rates at 5 and 7 years in favour of UFT plus surgery vs surgery alone (81.5% and 76.5%, respectively) in T1 and T2 tumours.

The use of adjuvant UFT is restricted to stage I NSCLC in the Asian population.

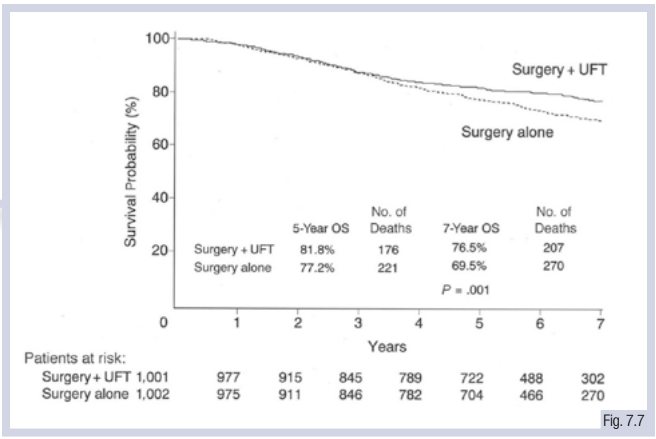


Fig. 7.7

OS, Overall survival; UFT, tegafur/uracil.

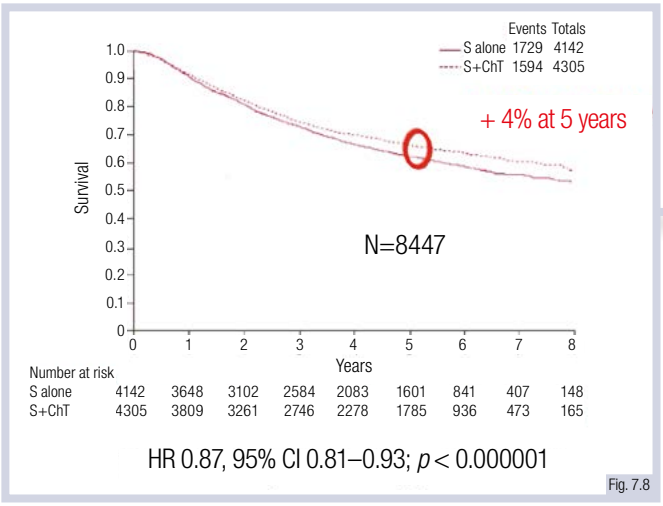


Fig. 7.8

ChT, Chemotherapy; CI, confidence interval; HR, hazard ratio; S, surgery.

The individual patient data (IPD) meta-analysis (8447 patients) showed an absolute benefit in OS at 5 years of 4% in all stages of adjuvant treatment.

Platinum-based ChT was used in 18 trials. In stage I patients, representing 65% of the cohort, the meta-analysis is not conclusive for stage IA.

The IPD meta-analysis of 15 trials (2385 patients) showed that preoperative ChT significantly increased survival (HR 0.87, 95% CI 0.78–0.96; $p = 0.007$).

No subgroup of patients was identified who derived more benefit from preoperative ChT based on age, PS, sex, histology and stage.

When preoperative ChT induces a response, there is a trend for greater benefit when adjuvant ChT is given (HR 0.78, 95% CI 0.64–0.95; $p = 0.02$).

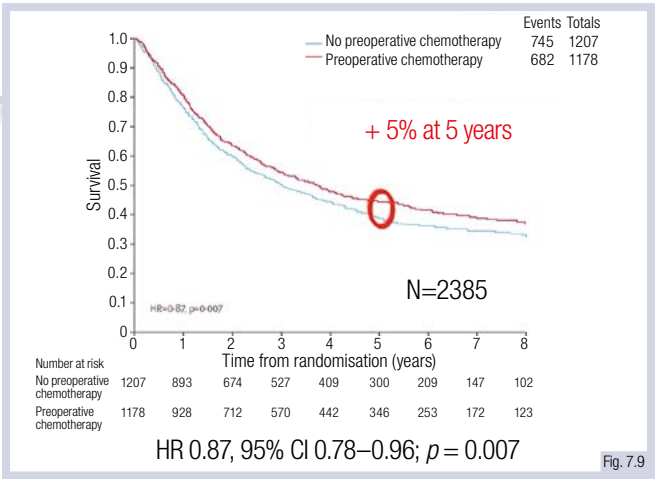


Fig. 7.9

CI, Confidence interval; HR, hazard ratio.

REVISION QUESTIONS

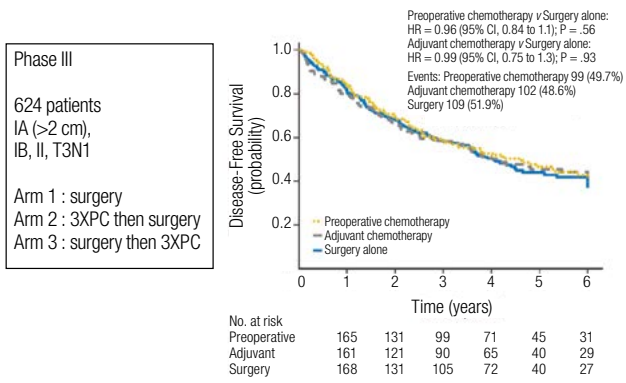
1. Which patients are eligible for adjuvant UFT?
2. What are the HRs between surgery and surgery + neoadjuvant or postoperative surgery in the two meta-analyses based on individual patient data?
3. Is there a group of patients who would derive more benefit from adjuvant ChT compared with preoperative ChT?

Adjuvant and neoadjuvant therapy (continued)

Two phase III trials have compared preoperative or adjuvant ChT with surgery alone, without pointing out a better setting based on DFS.

Compliance is improved with preoperative ChT. In the IFCT-0002 study, 90.4% of patients received 4 cycles of preoperative ChT in one arm compared with 75.2% in the other arm (2 cycles before and 2 cycles after surgery).

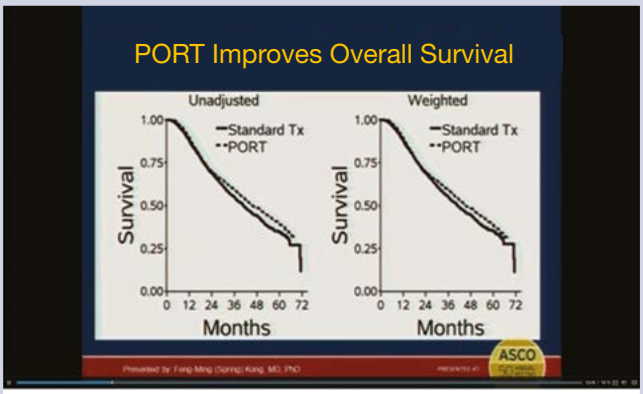
Preoperative ChT does not promote lung-sparing surgery, meaning that it does not decrease the rate of pneumonectomy vs lobectomy.



PC = paclitaxel 200 mg/m² + carboplatin AUC 6 q3w

Fig. 7.10

AUC, Area under the curve; CI, confidence interval; HR, hazard ratio; q3W, every 3 weeks.



In the National Cancer Data Base, PORT (n=1850) was compared to no PORT (2633) in patients with completely resected N2 NSCLC
OS was increased by 4.5% at 5 years

Fig. 7.11

NSCLC, Non-small cell lung cancer; OS, overall survival; PORT, postoperative radiotherapy; Tx, treatment.

Postoperative radiotherapy (PORT) remains controversial in completely resected NSCLC patients with pathologically involved mediastinal lymph nodes (N2); it is not a standard for stage I and II.

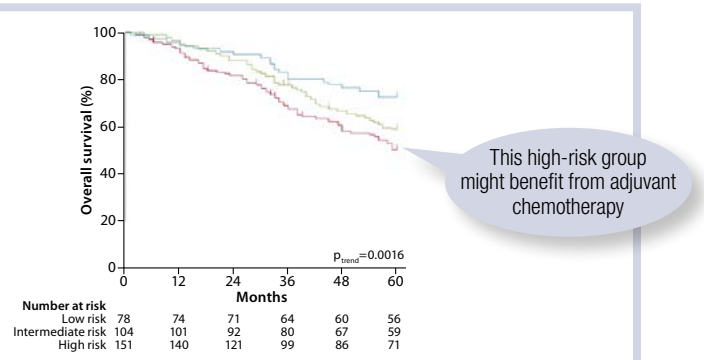
Recent data provide evidence of the possible benefit of PORT in patients with mediastinal nodal involvement.

A large multi-institutional randomised trial evaluating PORT in this patient population is under way.

No biomarker has been fully validated as able to identify subgroups of patients for whom adjuvant treatment would be of particular benefit.

Despite great efforts, no validated biological tools beyond tumour staging are available for identifying resistance to ChT (i.e. the excision repair cross-complementation group 1 [ERCC1] enzyme).

The figure shows an example of a 14-gene expression assay that uses quantitative polymerase chain reaction (qPCR) to identify patients with early-stage non-squamous NSCLC at high risk for mortality after surgical resection.



Overall survival for 330 patients with American Joint Commission on Cancer stage IA and IB disease considered to be low risk as per conventional pathological criteria (National Comprehensive Cancer Network); median survival was 113 months in the low-risk group, 88 months in the intermediate-risk group, and 70 months in the high-risk group

Fig. 7.12

REVISION QUESTIONS

1. How can you increase perioperative ChT compliance?
2. Are pneumonectomies a contraindication to perioperative ChT?
3. Is mediastinal radiotherapy a standard treatment for resected N2 NSCLC patients?

Adjuvant and neoadjuvant therapy (continued)

The RADIANT study explored the activity of 2-year treatment with erlotinib (150 mg/day) in patients with immunohistochemically or fluorescent *in situ* hybridisation (FISH)-evaluated epidermal growth factor receptor (*EGFR*)-positive tumours.

There was no difference in DFS (HR 0.90, 95% CI 0.74–1.10; $p = 0.0324$) or OS in the overall population (HR 1.13, 95% CI 0.08–1.44; $p = 0.324$).

In *EGFR*-mutated NSCLC patients, DFS was not significantly increased (HR 0.61, 95% CI 0.38–0.98; $p = 0.039$) and OS was similar (HR 1.09, 95% CI 0.5–2.1; $p = 0.81$). The use of EGFR tyrosine kinase inhibitors (TKIs) in this setting is not validated.

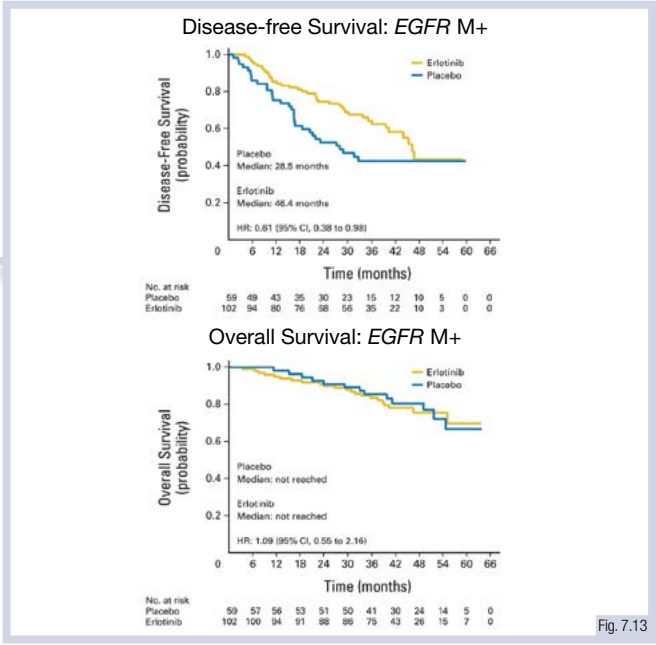


Fig. 7.13

CI, Confidence interval; *EGFR* M+, epidermal growth factor receptor, mutation positive; HR, hazard ratio.

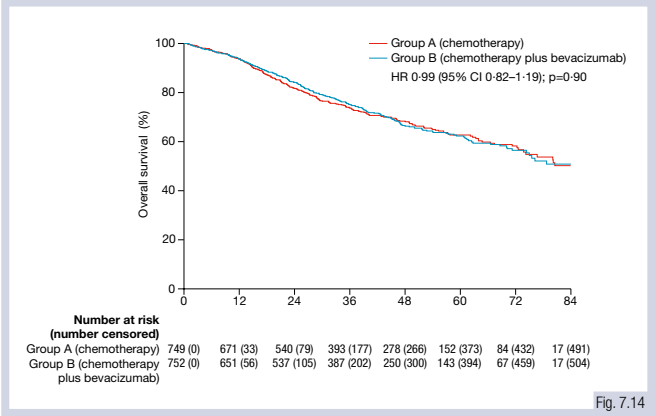


Fig. 7.14

CI, Confidence interval; HR, hazard ratio.

The use of the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab (15 mg/kg every 3 weeks for 1 year) did not improve OS.

Other non-ChT approaches include the MAGE-A3 antigen-specific vaccine, which has not shown any advantage in two of the three co-primary endpoints after accrual of >2000 patients.

Immune checkpoint inhibitors (such as anti-programmed cell death protein 1 [PD-1] or programmed death-ligand 1 [PD-L1] antibodies) are currently evaluated in the peri-operative setting. The first induction study with two injections of nivolumab showed impressive activity.

A major pathological response, defined as a tumour with no more than 10% viable tumour cells, occurred in 9 out of 20 resected tumours (45%).

Many ongoing randomised studies are exploring the role of induction or adjuvant immunotherapy, alone or in combination with ChT.

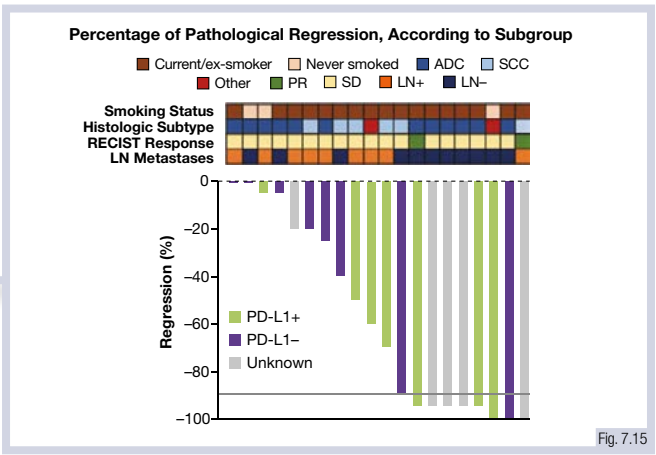


Fig. 7.15

ADC, Adenocarcinoma; LN, lymph node; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SCC, squamous cell carcinoma; SD, stable disease.

REVISION QUESTIONS

1. Which biomarker is mandatory for the adjuvant ChT indication?
2. Is cisplatin-based ChT indicated for a resected stage II NSCLC with *EGFR* mutation?
3. What is the role of immunotherapy in the perioperative setting?

Summary: Adjuvant and neoadjuvant therapy

- Perioperative ChT improves survival in resected NSCLC patients
- Meta-analysis of preoperative ChT and adjuvant ChT demonstrated a benefit that is in the same range in both settings
- Standard: cisplatin-based ChT
  - Standard: stage II-IIIA
  - Option: IB (>4 cm recommended)
  - Option: carboplatin
  - Criteria: <75 years / <2 months after surgery / PS 0-1 / no postoperative complications
- No biomarker is validated to select a subgroup of patients who might derive more benefit from perioperative ChT
- Never use targeted therapy (i.e. TKIs of activating mutations such as *EGFR*, anaplastic lymphoma kinase [*ALK*] or antiangiogenic agents)

Further Reading

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Treatment of metastatic non-small cell lung cancer

First-line chemotherapy

Chemotherapy (ChT) in metastatic non-small cell lung cancer (NSCLC) has reached a plateau.

A total of 1207 patients were randomly assigned to cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel, or carboplatin/paclitaxel.

The overall survival (OS) of all regimens was 7.4–8.1 months. There was no significant difference between the four treatment regimens.

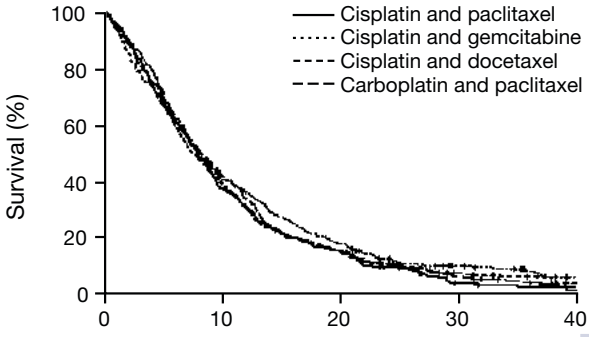


Fig. 8.1

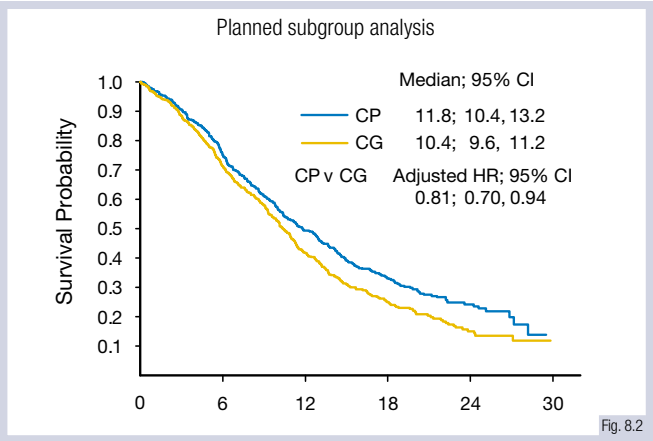


Fig. 8.2

CG, Cisplatin/gemcitabine; CP, cisplatin/pemetrexed; CI, confidence interval; HR, hazard ratio.

In 1725 ChT-naïve patients with stage IIIB or IV NSCLC, cisplatin/pemetrexed provided similar efficacy compared with cisplatin/gemcitabine.

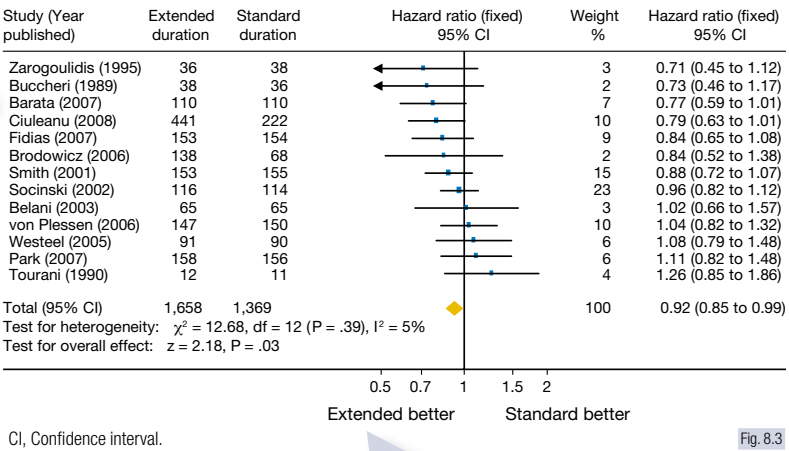
In the intent-to-treat population, OS for cisplatin/pemetrexed was non-inferior to cisplatin/gemcitabine (median survival, 10.3 vs 10.3 months, respectively, hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.84–1.05).

In a prespecified subgroup analysis, cisplatin/pemetrexed-treated patients with non-squamous histology had a significantly better survival than cisplatin/gemcitabine-treated patients.

Meta-analysis included 13 randomised clinical trials (RCTs) and 3027 patients receiving first-line (largely platinum-based) ChT for 3–4 cycles vs continuation of the same ChT for 6 cycles or until disease progression.

Extending ChT improved progression-free survival (PFS) substantially (HR 0.75, 95% CI 0.69–0.81; p < 0.00001) and showed no significant improvement in OS (HR 0.94, 95% CI 0.86–1.01; p = 0.10).

Extending ChT was associated with higher toxicity and impaired quality of life.



CI, Confidence interval.

Fig. 8.3

Overall survival analysis: extending chemotherapy beyond a standard duration

REVISION QUESTIONS

1. What is the best ChT regimen for first-line therapy?
2. What is the optimal duration of first-line ChT?
3. Is the histological subgroup important?

First-line chemotherapy in combination with antibodies

878 NSCLC patients (stage IIIB or IV) were treated with paclitaxel/carboplatin with or without bevacizumab. After 6 cycles, bevacizumab was administered every 3 weeks until disease progression.

The median survival was superior for the bevacizumab-containing regimen (12.3 vs 10.3 months, HR 0.79; p = 0.003). Similarly, PFS was improved (6.2 vs 4.5 months, HR 0.66; p < 0.001) with corresponding response rates of 35% and 15% (p < 0.001). In this study, rates of clinically significant bleeding were 4.4% and 0.7%, respectively (p < 0.001).

Patients with squamous cell tumours, tumour infiltration of large central vessels and clinically significant haemoptysis should not receive bevacizumab.

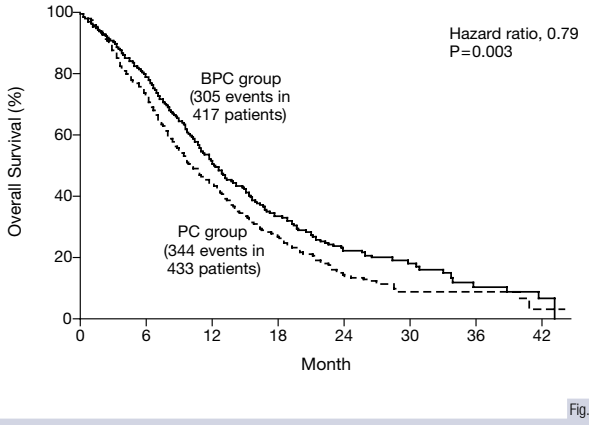


Fig. 8.4

BPC, Paclitaxel/carboplatin plus bevacizumab; PC, paclitaxel/carboplatin.

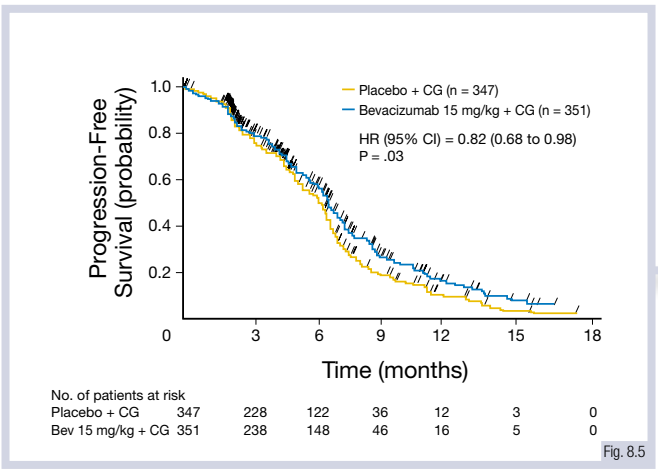


Fig. 8.5

CG, Cisplatin/gemcitabine; CI, confidence interval; HR, hazard ratio.

In a three-arm phase III study, 1043 patients received cisplatin/gemcitabine with or without low-dose (7.5 mg/kg) or high-dose bevacizumab (15 mg/kg). The rates of ≥grade 3 hypertension, bleeding and proteinuria were modestly higher in the bevacizumab arms than in the placebo arm.

PFS was significantly prolonged (low-dose group: median PFS 6.7 vs 6.1 months, HR 0.75; p = 0.003; high-dose group: median PFS 6.5 vs 6.1 months, HR 0.82; p = 0.03).

Median OS was >13 months in all treatment groups; OS was not significantly increased with the addition of bevacizumab. Most patients (62%) received multiple lines of post-study treatment.

Most squamous NSCLC tumours express epidermal growth factor receptor (EGFR) protein. Two phase III trials (FLEX and SQUIRE) demonstrated an OS benefit by the addition of the EGFR antibody cetuximab (HR 0.80) or necitumumab (HR 0.84) to first-line cisplatin-based ChT.

In the SQUIRE trial, there were more grade 3 or worse adverse events (72% vs 62%). The rate of grade 3/4 febrile neutropaenia was similar (in contrast to the FLEX study).

In the exploratory subgroup of EGFR-expressing tumours (95%), the survival benefit in the necitumumab group was more pronounced (median 11.7 vs 10.0 months, HR 0.79, 95% CI 0.69-0.92; p = 0.002).

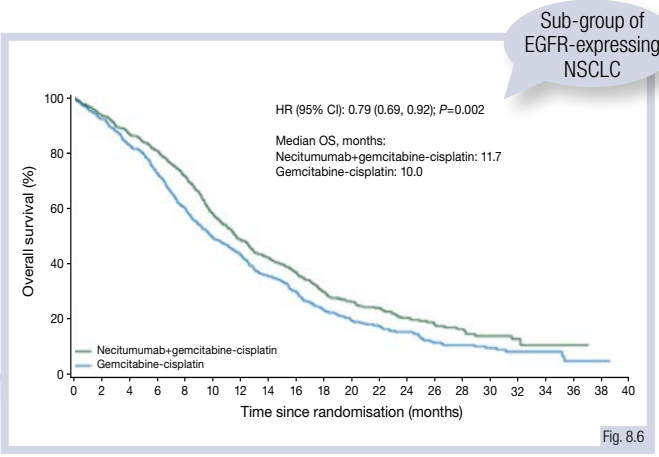


Fig. 8.6

CI, Confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS; overall survival.

REVISION QUESTIONS

1. What are the options for systemic first-line therapy?
2. What is the optimal duration of first-line ChT?
3. Is the histological subgroup important?
4. What is the benefit of adding antibody therapies to ChT in defined NSCLC subgroups?

Maintenance therapy

To test the hypothesis of switch maintenance, 663 patients with stage IIIB or IV NSCLC who had not progressed on 4 cycles of platinum-based ChT received pemetrexed (n=441) or placebo (n=222) until disease progression.

Pemetrexed significantly improved PFS (4.3 vs 2.6 months, HR 0.50, 95% CI 0.42–0.61; p < 0.0001) and OS (13.4 vs 10.6 months, HR 0.79, 95% CI 0.65–0.95; p = 0.012).

Maintenance therapy with pemetrexed was generally well tolerated. For patients with squamous histology, PFS was not significantly different (p = 0.896).

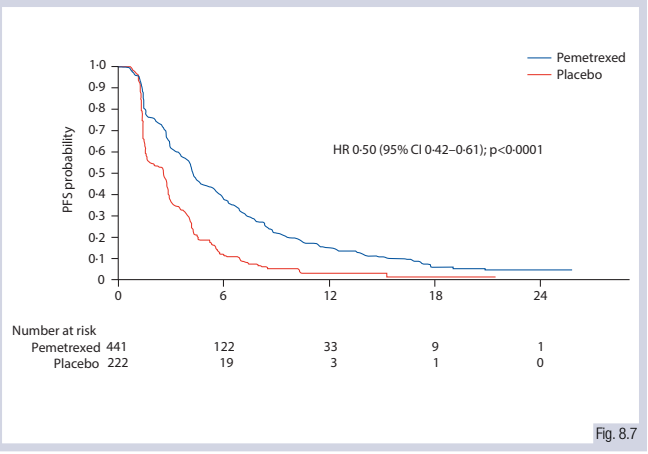


Fig. 8.7

CI, Confidence interval; HR, hazard ratio; PFS, progression-free survival.

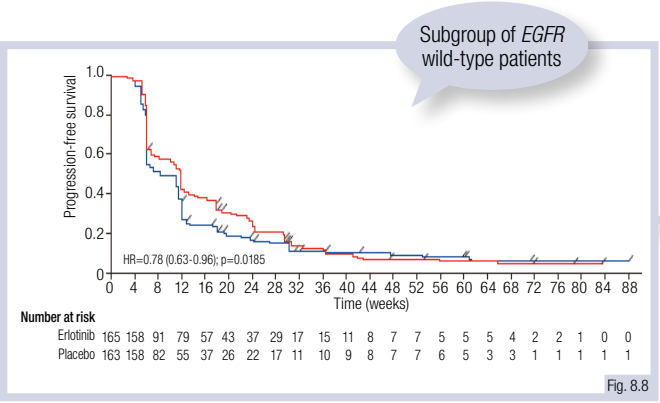


Fig. 8.8

EGFR, Epidermal growth factor receptor; HR, hazard ratio.

NSCLC patients without disease progression after first-line therapy received erlotinib (n=438) or placebo (n=451) until progression or unacceptable toxicity.

Overall, median PFS was significantly longer with erlotinib than with placebo (12.3 vs 11.1 weeks, HR 0.71, 95% CI 0.62–0.82; p < 0.0001).

However, in the phase III IUNO trial, OS with maintenance erlotinib was not superior to second-line treatment in patients without activating *EGFR* mutations. Consequently, erlotinib is not approved for maintenance therapy of *EGFR* wild-type patients.

In contrast to switch maintenance where a third agent is initiated after 4 cycles of platinum-based double-agent ChT, continuous maintenance uses an agent that was already part of the first-line treatment.

After 4 cycles of pemetrexed plus cisplatin, 539 stage IIIB/IV NSCLC patients received continuation maintenance with pemetrexed (n=359) or placebo (n=180).

Patients in the pemetrexed arm had superior PFS (4.1 vs 2.8 months; p < 0.0001) and OS (16.9 vs 14 months; p = 0.0191).

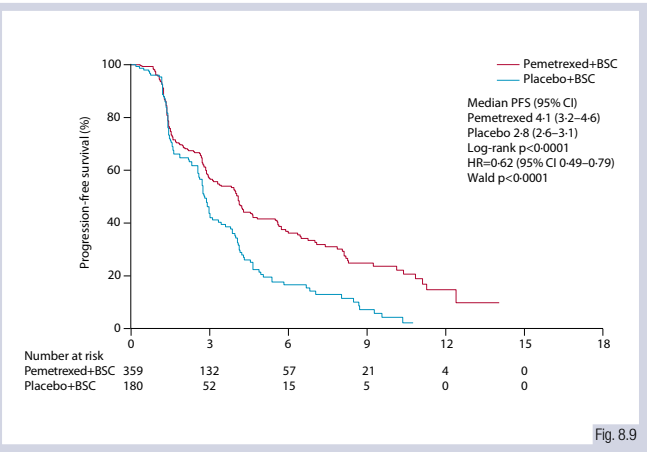


Fig. 8.9

BSC, Best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

REVISION QUESTIONS

1. What is the difference between continuous and switch maintenance?
2. Which patients should receive maintenance therapy?
3. If a patient does not undergo maintenance therapy, what are the optimal follow-up intervals?

Second-line therapy

Patients with stage IIIB/IV NSCLC and progression after platinum-based ChT were randomised to treatment with docetaxel 100 mg/m² (49 patients) or 75 mg/m² (55 patients) or best supportive care (BSC).

Time to progression was longer for docetaxel patients overall than for BSC patients (10.6 vs 6.7 weeks, respectively; p < 0.001), as was median survival (7.0 vs 4.6 months; log-rank test, p = 0.047).

No benefit in survival was seen for patients treated with docetaxel 100 mg/m². Conclusively, the benefits of docetaxel therapy at a dose of 75 mg/m² outweigh the risks.

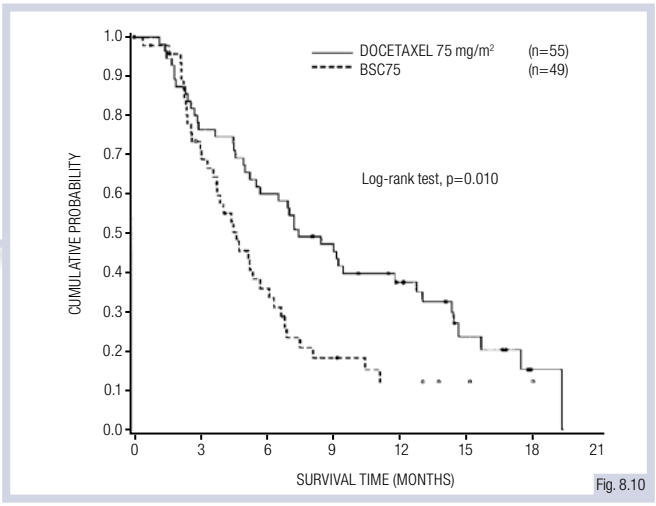


Fig. 8.10

BSC, Best supportive care.

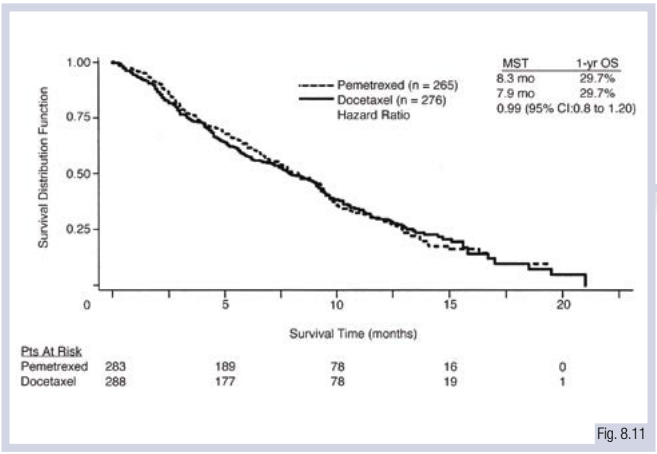


Fig. 8.11

CI, Confidence interval; MST, median survival time; OS, overall survival.

571 NSCLC patients with one prior ChT regimen were treated with pemetrexed 500 mg/m² or docetaxel 75 mg/m².

Treatment with pemetrexed resulted in equivalent PFS (2.9 months for each arm) and median survival time (8.3 vs 7.9 months for pemetrexed and docetaxel, p = 0.99). Pemetrexed therapy was associated with significantly fewer side effects compared with docetaxel.

In a retrospective subgroup analysis, PFS under pemetrexed was superior for non-squamous patients (median 3.4 vs 3.0 months) while it was inferior for patients with squamous NSCLC (2.3 vs 2.7 months).

After progression on one or two prior ChT regimens, 731 patients not eligible for additional ChT were randomly assigned in a 2:1 ratio to receive oral erlotinib or placebo.

For erlotinib and placebo, PFS was 2.2 months and 1.8 months, respectively (HR 0.61; p < 0.001) and OS was 6.7 months and 4.7 months (HR 0.70; p < 0.001).

In a retrospective analysis of 204 tumours, 34 (17%) had *EGFR* exon 19 deletion or exon 21 *L858R* mutations. After erlotinib therapy, response rates were higher in *EGFR* mutant tumours (27% vs 7%; p = 0.03) but no significant OS benefit was seen (wild-type *EGFR* HR 0.74; p = 0.09; mutant *EGFR* HR 0.55; p = 0.12).

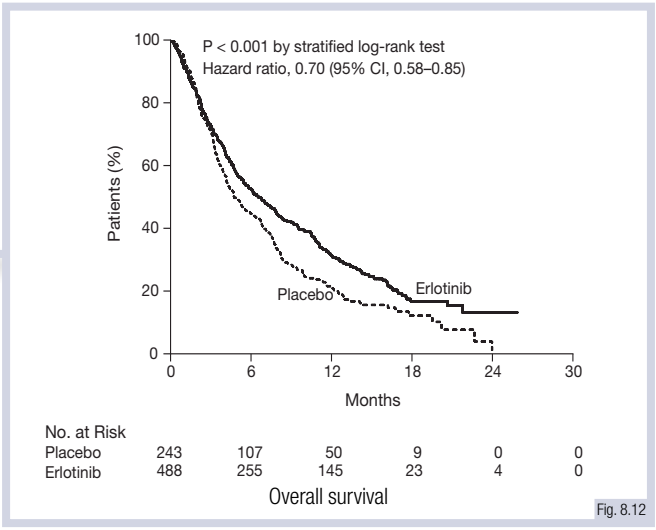


Fig. 8.12

CI, Confidence interval.

REVISION QUESTIONS

1. What are the treatment options for progressing NSCLC tumours after first-line therapy with ChT?
2. Is histology important for treatment selection of second-line therapy?
3. Is ChT the first choice for second-line therapy?

Second-line therapy (continued)

795 patients with stage IIIB or IV squamous NSCLC and progression after at least 4 cycles of platinum-based ChT were treated with afatinib (40 mg per day) or erlotinib (150 mg per day) until disease progression.

Treatment with afatinib was associated with significantly longer PFS (median 2.4 vs 1.9 months; HR 0.82; 95% CI 0.68–1.00; p = 0.0427) and OS (median 7.9 vs 6.8 months; HR 0.81, 95% CI 0.69–0.95; p = 0.0077).

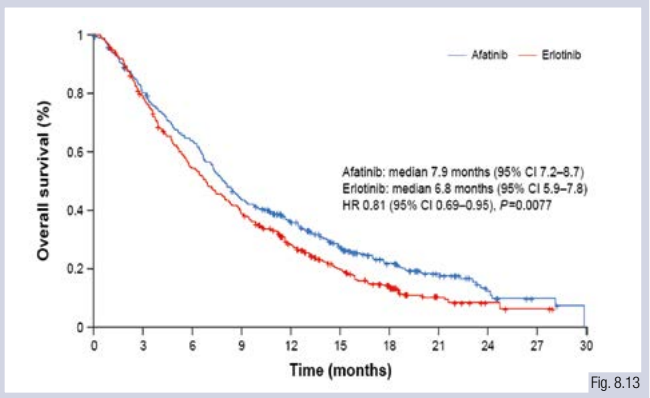


Fig. 8.13

CI, Confidence interval; HR, hazard ratio.

	Nintedanib+ docetaxel	Placebo+ docetaxel	HR (95% CI)	p value
PFS, months				
All patients	3.4	2.7	0.79 (0.68–0.92)	0.0019
Adenocarcinoma	4.0	2.8	0.77 (0.62–0.96)	0.0153
SCC	2.2	2.6	0.77 (0.62–0.96)	0.0200
OS, months				
All patients	10.1	9.1	0.94 (0.83–1.05)	0.2720
Adenocarcinoma	12.6	10.3	0.83 (0.70–0.99)	0.0359
SCC	8.6	8.7	1.01 (0.85–1.21)	0.8907

Fig. 8.14

CI, Confidence interval; HR, hazard ratio; OS, overall survival; PFS progression-free survival; SCC, squamous cell carcinoma.

1314 patients with histologically or cytologically confirmed stage IIIB/IV or recurrent NSCLC were randomised to therapy with docetaxel with or without nintedanib. All NSCLC histologies were included. PFS and OS data are displayed.

Nintedanib is a multi-tyrosine kinase inhibitor (TKI) inhibiting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR). Both OS and PFS were significantly prolonged only in the subgroup of patients with adenocarcinoma as part of pre-planned histological subgroup analyses.

Interestingly, particularly patients with disease progression as best response in first-line therapy or disease progression within 9 months of initiation of first-line ChT benefitted from the addition of nintedanib. So far, there is no biomarker for antiangiogenic treatment.

The phase III REVEL trial treated 1253 NSCLC patients after platinum-based therapy with docetaxel with or without the anti-VEGFR2 antibody ramucirumab. The primary endpoint was OS.

The numerical survival benefit was seen in both non-squamous (HR 0.83; p = 0.02) and squamous (HR 0.883; p = 0.19) NSCLC subgroups.

Median OS was 10.5 months (vs 9.1 months) for patients allocated to ramucirumab plus docetaxel (HR 0.86, 95% CI 0.75–0.98; p = 0.023). Median PFS was 4.5 vs 3.0 months (HR 0.76, 95% CI 0.68–0.86; p < 0.0001).

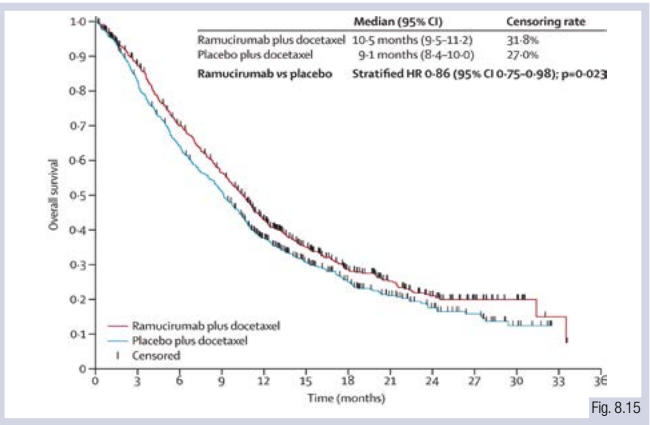


Fig. 8.15

CI, Confidence interval; HR, hazard ratio.

REVISION QUESTIONS

1. How can experiences from first-line treatment be used for selection of second-line therapy?
2. Does treatment with TKIs in unselected patients lead to improved survival?

Summary: Treatment of metastatic non-small cell lung cancer

- Histology: Defining the histological subgroup has an impact on selection of molecular screening and therapy options
- At least non-squamous NSCLC should be screened for activating *EGFR* and *BRAF-V600* mutations as well as activated *ALK* (anaplastic lymphoma kinase) and *ROS1*
- ChT: New cytotoxic agents display improved efficacy in defined patient subgroups
- Antiangiogenic agents improve PFS and may lead to prolonged OS
- Maintenance therapy should be considered for selected patients with good performance status after first-line therapy
- Second-line therapy does lead to survival benefit
- TKIs can be a treatment option in unselected NSCLC patients
- Systemic ChT with or without antiangiogenic agents remains a major treatment option in NSCLC

Further Reading

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Treatment of small cell lung cancer: chemotherapy and radiotherapy

General principles

80% of patients with small cell lung cancer (SCLC) present with metastatic (stage IV) disease.

20% have stage I–III SCLC, which overlaps with the former so-called 'limited stage'.

Very rarely, SCLC presents as a solitary nodule, stage I.

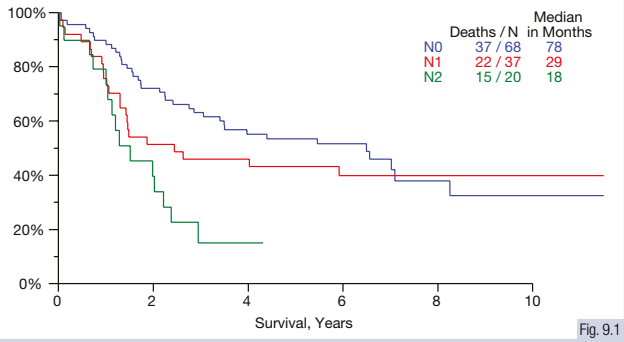


Fig. 9.1

SCLC, Small cell lung cancer.

Survival of patients with small cell lung cancer treated primarily by methods other than operation

Treatment	No. pt.	Survival, year/s < 1	1-2	2-3	7+
Radiation only	80	72	7	1	…
Radiation & radioisotopes	2	2	…	…	…
Chemotherapy only	30	28	2	…	…
Chemotherapy & radiation	95	82	6	6	1

Fig. 9.2

Early attempts to treat SCLC with surgery failed.

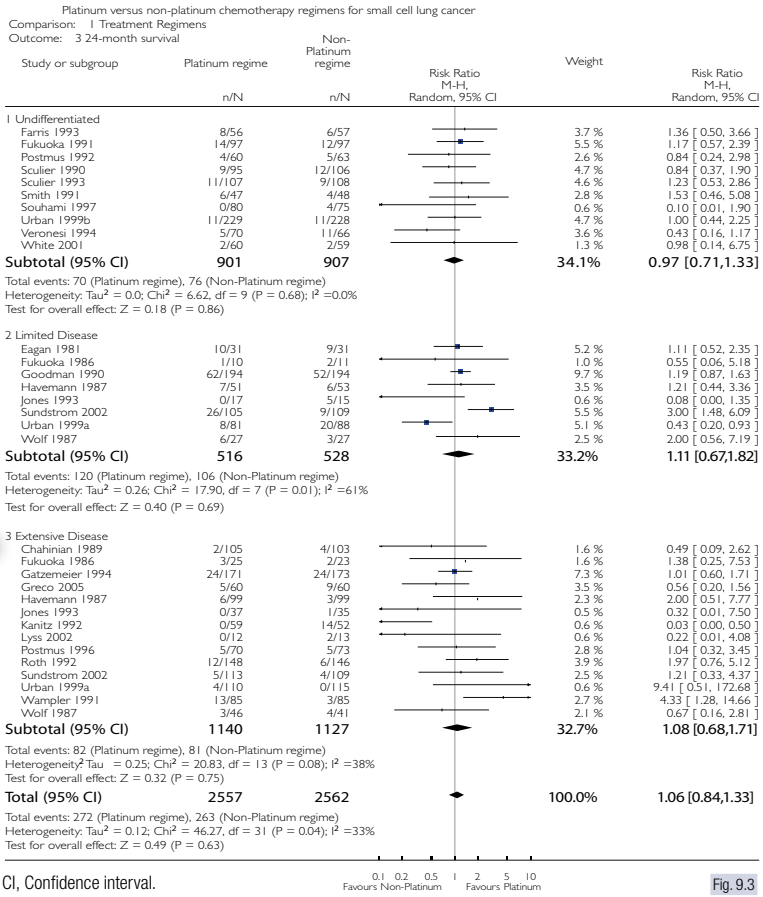
In early trials, radiotherapy (RT) was better than surgery, but still palliative when used alone.

The survival improvement was observed when patients were treated with cyclophosphamide.

Systemic treatment has improved survival in all SCLC stages and is the cornerstone of the treatment.

Non-platinum combinations (e.g. cyclophosphamide, doxorubicin, etoposide) are efficacious but less used than cisplatin/etoposide.

In stage I–III SCLC, cisplatin/etoposide is combined with concurrent chest RT.



CI, Confidence interval.

Fig. 9.3

REVISION QUESTIONS

1. What proportion of patients with newly diagnosed SCLC already have disseminated disease?
2. Does surgery have a major role to play in the management of non-disseminated SCLC?
3. What is the cornerstone of treatment of SCLC?

Disseminated disease: first-line treatment

SCLC is, in first line, a very chemosensitive disease. Rapid tumour responses are observed in over 80% of patients. Chemotherapy (ChT) is also useful in patients with a poor performance status, but at the cost of more toxicity.

The first-choice treatment is 4–6 cycles of etoposide and a platinum derivative (cisplatin or carboplatin).

Combinations other than platinum/etoposide may have similar activity, but this has not been consistently demonstrated. Cisplatin can probably safely be replaced by carboplatin in order to decrease toxicity and to facilitate the delivery.

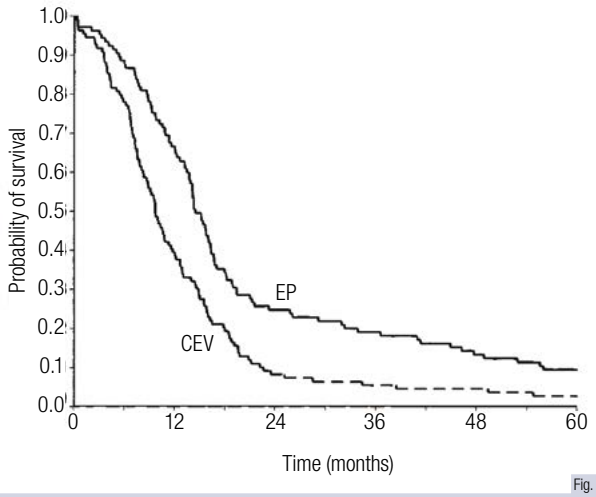


Fig. 9.4

CEV, Cyclophosphamide/epirubicin/vincristine; EP, etoposide/cisplatin.

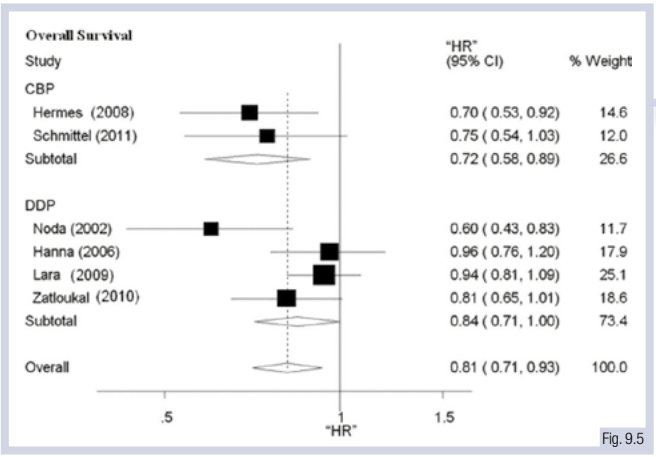


Fig. 9.5

CBP, Carboplatin; CI, confidence interval; DDP, cisplatin; HR, hazard ratio.

The combination of cisplatin/irinotecan was superior for survival to cisplatin and etoposide, but only in Asian populations.

Studies in Europe and the USA did not demonstrate a beneficial effect of cisplatin/irinotecan over cisplatin/etoposide, the latter remaining first choice.

European and USA patients experienced more toxicity with irinotecan than Asians, possibly due to genetic differences in topoisomerase I enzymes.

The concurrent administration of the programmed death-ligand 1 (PD-L1) inhibitor atezolizumab with carboplatin/etoposide ChT followed by atezolizumab maintenance, improved the median overall survival from 10.3 months to 12.3 months.

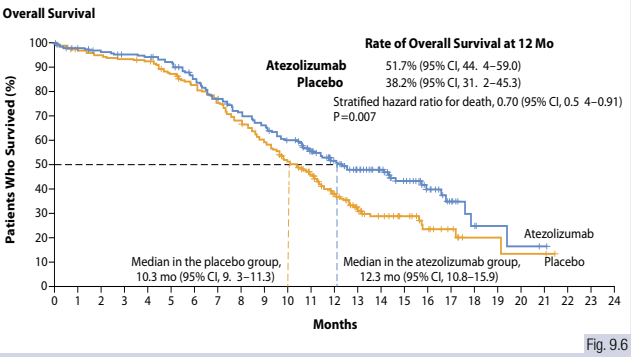


Fig. 9.6

CI, Confidence interval.

REVISION QUESTIONS

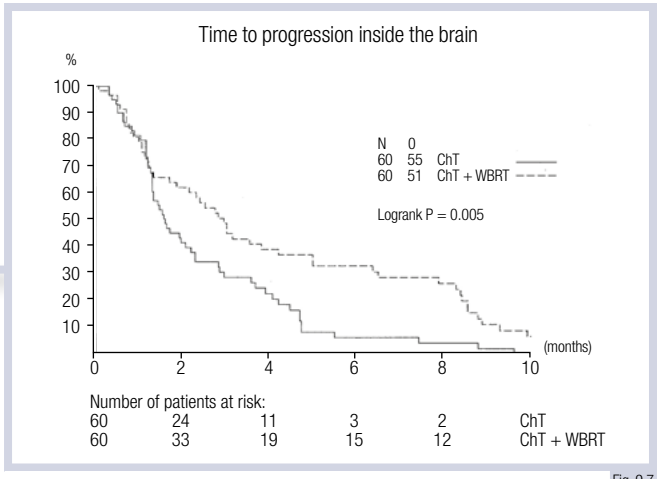
1. Is combination therapy acceptable in patients with a poor performance status?
2. Can cisplatin be substituted by carboplatin?
3. What is the impact of immune treatment in first-line for disseminated SCLC?

Disseminated disease: first-line treatment (continued)

Immediate whole-brain radiotherapy (WBRT) is indicated in patients with brain metastases and intracranial hypertension or neurological emergencies.

Asymptomatic brain metastases can be treated with systemic therapy and WBRT deferred to symptomatic relapse.

Directly after WBRT, systemic therapy can be given.



ChT, Chemotherapy; WBRT, whole-brain radiotherapy. Fig. 9.7

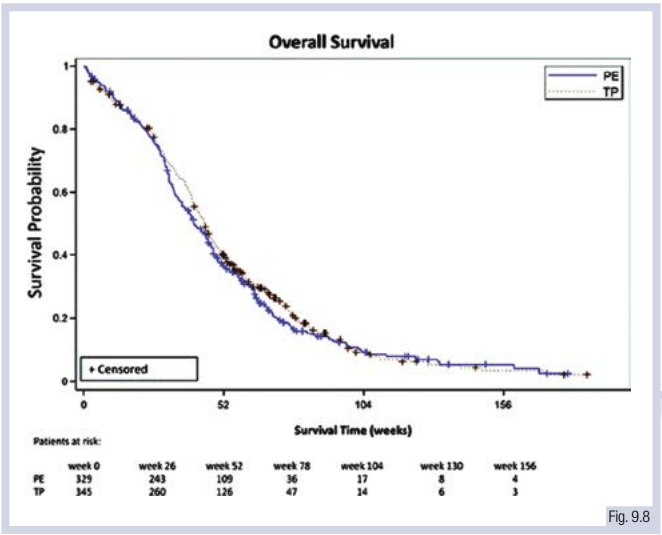


Fig. 9.8

PE, Cisplatin/etoposide; TP, topotecan/cisplatin.

Because of the fast response to systemic treatment, a superior vena cava syndrome can be treated with ChT alone.

Alternating non-cross-resistant drugs and increased total dose, dose intensity, number of courses or number of drugs have been unsuccessful.

The median survival is 8–13 months and the 5-year survival 5%.

Symptomatic brain metastases occur in nearly 50% of patients, even in those without detectable brain metastases at diagnosis.

Prophylactic cranial irradiation (PCI) given after ChT to patients showing any response and with a reasonable performance status decreases the incidence of symptomatic brain metastases.

PCI also increases survival in these cases. The addition of chest RT did not lead to an increased survival, but may be offered in selected patients (A).

In patients with a brain MRI negative for brain metastases, PCI with 3-monthly MRI surveillance did not offer a survival advantage over MRI surveillance and subsequent treatment of brain metastases (B).

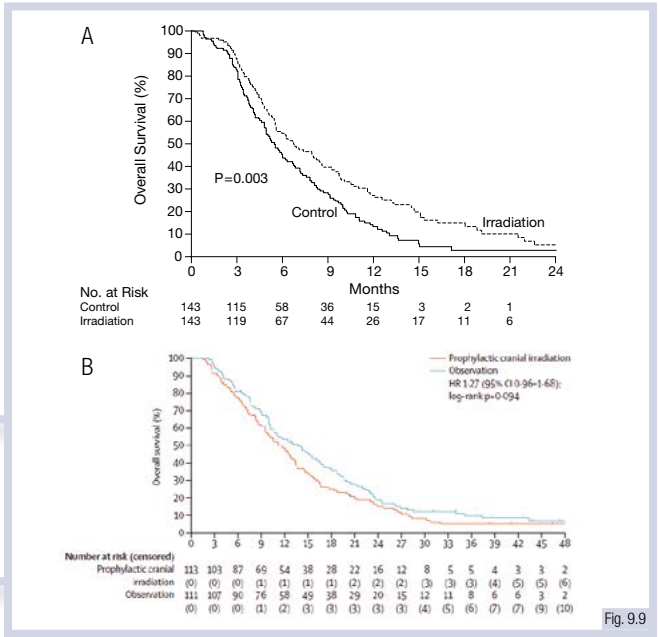


Fig. 9.9

CI, Confidence interval; HR, hazard ratio.

REVISION QUESTIONS

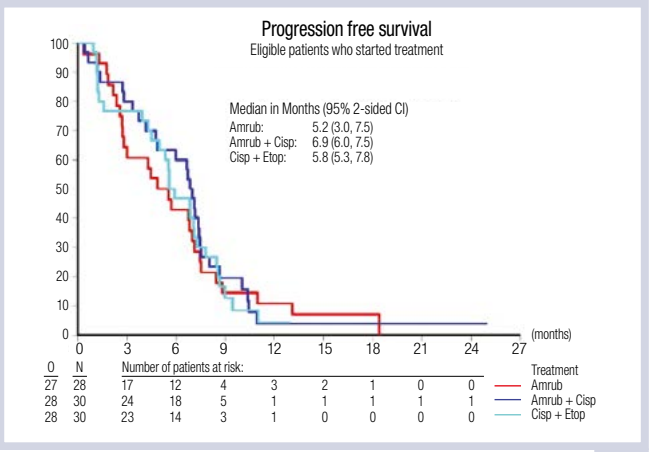
1. Should asymptomatic brain metastases at diagnosis be treated with WBRT?
2. What is the treatment of brain metastases with important neurological symptoms?
3. When is PCI given?
4. Should all patients that achieve remission after ChT receive chest RT?

Disseminated disease: second-line treatment

Virtually all patients with disseminated disease will relapse even after having achieved a remission with first-line ChT or chemo-immunotherapy.

Patients are classified as having a sensitive relapse when the recurrence is seen 90 days or more after the end of first-line treatment.

A resistant relapse is defined as a recurrence within 90 days after the end of first-line ChT.



Amrub, Amrubicin; Cisp, cisplatin; CI, confidence interval; Etop, etoposide.

Fig. 9.10

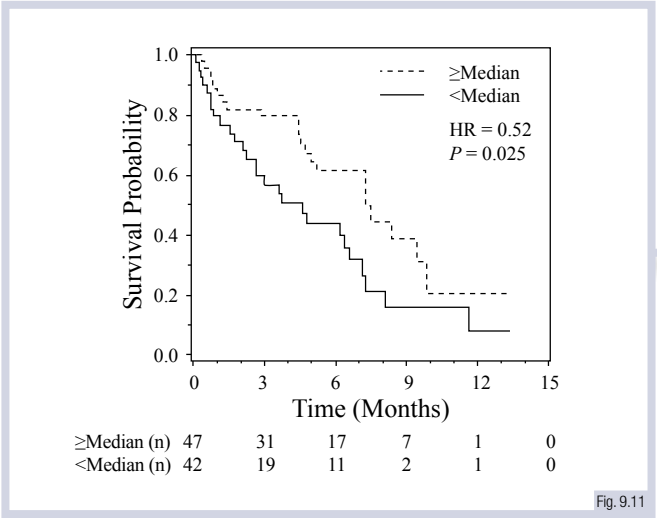


Fig. 9.11

HR, Hazard ratio.

If disease progresses during initial ChT, the SCLC is called refractory.

Second-line treatment is useful only in those patients in a good general condition and with adequate organ function.

In case of a sensitive relapse, the same ChT as initially given can be considered.

In case of a resistant relapse, second-line therapy results in less than 10% remissions, with a few months of life prolongation.

Topotecan is the only approved drug for resistant relapse in second line.

After platinum and etoposide, besides topotecan, cyclophosphamide, doxorubicin and vincristine are often given.

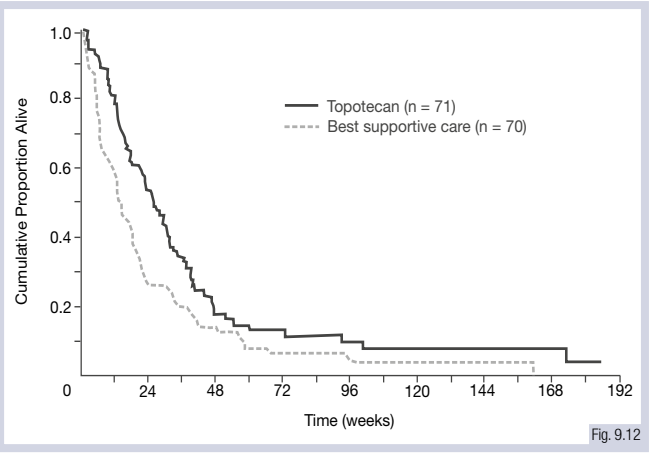


Fig. 9.12

REVISION QUESTIONS

1. When is the same ChT as in first line indicated at relapse?
2. What is a resistant relapse?
3. Which drug is approved for resistant relapse?

Localised disease

A rare subgroup of patients with very early stage SCLC, i.e. T1-2N0M0, may be considered for primary surgery.

Even after complete resection, adjuvant ChT is standard, as well as PCI.

In most patients, RT is the standard local treatment.

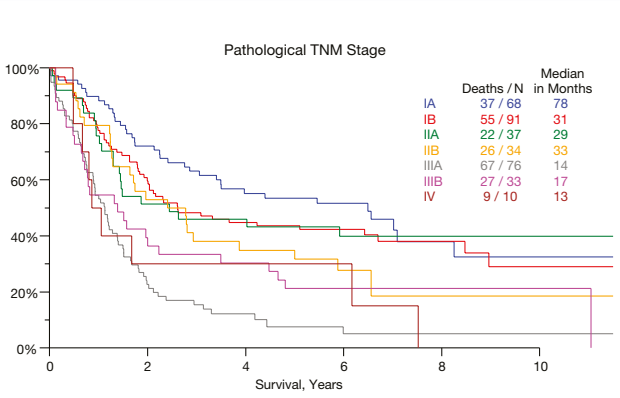


Fig. 9.13

TNM, Tumour, Node, Metastasis.

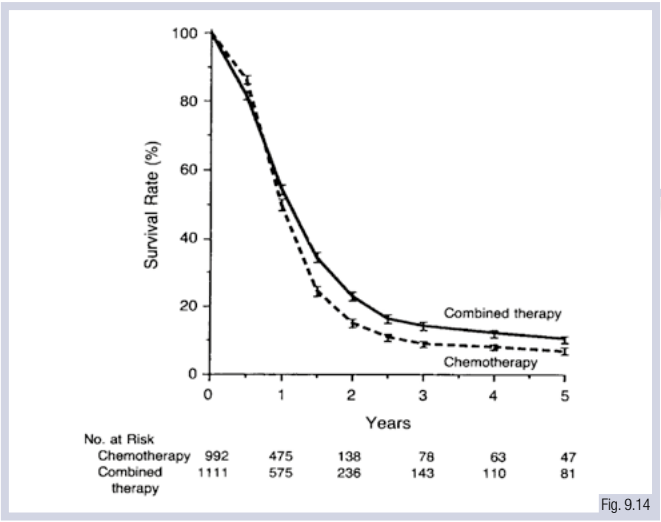


Fig. 9.14

Old meta-analyses showed that the addition of thoracic RT to ChT improved survival over ChT alone.

ChT delivered concurrently with chest RT is the first choice.

In frail patients, sequential ChT and chest RT may be considered.

The best results were achieved by combining 4 cycles of cisplatin/etoposide with chest RT.

New drug combinations have not improved survival.

There is no role for maintenance therapy after cisplatin/etoposide and thoracic RT. As an example, the addition of vandetanib did not improve the OS.

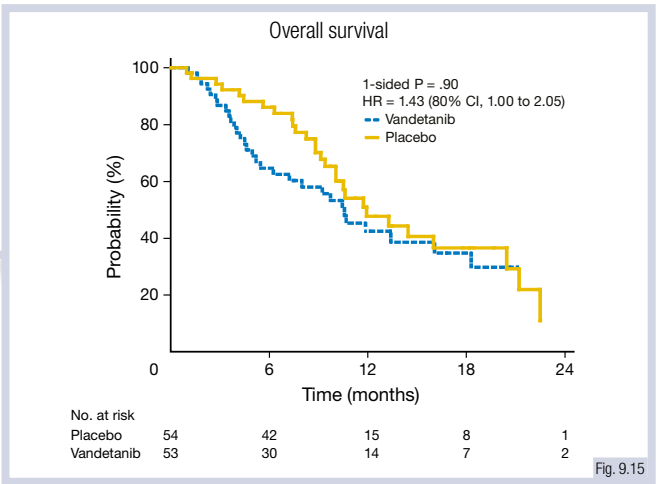


Fig. 9.15

CI, Confidence interval; HR, hazard ratio.

REVISION QUESTIONS

1. What is the role of surgery in SCLC?
2. What is the best drug combination for localised SCLC?
3. How should thoracic RT be combined with ChT?

Localised disease (continued)

Delivering chest RT in a short overall treatment time leads to a better survival than giving the same dose over a longer time. After a phase III trial comparing 45 Gy BID versus 66 Gy QD, the BID schedule remains standard of care.

Beginning chest RT as soon as possible after the start of ChT is associated with higher long-term survival.

Because of radiation-induced radiological changes, the remission status cannot be assessed adequately, except in the case of frank disease progression.

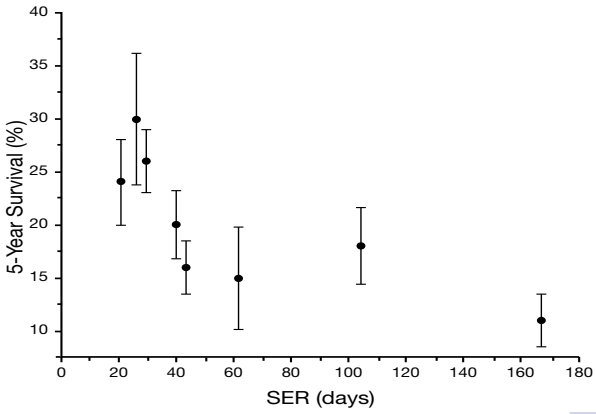


Fig. 9.16

SER, End of radiotherapy.

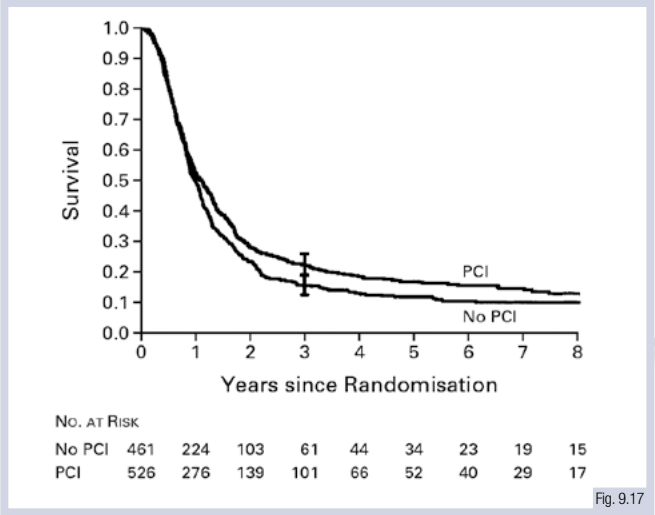


Fig. 9.17

PCI, Prophylactic cranial irradiation.

Even in patients with negative findings on brain imaging at diagnosis, 50% will subsequently develop brain metastases.

Patients with brain metastases have a median survival of 3 months. Prevention is thus essential.

PCI reduces the incidence of brain metastases by 50% and increases long-term survival.

PCI may lead to slight neurocognitive impairment, which may also be present at diagnosis and due to ChT.

PCI is standard in all patients who show no disease progression after ChT and thoracic RT and who are in a reasonable general condition.

PCI should be given within 4 weeks after the last administration of ChT.

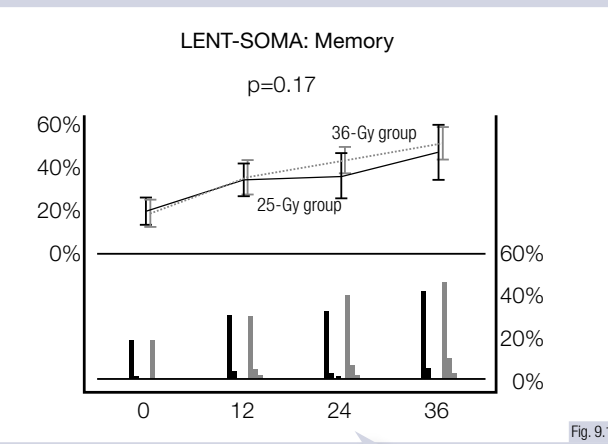


Fig. 9.18

LENT-SOMA, Late Effects Normal Tissue Task Force-Subjective, Objective, Management scale.

Proportion of patients in the four classes of unfavourable status [grade 1 (left), grade 2, grade 3 and grade 4 (right)] in each arm

REVISION QUESTIONS

1. How and when should thoracic irradiation be delivered?
2. Which patients should receive PCI?
3. When should PCI be given?

Localised disease: radiotherapy details

Two Phase III studies (USA and European Organisation for Research and Treatment of Cancer [EORTC]) compared the current standard RT schedule (45 Gy/30 twice-daily fractions of 1.5 Gy) with 66–70 Gy in 2 Gy per day, 5 days per week schedules. The EORTC (CONVERT) study, with a non-inferiority design, could not demonstrate that the experimental arm (66 Gy) was beneficial and the 45 Gy BID arm was numerically better for survival.

In both arms of these studies, thoracic RT began at day 1 of the second cycle of ChT.

Elective nodal irradiation could be omitted provided the RT volumes were defined by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scans.

Frequency and location of recurrences as assessed by CT

Recurrence	Patients (n)
None	21 (35)
Local	9 (15)
In field	3 (5.0)
Out of field	4 (6.7)
Both in field and out of field	2 (3.3)
Isolated local	2 (3.3)
Local and distant/nodal	7 (11.7)
Nodal	20 (33.3)
In field	8 (13.3)
Out of field	7 (11.7)
Both in field and out of field	5 (8.0)
Isolated nodal	2 (3.3)
Nodal and distant/nodal	18 (30.0)
Distant	34 (56.7)
Isolated distant	19 (31.7)
Distant and local/nodal	15 (25.0)
Isolated brain	9 (15.0)

CT, Computed tomography.

Fig. 9.19

Acute oesophagitis grade 3 occurred in 20% of patients treated with accelerated RT when elective nodal irradiation was omitted, which is similar to the incidence with 66 Gy in 33 QD fractions.

Oesophagitis healed within 3–6 weeks after the end of RT.

There is not a higher risk of radiation pneumonitis for accelerated RT compared with conventional RT.

Effect of modified radiotherapy compared with conventional radiotherapy on toxicity events

	Availability				Result				
Severe Toxicity	No. of Trials	No. of Patients	Toxicity Rate in Control Arm (%)	Toxicity Rate in Experimental Arm (%)	OR	95% CI	*P* Efficacy	I^2 (%)	*P* Heterogeneity
Small cell lung cancer									
Acute oesophageal	2	667	12	25	2.41	1.62 to 3.59	< .001	0	.99
Acute pulmonary	2	675	5	6	1.32	0.69 to 2.51	.40	0	.33
Acute cardiac	2	670	1	3	2.96	1.13 to 7.73	.03	0	.76
Haematological	2	674	83	86	1.22	0.81 to 1.86	.34	0	.36
Neutrophils	2	643	84	87	1.31	0.84 to 2.04	.23	0	.70
Platelets	2	666	38	30	0.70	0.50 to 0.98	.04	36	.21
Haemoglobin	2	673	18	19	1.06	0.71 to 1.59	.76	0	.35

CI, Confidence interval; OR, odds ratio.

Fig. 9.20

A higher dose of PCI was shown not to be beneficial.

The standard PCI dose remains 25 Gy in 10 daily fractions.

Avoidance of the hippocampus to preserve neurocognition is being evaluated in clinical studies.

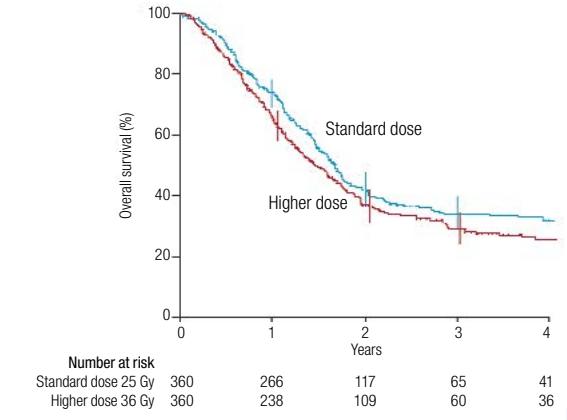


Fig. 9.21

Gy, Gray.

REVISION QUESTIONS

1. Which is the standard dose of chest RT?
2. What are the differences in late side effects of RT comparing accelerated RT with conventional fractionation?
3. What is the standard schedule of PCI?

Summary: Treatment of small cell lung cancer: chemotherapy and radiotherapy

- Standard of care is 4–6 cycles of etoposide and a platinum derivative (cisplatin or carboplatin), if available concurrently with atezolizumab (with carboplatin)
- Directly after palliative WBRT, systemic treatment can be administered
- PCI improves survival in all stages, but in stage IV disease MRI surveillance is an alternative
- Second-line treatment is useful in patients in a good general condition and with good organ function
- Topotecan is the only approved drug for resistant relapse in second line
- In limited disease early thoracic RT is standard of care, in extensive disease it should be considered as consolidation
- Delivering chest RT in a short overall treatment time leads to a better long-term survival than giving the same RT dose over a longer time

Further Reading

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Targeted therapy for oncogene-addicted metastatic non-small cell lung cancer

10

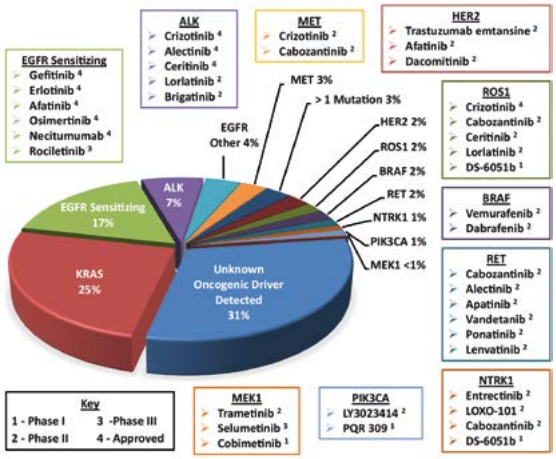
Epidermal growth factor receptor mutations and targeted therapy

Histologically defined non-small cell lung cancers (NSCLCs) are heterogeneous and consist of numerous molecular subsets.

Somatic mutations in the epidermal growth factor receptor (*EGFR*) gene are detected in 30%–40% of NSCLCs in Asian patients and in 10%–15% of NSCLCs in Caucasian patients.

Among the various types of *EGFR* mutations, deletion in exon 19 and L858R in exon 21 are the most common sensitising mutations, accounting for 90% of activating *EGFR* mutations.

Frequency of molecular aberrations in various driver oncogenes in lung adenocarcinomas and currently available drugs against oncogenic proteins



ALK, Anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2. Fig. 10.1

Randomised phase III trials comparing EGFR TKIs with platinum doublets in *EGFR*-mutant NSCLC

Trial	EGFR TKI	n	*EGFR* mutation	Response rate (%)	PFS (months)	OS (months)
NEJ002	Gefitinib	224	224	74 vs 31 *p* <0.001	10.8 vs 5.4 HR=0.30 (0.22-0.41)	30.5 vs 23.6
WJTOG-3405	Gefitinib	172	172	62 vs 32 *p* <0.0001	9.6 vs 6.6 HR=0.52 (0.38-0.72)	35.5 vs 38.8 HR=1.185 (0.76-1.83)
OPTIMAL	Erlotinib	154	154	83 vs 36 *p* <0.0001	13.7 vs 4.6 HR=0.16 (0.10-0.26)	22.7 vs 28.9 HR=1.04 (0.69-1.58)
EURTAC	Erlotinib	173	173	58 vs 15	9.7 vs 5.2 HR=0.37 (0.25-0.54)	19.3 vs 19.5 HR=1.04 (0.65-1.68)
ENSURE	Erlotinib	217	217	68.2 vs 39.3	11.0 vs 5.6 *p* <0.0001	NA
LUX-Lung 3	Afatinib	345	345	56 vs 23 *p* <0.001	11.1 vs 6.0 HR=0.58 (0.43-0.78)	28.2 vs 28.2 HR=0.88
LUX-Lung 6	Afatinib	364	364	67 vs 23 *p* <0.0001	11.0 vs 5.6 HR=0.28 (0.20-0.39)	23.1 vs 23.5 HR=0.93
ARCHER	Dacomitinib	452	452	76 vs 70 *p*=0.2541	14.7 vs 9.2 HR=0.59 (0.47-0.74)	34.1 vs 26.8 HR=0.76

EGFR, Epidermal growth factor receptor; HR, hazard ratio; NA, not applicable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor. Fig. 10.2

First-generation EGFR tyrosine kinase inhibitors (TKIs) (gefitinib, erlotinib) and second-generation TKIs (afatinib) are associated with a high response rate and prolonged progression-free survival (PFS) compared with a platinum doublet as first-line therapy.

Afatinib only demonstrated improvement in overall survival (OS) compared with platinum doublets in *EGFR*-mutant NSCLC. Dacomitinib improved PFS and OS compared to gefitinib.

Head-to-head comparison of second-generation EGFR TKIs, afatinib or dacomitinib, showed a higher response rate and longer PFS compared with gefitinib, but only dacomitinib showed significant improvement in OS (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.582-0.993).

Almost all patients ultimately develop resistance, with an average 9–14 months PFS.

Repeat biopsy revealed various different mechanisms of EGFR TKI resistance. Among them, T790m accounts for 50%–60% of acquired resistance mechanisms.

Other resistance mechanisms include c-met amplification, human epidermal growth factor receptor 2 (*HER2*) amplification, small cell lung cancer transformation or epithelial mesenchymal transition (EMT).

Mechanisms of *EGFR*-mutant NSCLC resistant to erlotinib and gefitinib

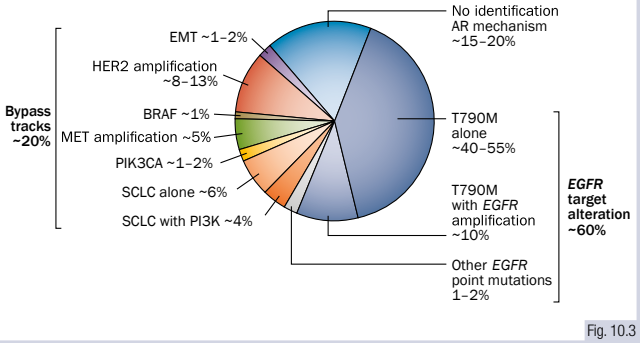


Fig. 10.3

AR, Acquired resistance; *EGFR*, epidermal growth factor receptor; EMT, epithelial mesenchymal transition; *HER2*, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

REVISION QUESTIONS

1. Is molecular profiling using next generation sequencing (NGS) essential to guide treatment in NSCLC?
2. How do you choose between first-generation EGFR TKIs, gefitinib or erlotinib, and second-generation TKIs, afatinib or dacomitinib?
3. Is repeat biopsy essential in patients who develop resistance to EGFR TKIs?

EGFR mutations: third-generation EGFR TKIs, cfDNA and resistance

Third-generation EGFR TKIs target both activating *EGFR* mutations and *T790M* but spare wild-type *EGFR*.

The third-generation EGFR TKI osimertinib produced significant improvements in objective response rate (ORR) and PFS compared with platinum/pemetrexed in *EGFR T790M*-positive NSCLC (A). Osimertinib also showed significant improvement in ORR and PFS compared with first-generation EGFR TKI as first-line therapy (B).

Osimertinib can penetrate the blood–brain barrier and has demonstrated activity in central nervous system (CNS) metastases.

Kaplan-Meier estimates of the duration of progression-free survival as assessed by investigators in the intention to treat population

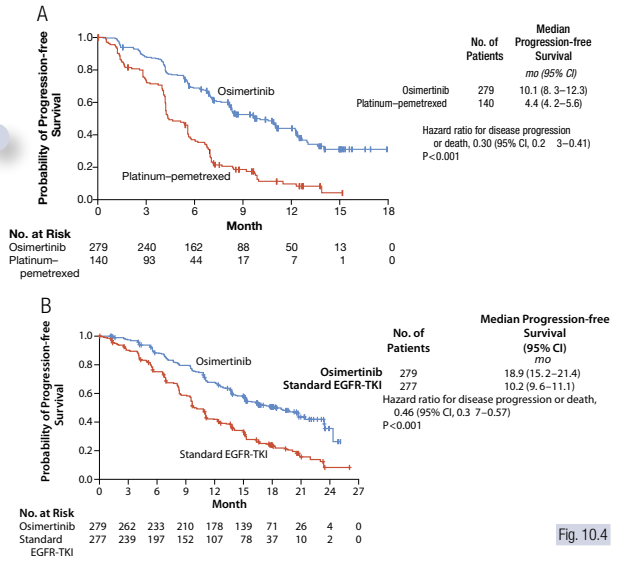


Fig. 10.4

CI, Confidence interval; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

Kaplan-Meier curves of PFS in *T790M*-positive (*T790M*+) and *T790M*-negative (*T790M*-) subpopulations treated with osimertinib. (A) Patients with *T790M*+ tumours have a dramatically longer PFS than patients with *T790M*- tumours. (B) Plasma genotyping for *T790M* fails to identify two subgroups with different PFS

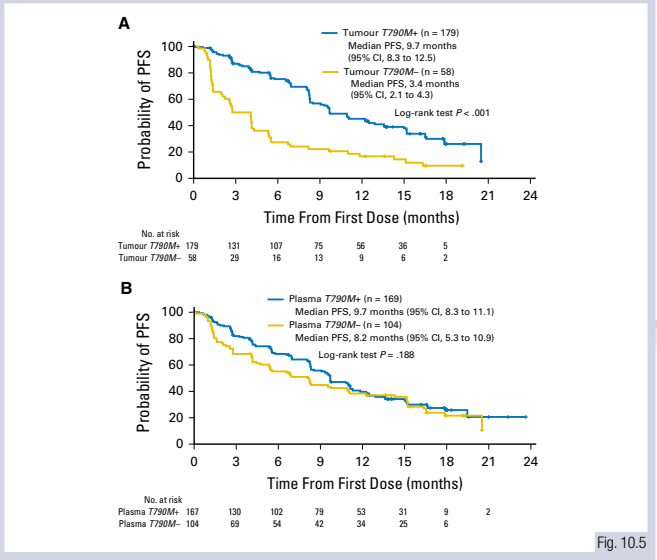


Fig. 10.5

CI, Confidence interval; PFS, progression-free survival.

Repeat biopsies can identify patients who may benefit from third-generation EGFR TKIs; however, repeat biopsies are invasive and not always possible due to tumour location, pattern of tumour or poor performance status.

Plasma genotyping is used as a screening test for *T790M* prior to performing an *EGFR*-resistance biopsy.

The sensitivity and specificity of plasma genotyping for *EGFR*-sensitising mutation and *T790M* mutation is 70%–85%.

Patients treated with third-generation EGFR TKIs also develop resistance within 8–11 months.

Resistance mechanisms include *EGFR C797S* mutation, loss of *T790M*, *EGFR* gene amplification, c-met amplification small cell lung cancer transformation or MAPK activation.

Evolution of resistance mechanisms is inevitable for survival of cancer cells, commonly leading to heterogeneity.

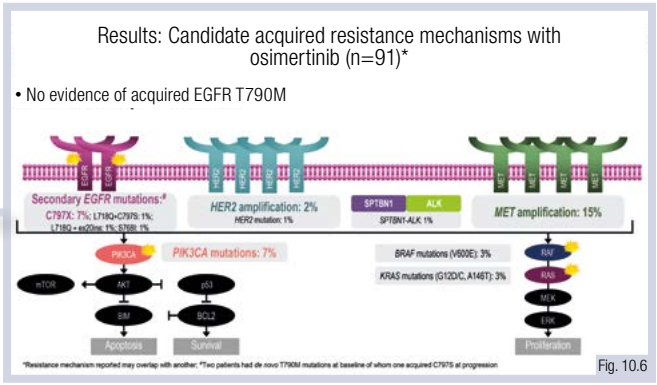


Fig. 10.6

ALK, Anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2; mTOR; mammalian target of rapamycin.

REVISION QUESTIONS

1. Is repeat biopsy essential for detection of *T790M*?
2. Can plasma genotyping replace tissue genotyping?
3. What would be the treatment options for patients who failed third-generation EGFR TKIs?

Anaplastic lymphoma kinase (*ALK*) rearrangements – crizotinib

ALK rearrangements are present in 3%–5% of NSCLCs and define a distinct molecular subtype of the disease.

Diagnostic assays for *ALK* rearrangements include fluorescent *in situ* hybridisation (FISH), immunohistochemistry and next-generation sequencing (NGS).

ALK rearrangements are associated with a younger age, lack of smoking history and adenocarcinoma histology.

(A) ALK fluorescent *in situ* hybridisation (FISH). Splitting of the red and green signals (white arrows) in ≥15% of cells is diagnostic of an *ALK* rearrangement. (B) ALK immunohistochemistry staining.

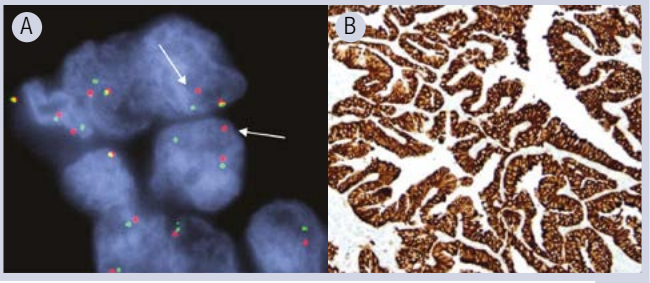


Fig. 10.7

ALK, Anaplastic lymphoma kinase.

Kaplan-Meier estimates of progression-free survival in PROFILE 1014

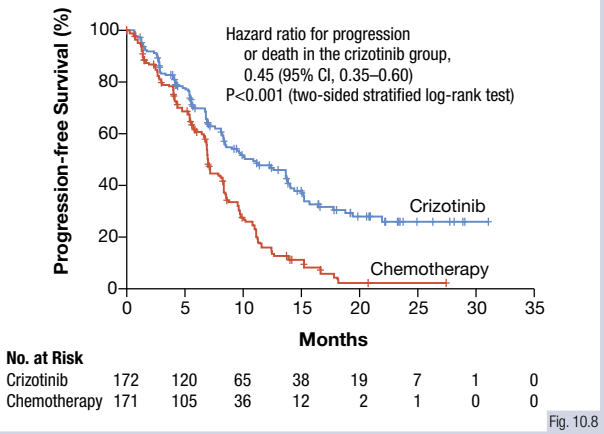


Fig. 10.8

CI, Confidence interval.

Crizotinib, a first-generation ALK inhibitor, provided the first evidence that *ALK*-positive (*ALK*+) lung cancers are targetable alterations.

In PROFILE 1014, crizotinib produced significant improvements in ORR and PFS compared with first-line platinum/pemetrexed in *ALK*+ patients.

Despite the significant activity of crizotinib, patients almost invariably develop resistance – typically within 7.7–10.9 months.

The central nervous system (CNS) is the most common site of relapse among patients receiving crizotinib due to insufficient penetration across the blood-brain barrier.

To combat crizotinib resistance, second-generation ALK inhibitors (ceritinib, alectinib, brigatinib) and third-generation ALK inhibitors have been developed. These agents are more potent and selective for ALK.

Second-generation ALK TKIs have demonstrated significant systemic and intracranial activity in crizotinib-resistant, *ALK*+ patients.

Brain magnetic resonance imaging (MRI) scans of an *ALK*+ patient following disease progression on crizotinib (left) and after treatment with the second-generation ALK inhibitor brigatinib (right)

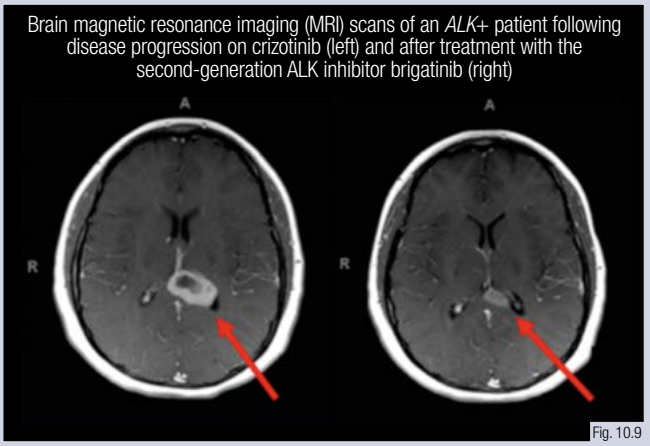


Fig. 10.9

ALK+, Anaplastic lymphoma kinase positive.

REVISION QUESTIONS

1. What is the preferred diagnostic test for detection of *ALK* rearrangements?
2. What is the role of crizotinib in the setting of newer second-generation ALK inhibitors?
3. What is the preferred approach for patients progressing in the CNS on crizotinib?

ALK rearrangements – second- and third-generation ALK inhibitors

In phase III studies, alectinib (ALEX, J-ALEX) and brigatinib (ALTA-1L) produced significant improvements in PFS compared with crizotinib in ALK inhibitor-naïve patients.

Alectinib also produced a significant improvement in the cumulative incidence of CNS progression (HR 0.16; P <0.001).

Second-generation ALK inhibitors are now standard therapies for newly diagnosed *ALK*+ patients. Each second-generation ALK inhibitor has a different toxicity profile.

Kaplan-Meier estimates of progression-free survival in the Global ALEX study

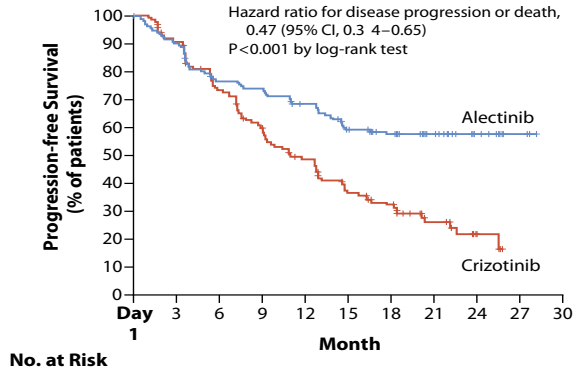


Fig. 10.10

CI, Confidence interval.

Breakdown of specific *ALK* resistance mutations among *ALK*+ patients progressing on each ALK inhibitor

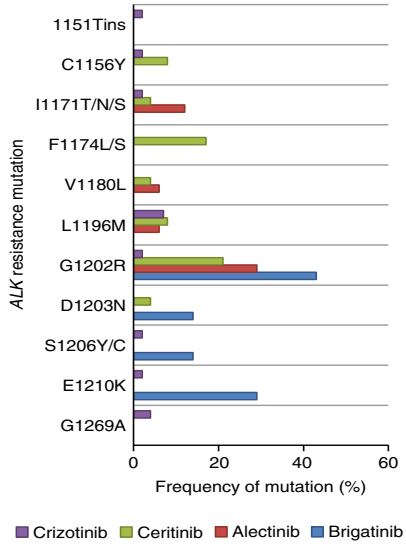


Fig. 10.11

ALK, Anaplastic lymphoma kinase.

Each ALK inhibitor is associated with a distinct spectrum of *ALK* resistance mutations upon progression.

ALK resistance mutations, particularly *ALK G1202R*, are more common after treatment with second-generation ALK inhibitors.

Repeat biopsies and circulating tumour DNA (ctDNA) assays are being studied as tools to guide treatment after progression on second-generation ALK TKIs.

Lorlatinib is a CNS-penetrant, third-generation ALK inhibitor designed to overcome *ALK* resistance mutations, including *ALK G1202R*.

Lorlatinib was associated with an ORR of 38.7% in *ALK*+ patients treated with two or more prior ALK inhibitors.

The most common adverse events on lorlatinib are hypercholesterolaemia, hypertriglyceridaemia, oedema and peripheral neuropathy. Cognitive effects are seen in 18% of patients.

Best percentage change in tumour size from baseline with lorlatinib in *ALK*+ patients previously treated with two or more ALK inhibitors

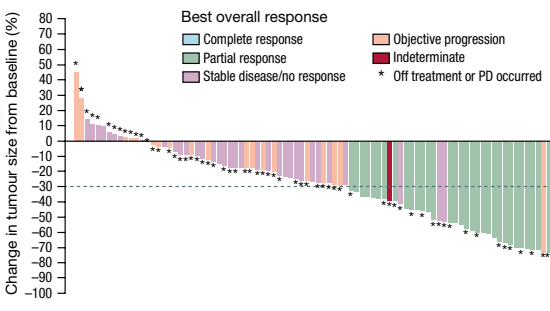


Fig. 10.12

*Indicates patients off treatment or progressive disease occurred.
ALK+, Anaplastic lymphoma kinase positive.

REVISION QUESTIONS

1. What is the preferred first-line agent for newly diagnosed *ALK*+ NSCLC?
2. Should *ALK*+ patients routinely undergo repeat biopsies or ctDNA analysis upon progression on second-generation ALK inhibitors?
3. What is the most common *ALK* resistance mutation after treatment with second-generation ALK inhibitors?

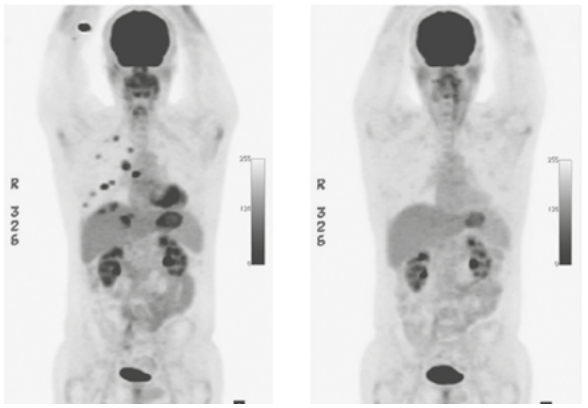
Additional oncogene-addicted targets: *ROS1*, *BRAF* and *RET*

ROS1 rearrangements define a distinct molecular subset of NSCLCs, identified in 1%–2% of patients.

ROS1 rearrangements confer sensitivity to treatment with the ALK/ROS1/MET inhibitor crizotinib.

In the PROFILE 1001 study, crizotinib was associated with an ORR of 72% and median PFS of 19.2 months among *ROS1*-positive (*ROS1*+) NSCLC patients.

Positron emission tomography (PET) of a *ROS1*-rearranged patient prior to and after treatment with crizotinib



Baseline After 7 weeks

Fig. 10.13

Maximum tumour response to dabrafenib and trametinib in *BRAF V600E*-mutant NSCLC

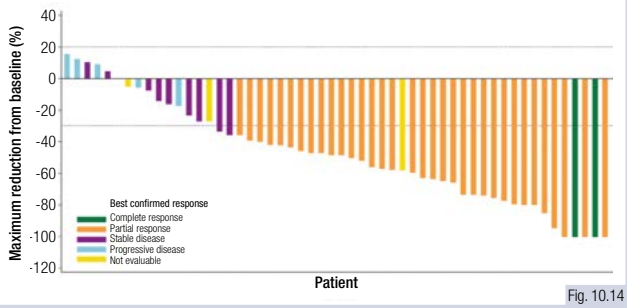


Fig. 10.14

NSCLC, Non-small cell lung cancer.

BRAF mutations are found in approximately 3%–4% of lung adenocarcinomas, but only half are *V600E* mutations.

The BRAF inhibitors dabrafenib and vemurafenib have been associated with single-agent response rates of 33% and 42%, respectively.

The combination of dabrafenib and trametinib (MEK inhibitor) achieved an ORR of 63.2% and median PFS of 9.7 months.

RET rearrangements are present in 1%–2% of NSCLCs and are generally mutually exclusive to other oncogenic drivers (e.g. *EGFR*, *ALK*).

Multikinase inhibitors (MKIs), such as cabozantinib and vandetanib, are associated with ORRs of 28% and 18%-53%, respectively.

Recently, two selective RET inhibitors, BLU-667 and LOXO-292, have been developed. Each has demonstrated promising anti-tumour activity in *RET*-positive (*RET*+) NSCLC.

Multitargeted kinase inhibitors with anti-RET activity evaluated to date

Agent	Other molecular targets	Trial ID	N	ORR
Cabozantinib	*VEGFR, MET, TIE2, AXL, FLT3, KIT*	NCT01639508	25	28%
Vandetanib	*VEGFR, HER, EGFR*	NCT01823068 UMIN000010095	17 17	18% 53%
Lenvatinib	*VEGFR1-3, FGFR1-4, PDGFR, KIT*	NCT1877083	25	16%
Sunitinib	*FR1-2, PDGFRβ, FLT3, KIT*	NCT01829217	35	NR
Ponatinib	*ABL, FLT3, KIT, FGFR, VEGFR, PDFGR*	NCT01813734 NCT01935336	20 110	NR NR
Apatinib	*VEGFR2*	NCT02540824	40	NR

Fig. 10.15

EGFR, Epidermal growth factor receptor; *FGFR*, fibroblast growth factor receptor; *HER*, human epidermal growth factor receptor; NR, not reached; ORR, objective response rate; *PDGFR*, platelet-derived growth factor receptor; *VEGFR*, vascular endothelial growth factor receptor.

REVISION QUESTIONS

1. What is the preferred therapy for *ROS1*+ lung cancer?
2. Should *BRAF*-mutant NSCLC patients be treated with a single-agent BRAF inhibitor?
3. What are the limitations of trials evaluating RET inhibitors to date?

Summary: Targeted therapy for oncogene-addicted non-small cell lung cancer

- Histologically defined NSCLCs are heterogeneous and consist of numerous small molecular subsets according to genomic alterations
- The discovery of *EGFR* mutations and the development of EGFR TKIs have revolutionised the clinical management of NSCLC
- The development of resistance to EGFR TKIs remains challenging
- *ALK* rearrangements define a distinct molecular subset of NSCLC that confer sensitivity to treatment with crizotinib
- As with the experience of EGFR inhibitors in *EGFR*-mutant NSCLC, *ALK*+ patients invariably develop resistance to crizotinib. To combat this problem, second- and third-generation ALK inhibitors have been developed
- Second-generation ALK inhibitors are now standard therapy for newly diagnosed, *ALK*+ NSCLC
- Based upon the success of targeted therapies in NSCLC patients harbouring *EGFR* mutations and *ALK* rearrangements, efforts are underway to identify additional therapeutic targets
- *BRAF V600E* mutations, *ROS1* rearrangements and *RET* rearrangements represent important new therapeutic targets in NSCLC

Further Reading

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Immunotherapy for thoracic malignancies: Part A – Non-small cell lung cancer

11

Lung cancer and the immune system

The immune system plays a key role in cancer through an intricately regulated process of immunosurveillance and immunoediting.

The immune system is now increasingly recognised as an important 'hallmark of cancer'.

Cancer cells can develop mechanisms of evading the immune system in order to proliferate and metastasise.

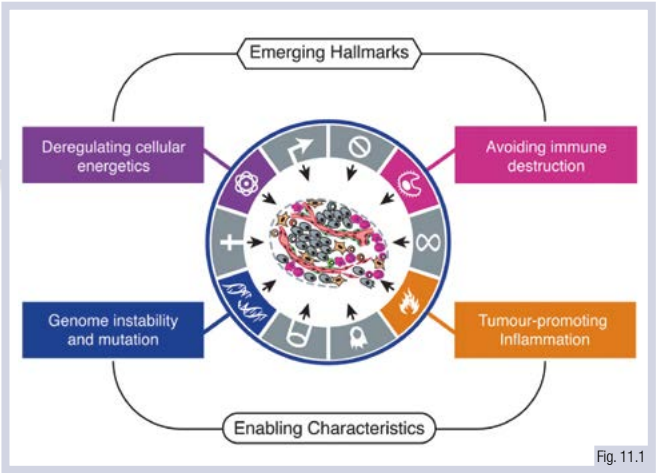
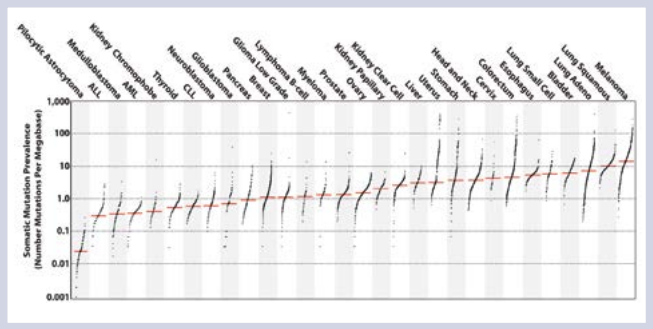


Fig. 11.1



ALL, Acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

Fig. 11.2

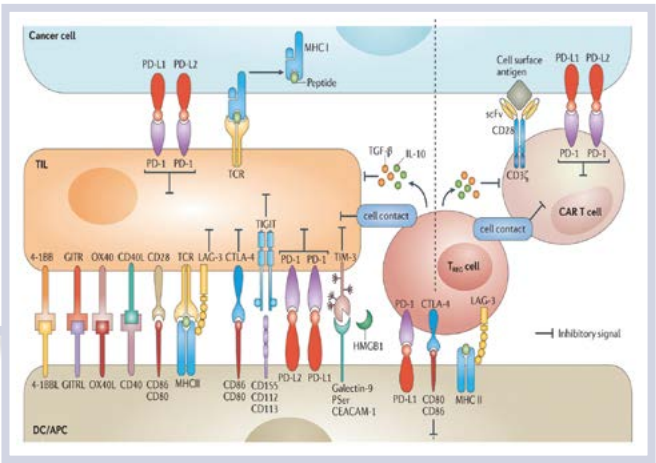
Lung cancer is characterised by a strongly immunosuppressive microenvironment.

However, recent observation of the high somatic mutational burden in non-small cell lung cancer (NSCLC) (squamous [SQ] and adenocarcinoma), second only to that of melanoma, suggests the existence of neoantigens and its potential immunogenicity.

Based on these data, several treatment strategies have been evaluated with immune checkpoint inhibitors in thoracic malignancies.

The advent of novel immunotherapy targeting immune checkpoints has revolutionised the landscape of management of solid malignancies in recent times, including advanced NSCLC.

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) pathways in particular have been identified to be druggable immune checkpoints allowing for immune-mediated self-destruction of cancer cells. Monoclonal antibodies (mAbs) blocking these checkpoints have been studied in recent trials.



APC, Antigen-presenting cell; CAR T cell, chimeric antigen receptor-modified T cell; CTLA-4, cytotoxic T-lymphocyte antigen 4; DC, dendritic cell; IL-10, interleukin-10; LAG 3, lymphocyte activation gene 3; MHC I/II, major histocompatibility complex I/II; PD-1/2; programmed cell death protein 1/2; PD-L1/2, programmed death-ligand 1/2; TCR, T cell receptor; TGFβ, transforming growth factor beta; TIL, tumour-infiltrating lymphocyte.

Fig. 11.3

REVISION QUESTIONS

1. What are the 'hallmarks of cancer'?
2. Describe how cancer cells avoid immune destruction.
3. How does the mutational burden in NSCLC compare to other solid malignancies?

The role of immune checkpoints: CTLA-4 and PD-1/PD-L1

Tumour-associated antigens are recognised and phagocytosed by dendritic cells (DCs) or antigen-presenting cells (APCs) and are presented on the major histocompatibility complex (MHC).

Following presentation to the T cell receptor (TCR), a second co-stimulatory signal is required for T cell activation. CD28 receptor on the T cell surface binds to CD80 (B7-1) or CD86 (B7-2), resulting in interleukin-2 (IL-2) and/or interferon (IFN) release and proliferation of T cells.

CTLA-4 present on regulatory T cells has a higher affinity to B7 ligand and often competitively binds to the B7 ligand, deactivating the immune system by arresting IL-2 secretion resulting in T cell anergy.

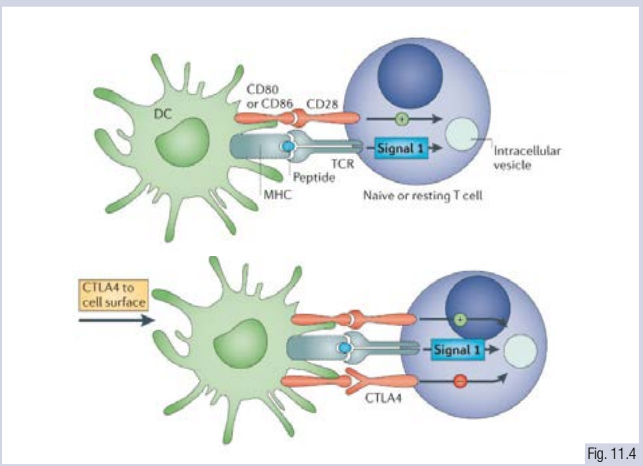


Fig. 11.4

CTLA-4, Cytotoxic T-lymphocyte antigen 4; DC, dendritic cell; MHC, major histocompatibility complex; TCR, T cell receptor.

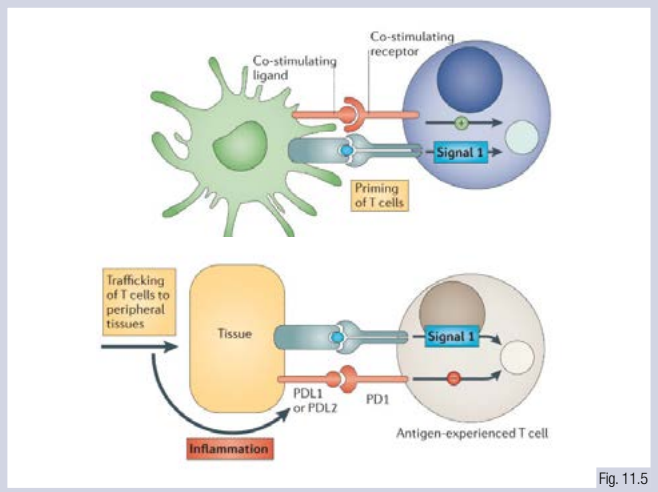


Fig. 11.5

PD-1, Programmed cell death protein 1; PD-L1/2, programmed death-ligand 1/2.

PD-1 receptors on the T cell surface interact with PD-L1, expressed upon IFN-γ or IFN type I stimulation and programmed death-ligand 2 (PD-L2) found on the membrane of cancer cells.

Following successful activation, as a $CD8^+$ cytotoxic T cell approaches a cancer cell, the PD-L1 or PD-L2 ligand expressed on the cancer cell binds to the PD-1 receptor on the T cell resulting in T cell anergy, and thus facilitating immune escape.

Under normal physiological circumstances, the binding of immune checkpoints to their receptors can help to maintain immune self-tolerance and protect tissues during the immune response to a pathogen.

Currently used immunotherapy agents for thoracic malignancies include mAbs against:

- CTLA-4: Ipilimumab (Immunoglobulin [Ig] G1) and tremelimumab (IgG2)
- PD-1: Nivolumab and pembrolizumab (both IgG4)
- PD-L1: Atezolizumab, durvalumab and avelumab (all IgG1)

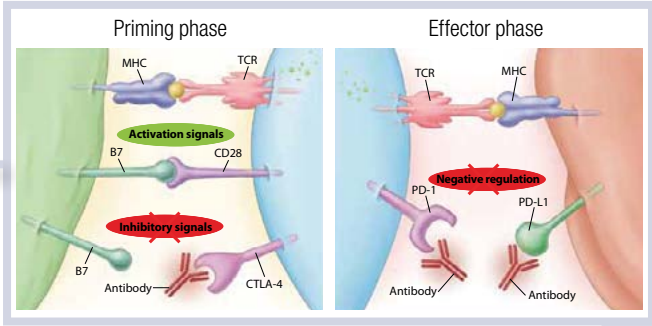


Fig. 11.6

CTLA-4, Cytotoxic T-lymphocyte antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T cell receptor.

REVISION QUESTIONS

1. What is the role of CTLA-4 in the immune response in cancer?
2. What is the effect of PD-1/PD-L1 interaction in advanced NSCLC?
3. List all the immune checkpoint inhibitors which have been approved for clinical use.

Immune checkpoint blockade for treatment-naïve advanced NSCLC

The phase III KEYNOTE-024 randomised 305 treatment-naïve advanced NSCLC (SQ and non-squamous [NSQ]) patients (pts) with high PD-L1 expression (≥50%) to pembrolizumab 200 mg Q3W or physician's choice of platinum-containing doublet chemotherapy (ChT).

Pts in the pembrolizumab arm had longer progression-free survival (PFS) and higher overall response rate (ORR) (44.8% vs 27.8%). At last follow-up, median overall survival (mOS) was 30.0 months with pembrolizumab vs 14.2 months with ChT (hazard ratio [HR] 0.63, p = 0.002).

Grade 3-5 adverse events (AEs) occurred in 31.2% and 53.3% of pts in the pembrolizumab and ChT groups, respectively. Quality of life was also improved in the pembrolizumab arm.

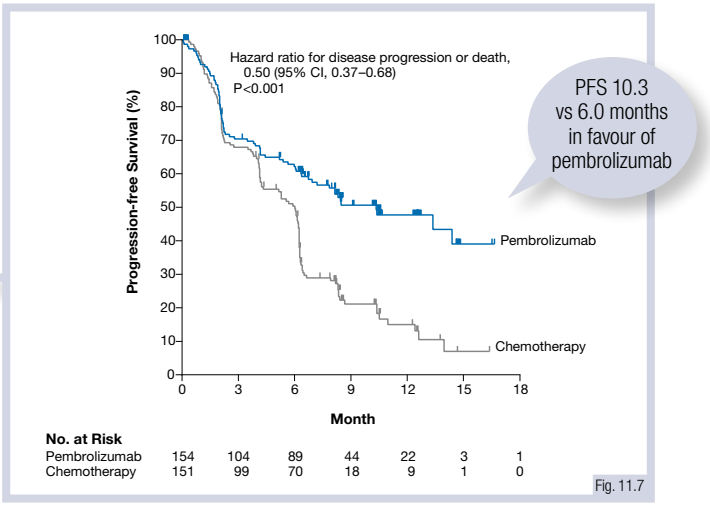


Fig. 11.7

CI, Confidence interval; PFS, progression-free survival.

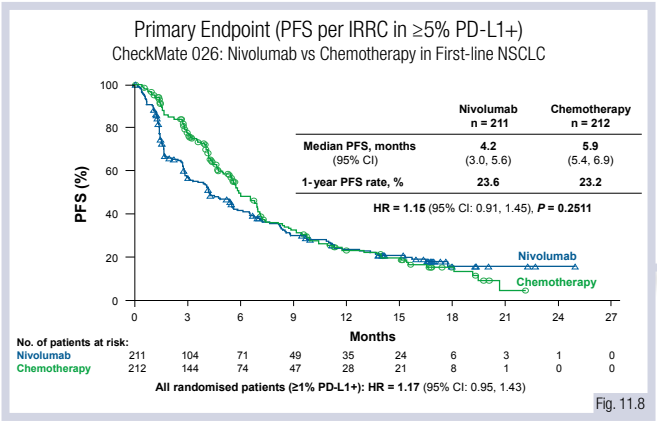


Fig. 11.8

CI, Confidence interval; HR, hazard ratio; IRRC, independent radiology review committee; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

The first-line CheckMate 026 phase III study randomised 541 pts with PD–L1 positive (≥1%) tumours (SQ and NSQ) to receive nivolumab 3 mg/kg Q2W (until disease progression or intolerable toxicity) or platinum-based ChT (up to 6 cycles).

The primary endpoint was not met: median PFS (mPFS) in pts with PD-L1 ≥5% was 4.2 and 5.9 months with nivolumab and ChT, respectively. ORR was 26% vs 33% and mOS was 14.4 vs 13.2 months (HR 1.02, 95% confidence interval [CI] 0.80-1.30) for the nivolumab and ChT arms, respectively.

Among all treated pts, grade 3-4 treatment-related AEs were 18% with nivolumab compared with 51% with doublet ChT.

The phase III KEYNOTE-189 study randomised (2:1) 616 treatment-naïve advanced NSQ NSCLC pts to receive platinum/pemetrexed ChT + pembrolizumab 200 mg Q3W or placebo followed by maintenance pemetrexed + pembrolizumab or placebo (up to 35 cycles).

ORR was higher in the pembrolizumab-combination arm (47.6% vs 18.9%, p < 0.001). mPFS and reported 12-month OS were significantly longer in the combination arm: 8.8 vs 4.9 months (HR 0.52, p < 0.001) and not reached vs 11.3 months, respectively. Response was observed across all PD-L1 strata, magnitude correlated to PD-L1, and best in PD-L1 ≥50% (ORR 61.4% vs 22.9%).

There was a similar incidence of grade 3-5 AEs between the two arms (67.2% vs 65.8%).

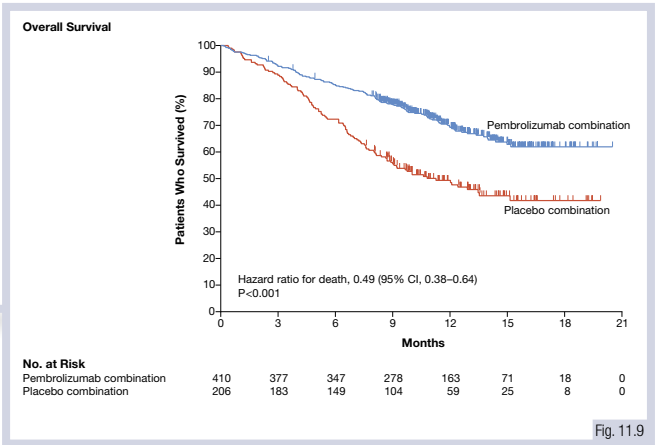


Fig. 11.9

CI, Confidence interval.

REVISION QUESTIONS

1. How does immunotherapy compare to standard platinum-doublet ChT in treatment-naïve advanced NSCLC?
2. What is the cut-off for PD-L1 positivity in KEYNOTE-024?
3. How do the endpoints of CheckMate 026 compare with KEYNOTE-024?

Immune checkpoint blockade for treatment-naïve advanced NSCLC (continued)

The phase III IMpower150 randomised 1202 advanced NSQ NSCLC pts (1:1:1) to atezolizumab/carboplatin/paclitaxel (ACP), bevacizumab/carboplatin/paclitaxel (BCP), or atezolizumab/BCP (ABCP) Q3W, followed by maintenance atezolizumab, bevacizumab, or both. The ABCP and BCP groups were compared (statistical hierarchical analysis).

mPFS and mOS with ABCP vs BCP were 8.3 vs 6.8 months (HR 0.62, p < 0.001) and 19.2 vs 14.7 months (HR 0.78, p = 0.02), respectively. PFS benefit was more marked in the effector T cell (Teff)-high subpopulation and correlated to PD-L1 expression.

Grade 3-5 toxicities were slightly higher in ABCP vs BCP, 58.5% vs 50.0%.

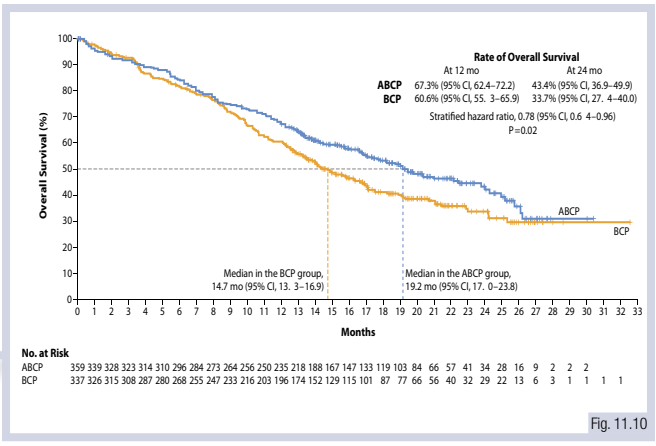


Fig. 11.10

CI, Confidence interval; BCP. bevacizumab/carboplatin/paclitaxel; ABCP, atezolizumab/BCP.

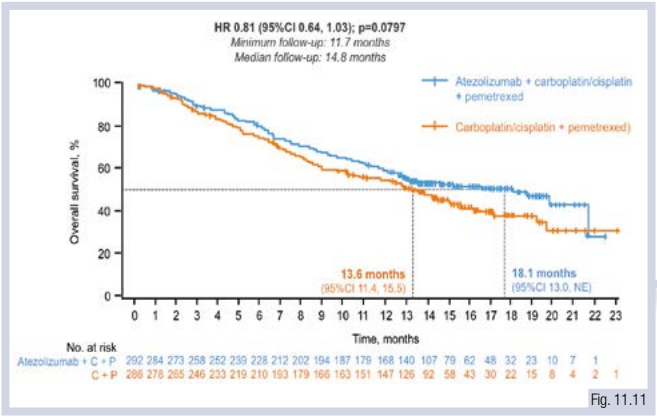


Fig. 11.11

C, Carboplatin (or cisplatin); CI, confidence interval; HR, hazard ratio; NE, not estimable; P, pemetrexed.

In the phase III IMpower132, 578 advanced NSQ NSCLC pts were randomised 1:1 to receive cisplatin (or carboplatin) + pemetrexed followed by maintenance pemetrexed with or without atezolizumab 1200 mg Q3W, until disease progression.

Addition of atezolizumab improved mPFS (7.6 vs 5.2 months, HR 0.60, p < 0.0001) but did not show statistically significant OS benefit (18.1 vs 13.6 months). The rate of grade 3-4 AEs was higher with the addition of atezolizumab, 53.6% vs 39.1% than with ChT alone.

Similarly in the phase III IMpower130, ACP was superior to ChT alone (OS 18.6 vs 13.9 months, HR 0.79, p = 0.033).

The phase III KEYNOTE-407 study randomised (1:1) 559 advanced SQ NSCLC pts to first-line carboplatin/paclitaxel (or nab-paclitaxel)/pembrolizumab 200 mg Q3W or placebo up to 35 cycles.

Irrespective of PD-L1 expression, but with a proportional magnitude of activity, the addition of pembrolizumab prolonged both mPFS and mOS: 6.4 vs 4.8 months (HR 0.56, p < 0.001) and 15.9 vs 11.3 months (HR 0.64, p < 0.001), respectively.

Adding pembrolizumab did not increase grade 3-5 toxicities (69.8% vs 68.2%) but led to a higher treatment discontinuation rate (13.3% vs 6.4%).

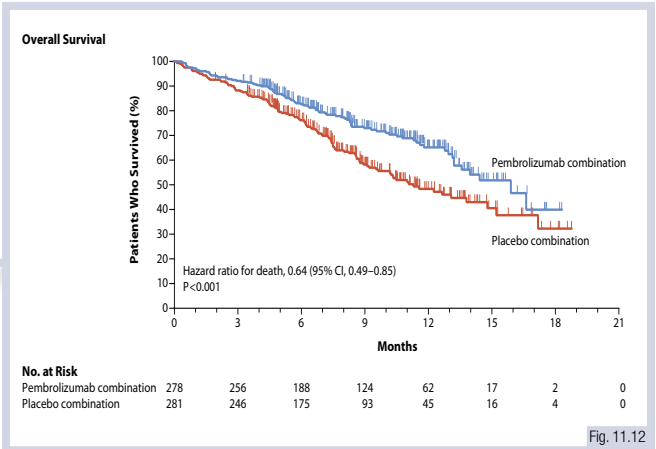


Fig. 11.12

CI, Confidence interval.

Immune checkpoint blockade for treatment-naïve advanced NSCLC (continued)

In the phase III IMpower131 study 1021 pts with advanced SQ NSCLC were randomised (1:1:1) to carboplatin/nab-paclitaxel plus atezolizumab 1200 mg Q3W or carboplatin/nab-paclitaxel or carboplatin/paclitaxel.

The addition of atezolizumab led to a modest improvement in mPFS, 6.3 vs 5.6 months (HR 0.71, p = 0.0001) with carboplatin/nab-paclitaxel with no gain in OS at interim analysis. Results from the carboplatin/paclitaxel arm are still awaited.

Grade 3-4 toxicity rates were higher with the addition of atezolizumab, 20% vs 10% with carboplatin/nab-paclitaxel.

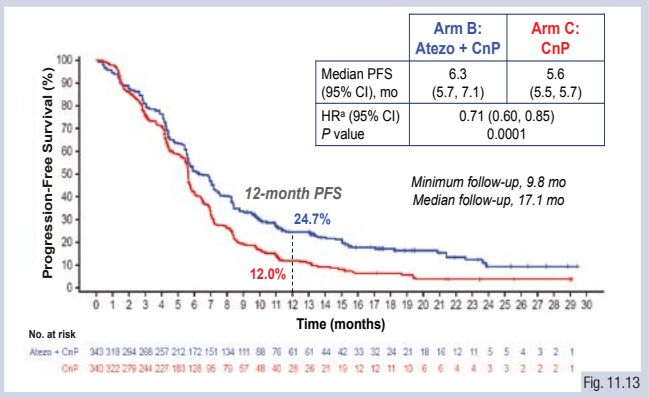


Fig. 11.13

Atezo, Atezolizumab; CnP, carboplatin/nab-paclitaxel; CI, confidence interval; HR, hazard ratio; PFS, progression free survival.

REVISION QUESTIONS

1. Is it safe to use immunotherapy and ChT concurrently in advanced NSCLC?
2. What is the current evidence for the use of anti-PD-L1 agents in treatment-naïve NSCLC?
3. Is there a role for maintenance immunotherapy after first-line treatment in advanced NSCLC?

Second-line therapy

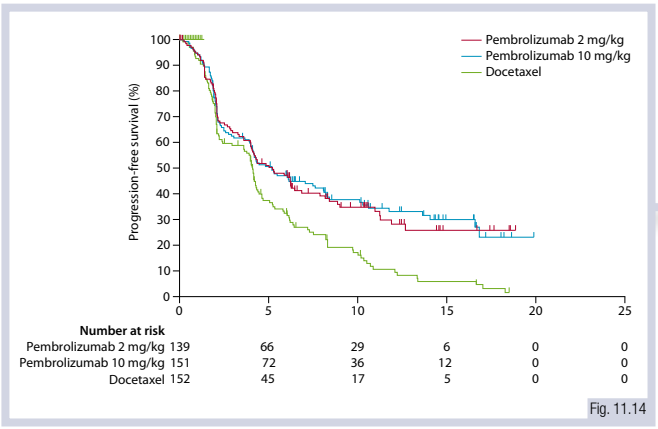


Fig. 11.14

The phase III study KEYNOTE-010 randomised 1034 PD-L1 positive (≥1%) pts to receive pembrolizumab 2 mg/kg or pembrolizumab 10 mg/kg, or docetaxel 75 mg/m^2.

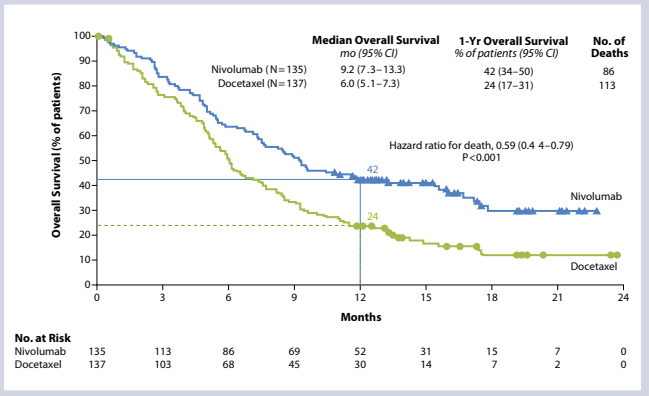
PFS was significantly longer in both pembrolizumab arms compared with docetaxel: 2 mg/kg subgroup – 5.0 vs 4.1 months, HR 0.59, p = 0.0001; and 10 mg/kg subgroup – 5.2 vs 4.1 months, HR 0.59, p < 0.0001.

OS was also longer in the pembrolizumab arms: 2 mg/kg – 14.9 vs 8.2 months, HR 0.54, p = 0.0002; and 10 mg/kg – 17.3 vs 8.2 months, HR 0.50, p < 0.0001. Subgroup analysis for pts with PD-L1 ≥50% showed even higher PFS and OS benefit. Pembrolizumab is approved for pre-treated pts with PD-L1 expression ≥1%.

In the phase III study CheckMate 017, 272 pts with advanced SQ NSCLC (unselected for PD-L1 expression) were randomised to receive nivolumab 3 mg/kg Q2W or docetaxel 75 mg/m^2 as second-line treatment. The primary endpoint was OS.

Pts in the nivolumab arm had longer OS (9.2 vs 6.0 months, HR 0.59, p < 0.001), longer PFS (3.5 vs 2.8 months, HR 0.62, p < 0.001) and higher ORR (20% vs 9%, p = 0.008).

Nivolumab was also better tolerated than docetaxel with significantly lower incidence of grade 3-4 AEs (7% vs 55%).



CI, Confidence interval.

Fig. 11.15

Second-line therapy (continued)

Similarly, CheckMate 057 randomised 290 pre-treated NSQ pts to nivolumab 3 mg/kg Q2W or docetaxel 75 mg/m^2.

Pts treated with nivolumab had longer OS (12.2 vs 9.5 months, HR 0.75, p = 0.002) and higher ORR (19% vs 12%, p = 0.02) but no difference in PFS.

A subgroup analysis showed no difference in OS for PD-L1 <1% and increased benefit on OS with higher PD-L1 expression. Nivolumab is approved as second-line treatment in both histologies, regardless of PD-L1 expression.

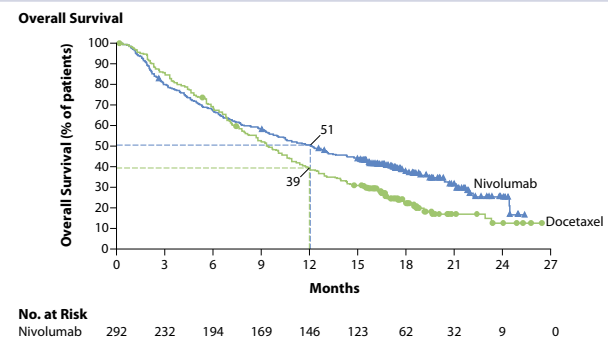


Fig. 11.16

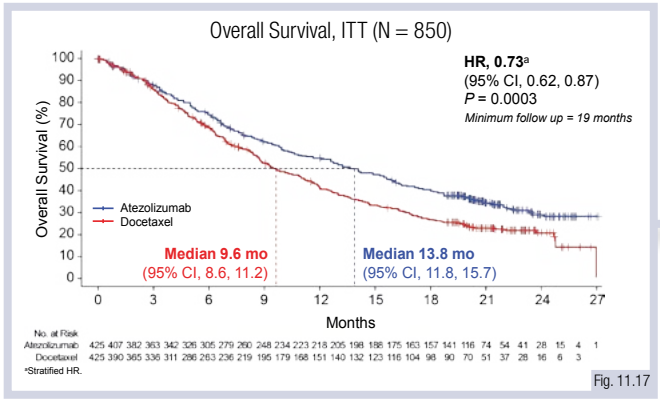


Fig. 11.17

CI, Confidence interval; HR, hazard ratio; ITT, intention to treat.

Following the positive phase II POPLAR study, in the phase III OAK study, 850 pts were randomised to either anti-PD-L1 atezolizumab 1200 mg Q3W or docetaxel 75 mg/m^2 as second- or third-line treatment.

In the intention-to-treat (ITT) cohort, pts receiving atezolizumab had longer OS (13.8 vs 9.6 months) and duration of response (16.3 vs 6.2 months).

The survival benefit was observed irrespective of PD-L1 expression and grade 3-4 AEs were less frequent with atezolizumab (15% vs 43%).

REVISION QUESTIONS

1. What is the role for immunotherapy in pre-treated advanced NSCLC?
2. How does the AE profile compare with that for standard second-line ChT with docetaxel?
3. Is there an OS advantage in using immunotherapy?

Immunotherapy for locally advanced NSCLC

The phase III PACIFIC study randomised 713 pts (2:1), with unresectable stage III NSCLC after concurrent chemoradiotherapy (CRT), to durvalumab 10 mg/kg Q2W or placebo up to 12 months.

At 24 months, mPFS was 17.2 vs 5.6 months (HR 0.51, p < 0.01) and OS 66.3% vs 55.6% (HR 0.68, p = 0.0025).

The incidence of grade 3-4 AEs and discontinuation rate were similar – durvalumab vs placebo arms: 30.5% vs 26.1% (pneumonitis 4.8% vs 2.6%) and 15.4% vs 9.8%, respectively.

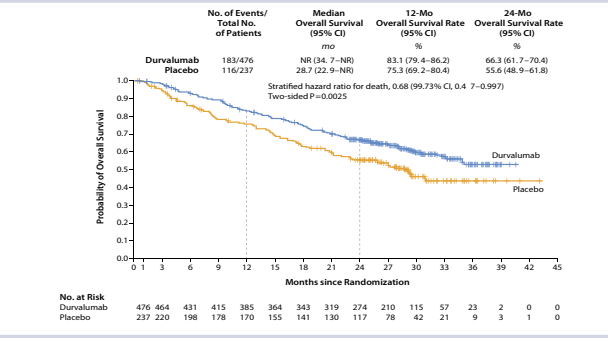


Fig. 11.18

CI, Confidence interval; NR, not reached.

REVISION QUESTIONS

1. Is there an OS advantage in using immunotherapy in locally advanced NSCLC?
2. How does the AE profile compare with current standard of care in locally advanced NSCLC?
3. Is there a significant rate of pneumonitis using immunotherapy following concurrent CRT?

PD-L1 expression as a biomarker

High levels of expression of PD-L1 in tumours suggests the mechanisms of immune avoidance are active and therefore a target for this therapeutic approach.

The vast majority of published studies have shown consistently higher ORR and longer OS in pts with higher expression of PD-L1 by immunohistochemistry (IHC).

PD-L1 expression is heterogeneous and the biopsy sample may not reflect the overall disease burden. Furthermore, PD-L1 protein expression is a continuous variable from zero to high levels.

	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Primary antibody clone used in the assay system	28-8 (Dako)	22C3 (Dako)	SP142 (Ventana)	SP263 (Ventana)
Interpretative scoring	Tumour cell membrane	Tumour cell membrane	Tumour cell membrane Infiltrating immune cells	Tumour cell membrane
Instrument and detection systems required	EnVision Flex on Autostainer Link 48	EnVision Flex on Autostainer Link 48	Optiview Detection and Amplification on Benchmark ULTRA	Optiview Detection on Benchmark ULTRA

Fig. 11.19

Assay comparison: overall percentage agreement in patient classification when staining assay is 'mismatched' with the clinical cut-off

Assay clone used for slide staining	Scoring algorithm			
	22C3 1% TPS	28-8 1% TPS	SP142 TC1/IC1	SP263 25% TPS
22C3	38/38 (100%)	36/38 (94.7%)	33/38 (86.8%)	34/38 (89.5%)
28-8	36/38 (94.7%)	38/38 (100%)	31/38 (81.6%)	33/38 (86.8%)
SP142	24/38 (63.2%)	24/38 (63.2%)	38/38 (100%)	25/38 (65.8%)
SP263	34/38 (89.5%)	34/38 (89.5%)	22/38 (86.8%)	38/38 (100%)

IC, Immune cell; TC, tumour cell; TPS, tumour proportion score.

Fig. 11.20

Different trials with different drugs have defined their own threshold for PD-L1 'positivity', which varies from over 1%, 25% or 50% of tumour cells.

There are currently at least five anti-PD-1/PD-L1 agents with their own specifically developed PD-L1 IHC assay validated in their respective clinical trials.

The Blueprint PD-L1 IHC Assay Comparison Project aimed to provide information on the analytical and clinical comparability of 4 PD-L1 IHC assays used in clinical trials. It revealed that 3 out of the 4 assays were closely aligned on tumour cell staining, while the 4th showed consistently fewer tumour cells stained.

REVISION QUESTIONS

1. Is PD-L1 a strict predictive biomarker in NSCLC?
2. Define what is considered positive PD-L1 expression.
3. What are the current issues with the use of PD-L1 as a biomarker?

CTLA-4 blockade and combination strategies for NSCLC

The phase III CA184-041 study investigated a phased combination of ipilimumab 10 mg/kg plus paclitaxel/carboplatin as first-line therapy compared with ChT alone in advanced SQ NSCLC.

The addition of ipilimumab did not significantly improve OS (13.4 vs 12.4 months, HR 0.91, p = 0.25).

The safety profile of ipilimumab in lung cancer was consistent with previous studies with this drug.

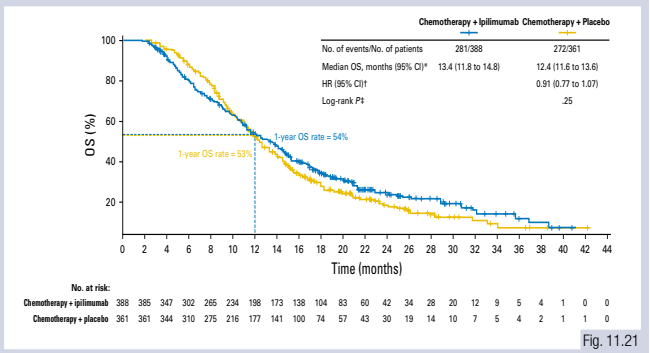


Fig. 11.21

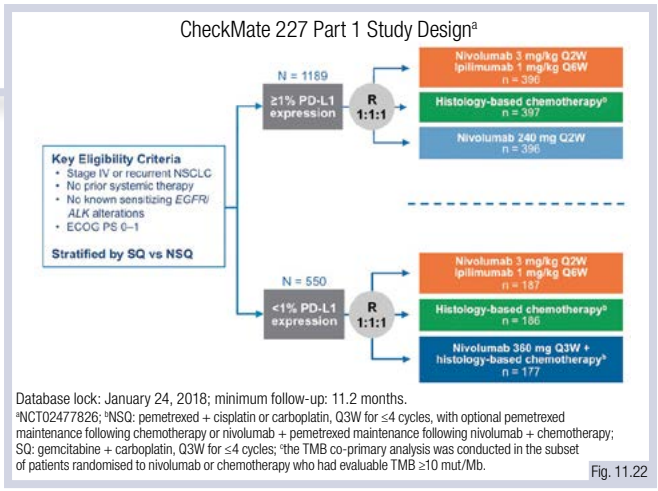
CI, Confidence interval; HR, hazard ratio; OS, overall survival.

CTLA-4 blockade and combination strategies for NSCLC (continued)

The multipart phase III CheckMate 227 study evaluated nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W vs histology-based ChT in treatment-naïve advanced NSCLC pts.

Pts were stratified according to PD-L1 ≥1% or <1%, and then randomised in a ratio of 1:1:1 to treatment arms as shown.

Primary endpoint was PFS in high tumour mutational burden (TMB) (≥10 mutations per megabase [mut/Mb]). In the ITT population (irrespective of PD-L1 expression), mPFS was 4.9 months with nivolumab/ipilimumab vs 5.5 months with ChT.



Database lock: January 24, 2018; minimum follow-up: 11.2 months.
[a]NCT02477826; [b]NSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤4 cycles, with optional pemetrexed maintenance following chemotherapy or nivolumab + pemetrexed maintenance following nivolumab + chemotherapy; SQ: gemcitabine + carboplatin, Q3W for ≤4 cycles; [c]the TMB co-primary analysis was conducted in the subset of patients randomised to nivolumab or chemotherapy who had evaluable TMB ≥10 mut/Mb.

Fig. 11.22

ALK, Anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; mut/MB, mutations per megabase; NSCLC, non-small cell lung cancer; NSQ, non-squamous; PD-L1, programmed death-ligand 1; SQ, squamous; TMB, tumour mutational burden; R, randomised.

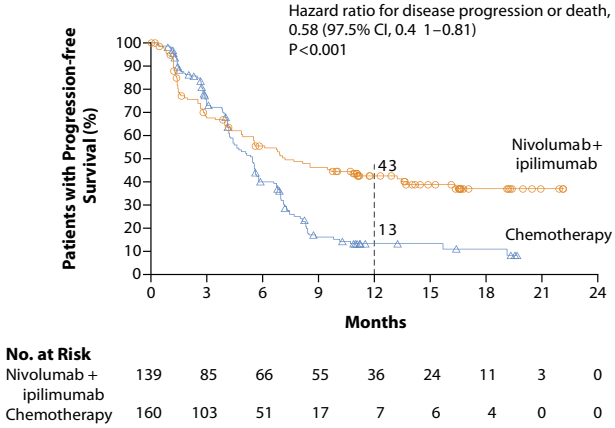


Fig. 11.23

CI, Confidence interval.

The combination of nivolumab and ipilimumab confers better PFS in pts with high TMB compared with ChT; mPFS 7.2 vs 5.5 months (HR 0.58, p < 0.001).

There was also a higher ORR in this cohort (45.3% vs 26.9%), with median duration of response not reached at last follow-up, compared with 5.4 months with ChT.

Both combination immunotherapy and ChT had similar rates of grade 3-4 AEs, 31.2% vs 36.1%, respectively.

Following the phase Ib study (NCT02000947) in pts with advanced NSCLC, durvalumab 20 mg/kg + tremelimumab 1 mg/kg dose was selected for further studies.

Although the phase III MYSTIC (first line) did not meet its primary PFS or OS endpoints, pts with high TMB (≥16 mut/Mb) had longer OS with the combination immunotherapy compared with ChT (16.5 vs 10.5 months, HR 0.62).

Similarly, the phase III ARCTIC study (at least two prior systemic treatments) did not meet its primary endpoints of PFS or OS benefit.

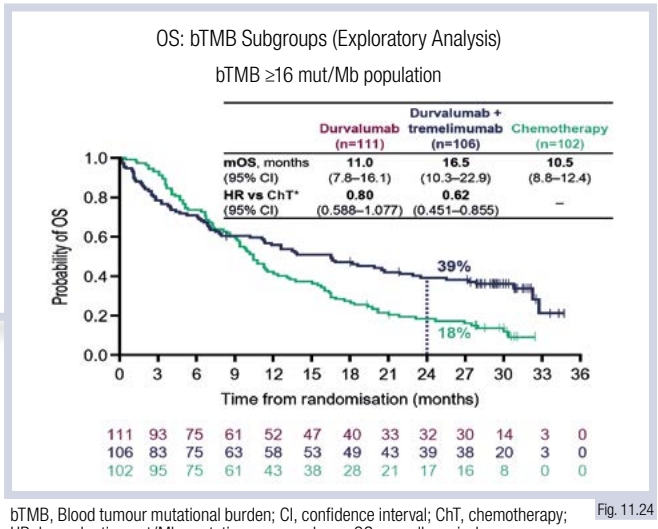


Fig. 11.24

bTMB, Blood tumour mutational burden; CI, confidence interval; ChT, chemotherapy; HR, hazard ratio; mut/Mb, mutation per megabase; OS, overall survival.

REVISION QUESTIONS

1. Is there a role for CTLA-4 blockade in advanced NSCLC?
2. Is the combination of immunotherapy with ChT safe in the treatment of NSCLC?
3. Is the combination of dual checkpoint inhibitors more effective in advanced NSCLC?

Summary: Immunotherapy for thoracic malignancies: Part A – Non-small cell lung cancer

- The high somatic mutational burden in NSCLC suggests its potential immunogenicity
- Immunotherapy targeting PD-1 and PD-L1 has been demonstrated to be efficacious in patients with advanced NSCLC, and superior to standard-of-care ChT in both ChT-naïve and pre-treated patients
- So far, patients with *EGFR*-mutated NSCLC have been shown to present with a lower activity of immunotherapy, albeit numbers are still small and randomised trials are awaited. Very few anaplastic lymphoma kinase (*ALK*)-rearranged NSCLC patients have been treated and reported so far
- High neoantigen burden and molecular smoking signatures are associated with increased objective response and prolonged PFS with immunotherapy
- Immunotherapy results in durable clinical benefit in a subset of patients, yet to be characterised
- Patient selection may maximise the benefits from immunotherapy and remains a key area for research
- Currently PD-L1 remains the main biomarker in selecting patients for immunotherapy, despite obvious limitations and a need for homogenisation and certification of testing. Better biomarkers will be needed
- Ongoing clinical trials are investigating the safety and efficacy of immunotherapy drugs when used in combination with each other (targeting CTLA-4 and PD-1 or PD-L1) or in addition to ChT +/- targeted therapy

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B

More advanced knowledge

12 Malignant pleural mesothelioma

Clinical presentation and pathology

Malignant pleural mesothelioma (MPM) incidence is increasing worldwide due to extensive exposure to asbestos. The latency to disease onset often exceeds 40 years. Therefore MPM is mostly diagnosed in the elderly (at least in Europe and the USA).

The typical onset of symptoms of MPM includes progressive dyspnoea (mainly due to pleural effusion), cough and thoracic pain.

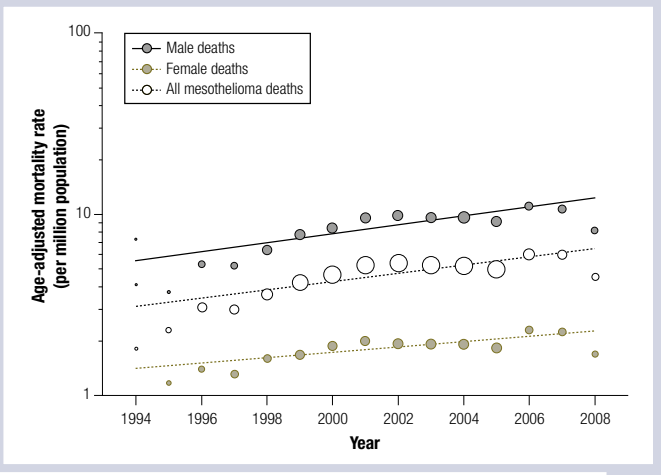


Fig. 12.1

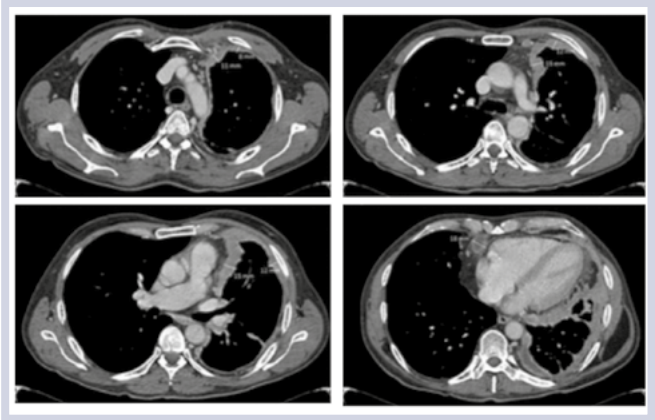


Fig. 12.2

MPM staging follows the revised 8th edition of the TNM (Tumour, Node, Metastasis) classification. Diagnostic and staging procedures include chest and abdominal computed tomography (CT) scan and video-assisted thoracoscopic surgery (VATS).

Response assessment uses the modified Response Evaluation Criteria in Solid Tumours (RECIST) method, which is based on unidimensional measurements of tumour thickness perpendicular to the chest wall or mediastinum on CT scan.

The diagnosis should be established by an experienced pathologist.

Three histological subtypes are reported: epithelioid, biphasic (or mixed) and sarcomatoid. MPM is defined as biphasic when each component occupies at least 10% of a sample.

Histology is a major prognostic factor in MPM, with epithelioid tumours carrying the best prognosis, while biphasic and sarcomatoid MPMs have the worst outcomes.

Approximately 60%–80% of MPMs are epithelioid, 10%–15% biphasic, and <10% sarcomatoid. The epithelioid pleomorphic subtype is associated with a poor prognosis, similar to that of sarcomatoid malignant mesothelioma.

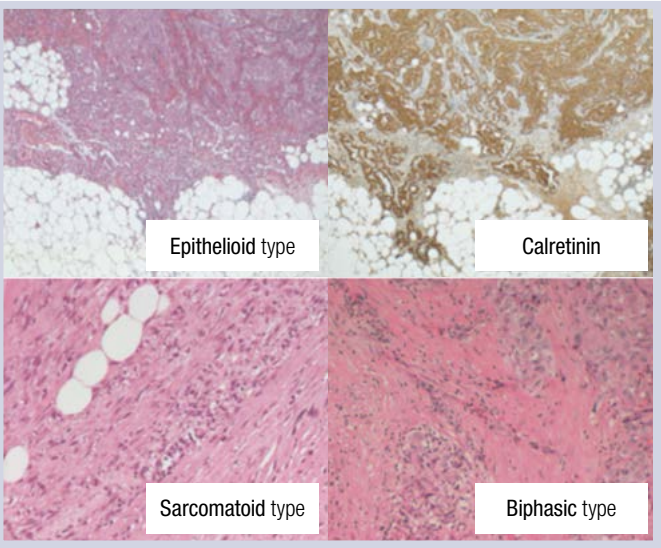


Fig. 12.3

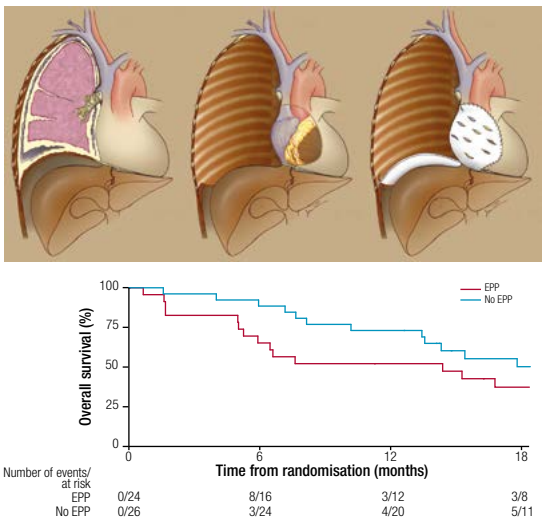
REVISION QUESTIONS

1. What are the most frequent symptoms of MPM?
2. What is the most frequent histological subtype of MPM?
3. What are the suggested staging procedures?

Surgery and multimodality treatment

Only a minority of MPM patients are amenable to surgical resection. The role of surgery is debated. The two proposed interventions are extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D).

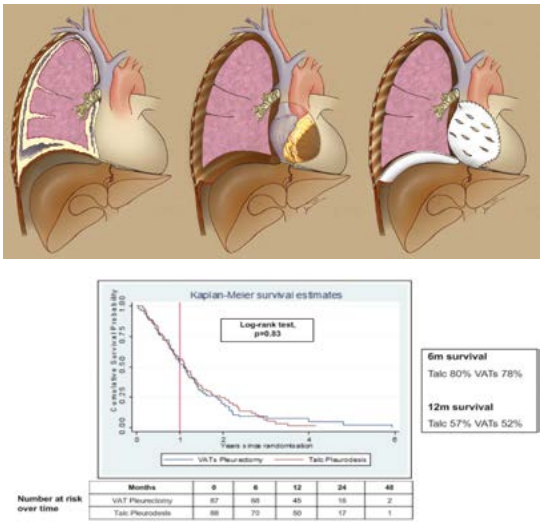
EPP is an aggressive procedure entailing *en bloc* resection of the parietal and visceral pleura with the enclosed lung, pericardium, ipsilateral diaphragm and mediastinal nodes. Postoperative morbidity is high (up to 50%), but mortality is <5%. In the only available randomised trial (the MARS trial), EPP within multimodality treatment offered no survival benefit compared with chemotherapy (ChT) alone.



EPP, Extrapleural pneumonectomy. Fig. 12.4

P/D allows the removal of the visceral, parietal and pericardial pleura; morbidity and mortality are lower, but cytoreduction is less effective than with EPP. However, no intervention has shown significant curative/long-term success.

In a randomised trial (the MesoVATS trial), P/D was compared to talc pleurodesis. Better effusion control but no survival benefit was achieved with P/D.



VATs, Video-assisted thoracoscopic surgery. Fig. 12.5

Intensity-modulated radiotherapy (IMRT) improves tumour coverage and normal tissue sparing; however, lung toxicity is a major concern, mainly after P/D.

When postoperative radiotherapy (PORT) is applied, strict constraints must be adhered to. In a randomised trial, use of hemithoracic IMRT after neoadjuvant ChT and EPP did not improve survival or loco-regional control.

Recent randomised trials (SMART and PIT) have shown that prophylactic radiotherapy (RT) should not be routinely used to prevent procedure-tract metastases in mesothelioma.

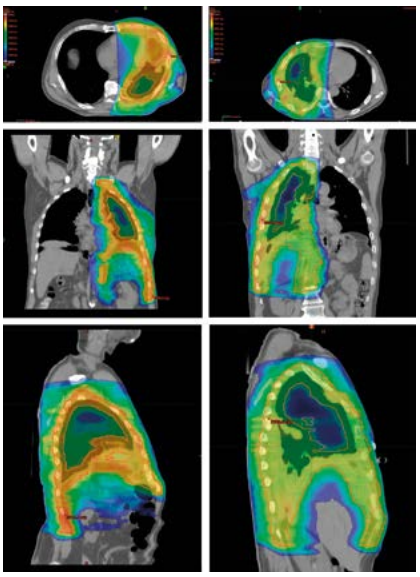


Fig. 12.6

REVISION QUESTIONS

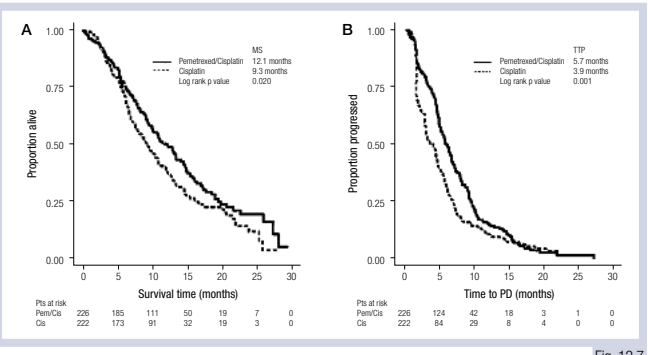
1. What is the role of surgery in MPM?
2. What are the proposed surgical interventions?
3. Is RT with IMRT a standard procedure?

Systemic treatment: state of the art and future outlook

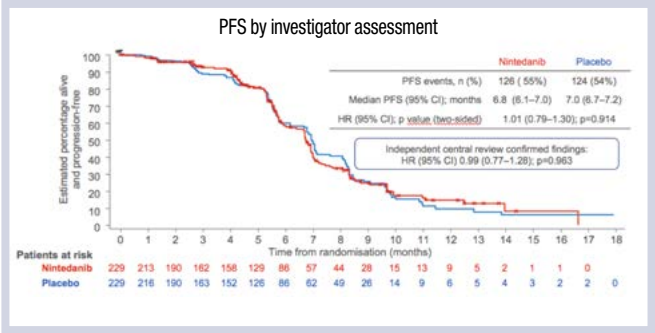
The combination of cisplatin and pemetrexed is the standard first-line treatment, with a median time to progression (TTP) of 5.7 months and a median overall survival (OS) of 12.1 months.

Schedules with carboplatin have shown similar outcomes with a more favourable toxicity profile; 4–6 cycles are usually administered.

Nearly all MPM patients progress during or after first-line treatment. The role of second-line treatment in MPM is not established. Several phase II and III trials have exploited different chemotherapeutic (e.g. gemcitabine, vinorelbine) and targeted agents, but activity has been shown to be generally modest.



MS, Median survival; PD, progressive disease; TTP, time to progression. Fig. 12.7

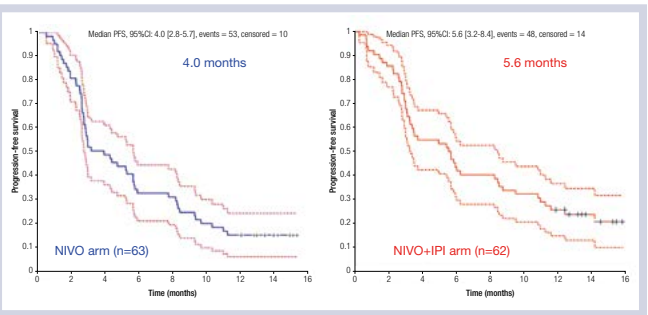


CI, Confidence interval; HR, hazard ratio; PFS, progression-free survival. Fig. 12.8

Angiogenesis: In the randomised phase II-III MAPS study of 448 patients, the addition of bevacizumab to pemetrexed/cisplatin was associated with an improvement in PFS and OS. In the LUME-Meso study, no benefit in response rate, PFS and OS was observed with the addition of nintedanib to cisplatin/pemetrexed in the first-line setting.

Mesothelin is highly expressed in mesothelioma, mainly in the epithelioid subtype. Several strategies targeting this pathway have been exploited, unfortunately with discouraging results. A randomised phase II trial comparing anetumab ravtansine (an antibody–drug conjugate) to vinorelbine failed to improve PFS.

Immune checkpoint inhibitors (ICIs): Response rates (RRs) of 9%-29% and disease control rates (DCRs) of 38%-72% were reported in phase II trials with pembrolizumab, nivolumab and avelumab in pretreated patients. Combinations with nivolumab/ipilimumab (the MAPS2 study) showed RR of 28% and 12-week DCR of 52% in the same setting. Ongoing trials are exploring ChT plus programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors as first-line treatment in unresectable MPM. The low mutational burden and the highly immune-suppressive microenvironment of MPM limit the activity of ICIs targeting PD-1/PD-L1 in mesothelioma. A deeper knowledge of tumour biology, including evaluation of other immune checkpoints, could help to fully exploit the immune axis as a valid target.



CI, Confidence interval; IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival. Fig. 12.9

REVISION QUESTIONS

1. What is the standard first-line treatment in MPM?
2. What are the options for second-line treatment?
3. What is the role of ICIs in the treatment of MPM?

Summary: Malignant pleural mesothelioma

- The incidence of MPM is increasing worldwide due to asbestos exposure
- There are three main histological subtypes of MPM (epithelioid, sarcomatoid and biphasic), with different outcomes
- The role of surgery and IMRT in this disease is still undefined
- The combination of pemetrexed with cisplatin is the standard first-line treatment in patients with unresectable MPM; carboplatin plus pemetrexed is a valid option, especially in elderly patients
- In patients progressing after a pemetrexed-based regimen, there is no standard second-line therapy, and this remains an ideal field in which to test new agents
- Inhibition of angiogenesis, targeting of mesothelin and immunotherapy with ICIs are the main pathways explored in clinical trials
- The association of anti-angiogenic agents (bevacizumab, nintedanib) to standard ChT in the first-line setting has provided inconclusive data and is not going to modify the standard of care
- Mesothelin-targeting agents have failed to improve survival, so far
- ICIs as single agents or in combination show limited benefit, likely due to the low mutational burden and the highly immune-suppressive microenvironment of MPM
- A deeper knowledge of the complex biology of MPM is needed to exploit new agents and combinations able to improve its poor outcome

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13 Thymic malignancies

Pathology, staging and prognostic factors

Thymic malignancies are rare epithelial tumours arising in the anterior mediastinum. The current histopathological classification distinguishes thymomas from thymic carcinomas. Neuroendocrine tumours – carcinoids, large and small cell – may also occur.

Thymomas are further subdivided into different types (so-called A, AB, B1, B2, and B3) based upon the atypia of tumour cells, the relative proportion of the associated non-tumoural lymphocytic component, and resemblance to the normal thymic architecture. Thymic carcinomas are similar to their extrathymic counterpart, the most frequent subtype being squamous cell carcinoma.

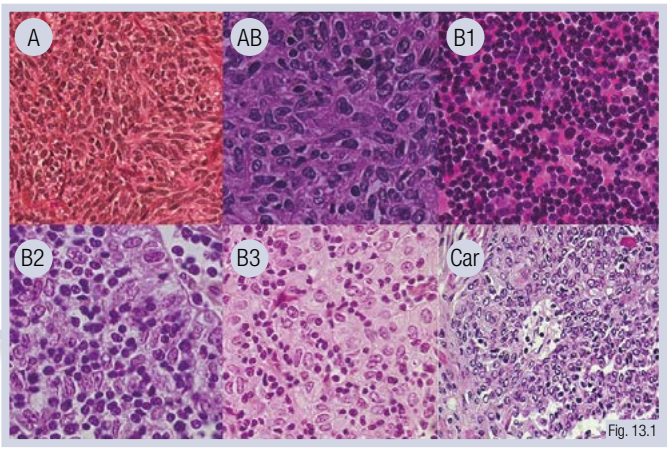

Fig. 13.1

The histopathological diagnosis is mostly based on morphology; recommended antibodies for immunohistochemistry include: pancytokeratin (AE1/3); CD5 (T cells, epithelial cells of carcinomas); CD117 (epithelial cells of carcinomas); TdT (immature T cells), and desmin (myoid cells in the medulla).

TNM Staging

T – Primary Tumour
- T1 Tumour encapsulated or extending into the mediastinal fat, may involve the mediastinal pleura.
- T1a No mediastinal pleural involvement
- T1b Direct invasion of the mediastinal pleura
- T2 Tumour with direct involvement of the pericardium (partial or full thickness)
- T3 Tumour with direct invasion into any of the following; lung, brachiocephalic vein, superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or vein
- T4 Tumour with direct invasion into any of the following; aorta (ascending, arch or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, or oesophagus

N – Regional Lymph Nodes
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in anterior (perithymic) lymph nodes
- N2 Metastasis in deep intrathoracic or cervical lymph nodes

M – Distant Metastasis
- M0 No pleural, pericardial or distant metastasis
- M1 Distant metastasis
- M1a Separate pleural or pericardial nodule(s)
- M1b Distant metastasis beyond the pleura or pericardium

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T Any T	N1 N0, N1	M0 M1a
Stage IVB	Any T Any T	N2 Any N	M0, M1a M1b

TNM, Tumour, Node, Metastasis.

Fig. 13.2

The Tumour, Node, Metastasis (TNM) 8th edition staging system is replacing the historical Masaoka–Koga staging.

In this system, Masaoka–Koga stage I (encapsulated tumours), stage II (IIa with a microscopic invasion of the capsule; IIb with an invasion of the capsule or surrounding fatty tissue, or adherent to the mediastinal pleura or the mediastinum), and some stage III are grouped together into the TNM stage I cluster.

Stage III is further subdivided into TNM stage IIIA and IIIB based on the resectability of the invaded structures.

Besides complete resection, tumour stage at baseline represents the most significant prognostic factor for survival.

The World Health Organization (WHO) classification is correlated with stage at diagnosis, as 80%–90% of type A to B1 thymomas present as stage I–II tumours, whereas 50%–60% of type B2 and 60%–80% of type B3 thymomas and carcinomas present with stage III–IV extent. Thus histology was also reported as a prognostic factor in thymic epithelial tumours.

REVISION QUESTIONS

1. Are thymomas epithelial or lymphoid malignancies?
2. What is the standard staging system for thymic tumours?
3. What is the most significant prognostic factor in thymic tumours?

Clinical features, diagnosis and surgery

One third of patients are asymptomatic. Another third of patients present with local symptoms such as cough, dyspnoea or chest pain. The remaining third present with autoimmune disorders, most commonly myasthenia gravis.

Myasthenia gravis is found in 30% of patients with thymoma, and is caused by circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction.

Systematic immunological check-up is recommended when a diagnosis of thymoma is suspected, including complete blood cell count with reticulocytes, serum protein electrophoresis, as well as anti-acetylcholine receptor and antinuclear antibody tests.

Most frequent differential diagnoses of anterior mediastinal masses include thymic hyperplasia, lymphoma and benign or malignant germ cell neoplasms; surgical biopsy is frequently required.

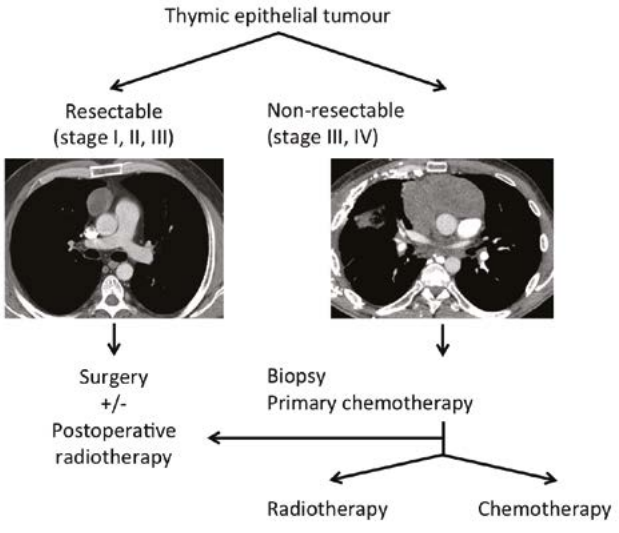

Fig. 13.3

The treatment strategy for thymic epithelial tumours is primarily based on whether the tumour may be resected upfront or not. If complete resection is deemed to be achievable, upfront surgery represents the first step in the treatment; if not, primary chemotherapy (ChT) is administered, part of a curative-intent sequential strategy integrating subsequent surgery or radiotherapy (RT).

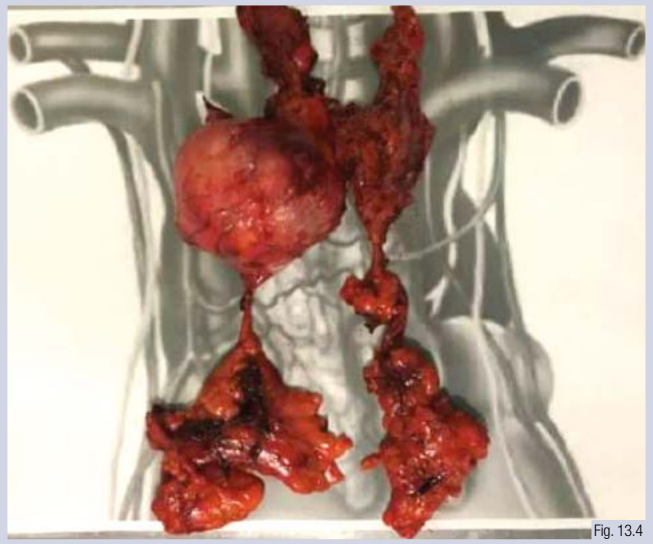
Fig. 13.4

Surgical principles are as follows:

- Median sternotomy as the standard approach
  - minimally invasive surgery is possible
- Complete exploration of the pleural cavities
- Complete thymectomy, including the tumour, normal thymus and mediastinal fat
- *En bloc* resection of involved structures: lung, vessels, pleural implants, phrenic nerves
- Marking of areas of uncertain margins with clips
- Nodal resection and sampling for invasive tumours
- Frozen section not recommended for margin assessment

Surgical pathology diagnosis requires communication between surgeons and pathologists. Orientation of the specimen and designation of involved structures, organs, or areas of concern may be done using a mediastinal board.

REVISION QUESTIONS

1. What is the most frequent autoimmune disorder observed in patients with thymoma?
2. What is the first step in the treatment strategy for thymic tumours?
3. What are the surgical principles for thymic tumour resection?

Radiotherapy and chemotherapy; prognostic factors

Postoperative RT aims at decreasing the risk of mediastinal recurrence. Proposed indications, based on expert opinion, are summarised in the table.

The principles of RT include: the use of conformal techniques; a clinical target volume including the whole thymic space, the tumour and its extensions, and the anterior, superior, and middle mediastinum; a total dose ranging from 40 to 60 Gy.

Definitive RT may be delivered for advanced non-resectable thymic tumours, after induction ChT. Concurrent chemoradiotherapy (CRT) may be an option in thymic carcinomas.

Masaoka–Koga stage	Postoperative radiotherapy (RT) / chemotherapy (ChT)
Stage I	Complete resection: - Thymoma: no postoperative RT - Thymic carcinoma: consider postoperative RT Incomplete resection: Postoperative RT
Stage IIa	Complete resection: - Type A-B2 thymoma: no postoperative RT - Type B3 thymoma–thymic carcinoma: consider postoperative RT Incomplete resection: Postoperative RT Thymic carcinoma: Consider postoperative ChT
Stage IIb	Complete resection: - Type A-B1 thymoma: no postoperative RT - Type B2-B3 thymoma–thymic carcinoma: consider postoperative RT Incomplete resection: Postoperative RT Thymic carcinoma: Consider postoperative ChT
Stage III-IVa	Postoperative RT, with boost on areas of concern Thymic carcinoma: Consider postoperative ChT

Fig. 13.5

Regimen	Agents	Doses
ADOC	Doxorubicin Cisplatin Vincristine Cyclophosphamide	40 mg/m^2 / 3 w 50 mg/m^2 / 3 w 0.6 mg/m^2 / 3 w 700 mg/m^2 / 3 w
CAP	Cisplatin Doxorubicin Cyclophosphamide	50 mg/m^2 / 3 w 50 mg/m^2 / 3 w 500 mg/m^2 / 3 w
PE	Cisplatin Etoposide	60 mg/m^2 / 3 w 120 mg/m^2/ × 3 / 3 w
VIP	Etoposide Ifosfamide Cisplatin	75 mg/m^2 × 4d / 3 w 1.2 g/m^2 × 4d / 3 w 20 mg/m^2 × 4d / 3 w
Carbo-Px	Carboplatin Paclitaxel	AUC 5 / 3 w 225 mg/m^2 / 3 w

AUC, Area under the curve.

Fig. 13.6

Primary ChT refers to ChT delivered as the first part of the multimodal curative-intent treatment of locally advanced non-resectable thymic tumours, and is subsequently combined with surgery or RT. Major regimens are presented in the table. There is currently no rationale to support the use of postoperative ChT in thymomas; this may be discussed in thymic carcinoma.

ChT may be administered as the sole treatment modality for metastatic, unresectable, recurrent disease not eligible for RT. Regimens are similar to those for primary ChT (table). Paclitaxel may be preferred for first-line for carcinomas. Single agents represent options for subsequent lines.

The treatment of recurrences relies, besides surgery and RT if feasible, on systemic treatment. ChT but also anti-angiogenic multikinase inhibitors such as sunitinib and targeted agents including octreotide and everolimus.

Immunotherapy is currently assessed in ongoing clinical trials in thymic carcinomas. Frequent and severe immune-related adverse events may occur, including myocarditis, myositis and Lyell's syndrome.

When interpreting prognostic data, one must take into consideration that only 50% of patients overall actually die from tumour progression; causes of death include autoimmune diseases and non-related disorders (each accounting for 25%).

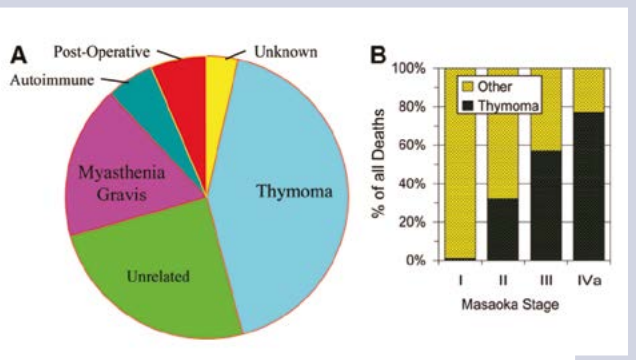

Fig. 13.7

REVISION QUESTIONS

1. Is postoperative RT delivered after complete resection of stage I thymoma?
2. What are the two major ChT drugs delivered in thymic tumours?
3. Which targeted therapies may be used in advanced disease?

Summary: Thymic malignancies

- Thymic tumours are rare epithelial malignancies; the pathological classification distinguishes thymomas and thymic carcinomas
- Thymomas may be associated with autoimmune disorders, such as myasthenia gravis
- Tumour stage is assessed using the TNM 8th edition
- Surgery is the mainstay of the treatment of thymic tumours. Upfront resection is the standard strategy for resectable tumours
- Postoperative RT may be delivered, depending on the completeness of surgical resection, tumour stage and histology
- For unresectable locally advanced tumours, primary ChT is the standard, aiming at allowing subsequent R0 surgical resection or, alternatively, sequential definitive RT
- The main ChT regimens include doxorubicin- and cisplatin-based protocols
- Major prognostic factors include tumour stage, completeness of surgical resection and histology

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14 Neuroendocrine tumours of lung origin

Clinical presentation and pathology

Lung neuroendocrine tumours (NETs) account for fewer than 1% of all pulmonary neoplasms; the incidence of these neoplasms has risen dramatically over the past 30 years.

The tumours may be associated with multiple endocrine neoplasia type 1 (MEN-1) in 4%–8% of cases.

Typical symptoms of lung NETs include obstructive pneumonia, atelectasis and wheezing as a result of central airway obstruction due to tumour mass.

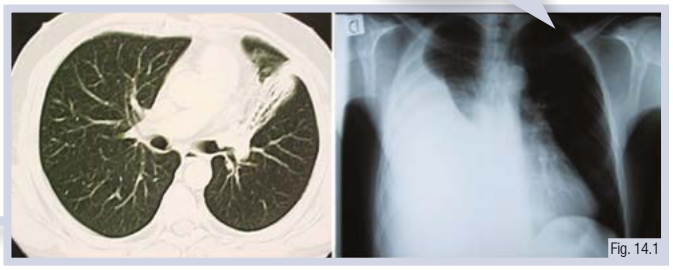


Fig. 14.1

Although NETs of the lung arise from cells capable of producing serotonin and adrenocorticotrophin hormones, hypersecretion of bioactive amines is rare.

They include a wide range of tumours, from well-differentiated to poorly differentiated small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC).

The 2015 World Health Organization (WHO) classification combines architectural growth patterns, mitotic index and the presence of necrosis. It separates this group of tumours into 4 major categories, including typical carcinoid (TC), atypical carcinoid (AC), small cell carcinoma (or SCLC) and LCNEC.

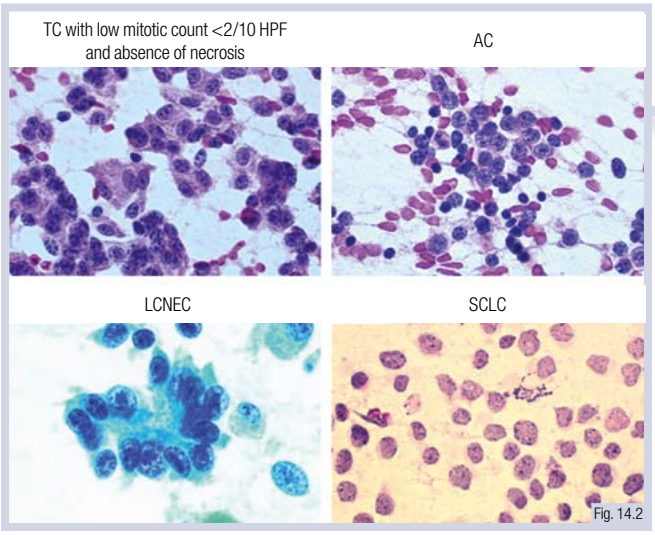


Fig. 14.2

AC, Atypical carcinoid; HPF, high-power field; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung cancer; TC, typical carcinoid.

Histological type	Necrosis	Mitotic count
TC	Absent	<2/10 HPF
AC	Present focal	2–10/10 HPF
LCNEC	Present (extensive)	>10 HPF, usually >30 HPF
SCLC	Present (extensive)	>10 HPF, usually >60 HPF

AC, Atypical carcinoid; HPF, high-power field; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung cancer; TC, typical carcinoid.

Histological subtype is the most important prognostic factor, the survival of TC being higher than AC, while LCNEC and SCLC have the worst outcome.

Nodal status is another important prognostic factor. Up to 60% of patients with AC have lymph node metastases and a 5-year survival of 61% to 88%.

Lymph node metastases are present in more than 15% of cases of TC lung NETs, and 5-year survival exceeds 90%.

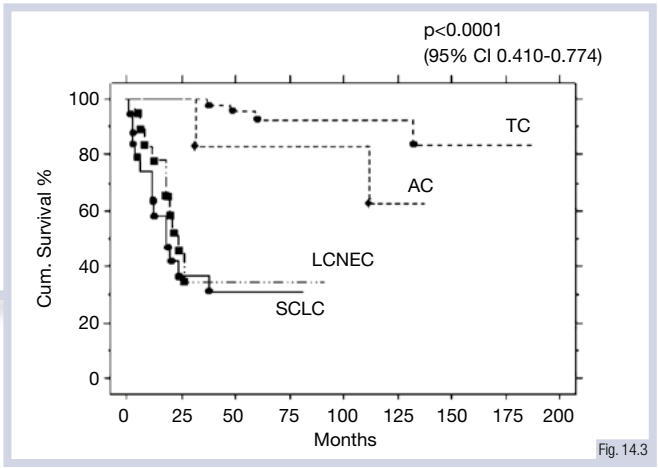


Fig. 14.3

AC, Atypical carcinoid; CI, confidence interval; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung cancer; TC, typical carcinoid.

REVISION QUESTIONS

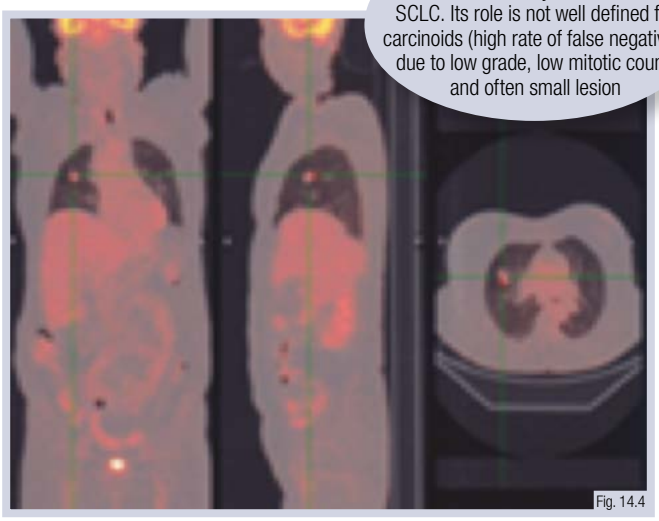
1. How frequent are NETs among lung malignancies?
2. What are the four types of lung NETs?
3. What are the most important prognostic factors for lung NETs?

Staging and local treatment

Biochemical evaluations: chromogranin A and plasma neuron-specific enolase (NSE) for well-differentiated lung NETs; 5-hydroxyindoleacetic acid (HIAA) in patients with carcinoid syndrome; adrenocorticotropic hormone (ACTH) and urinary-free cortisol in patients with Cushing syndrome.

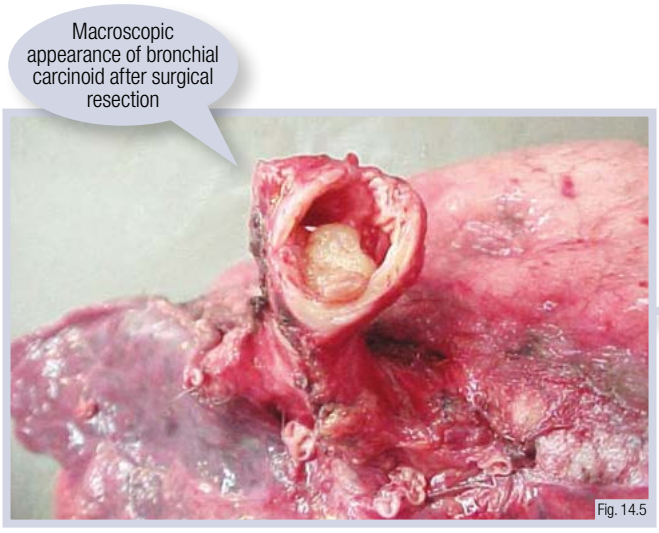
Computed tomography (CT) of the chest may indicate a diagnosis of lung NETs. Bronchoscopy is the best procedure to detect central bronchial NETs.

^{68}Gallium positron emission tomography (PET) and somatostatin receptor scintigraphy when somatostatin receptors are expressed can be informative.



FDG-PET, Fluorodeoxyglucose positron emission tomography; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell carcinoma.

For more aggressive bronchial NETs such as LCNEC and SCLC, a fluorodeoxyglucose (FDG)-PET scan would be more informative.



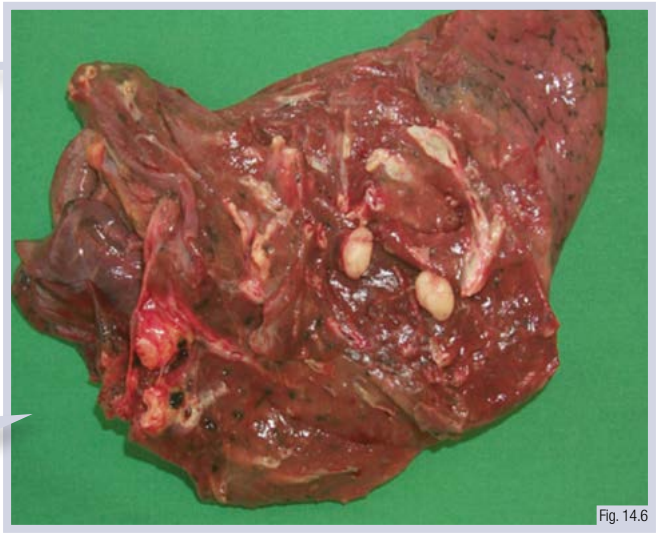
The surgical approach depends upon the size, location and tissue type. The cornerstone of therapy for TC and AC is resection, considered even in resectable advanced disease. The surgical approach for SCLC is restricted to very limited disease and to stage I-IIIA for LCNEC.

The surgical techniques of choice are lobectomy or sleeve resection. Pneumonectomy should be avoided except in selected cases.

Systemic nodal dissection should be performed since lymphonodal metastases may be present in up to 15% of cases in TC and >60% in AC.

Bronchoscopic laser excision of intraluminal typical bronchial NETs should be considered as a suboptimal treatment and reserved for inoperable patients.

The 5-year survival rate is 87%–90% in TC, 44%–78% in AC, 15%–57% in LCNEC, and 15%–57% in SCLC.



REVISION QUESTIONS

1. What is the best diagnostic procedure to detect central bronchial NETs?
2. What is the main therapy for bronchial NETs?
3. Which NET subtype has the best 5-year survival rate?

Systemic treatment

Cytotoxic treatment combined with surgical resection, when indicated, has been the standard for metastatic lung NETs.

Available chemotherapy regimens for TC and AC include a combination of streptozotocin plus 5-fluorouracil/doxorubicin.

Temozolomide alone, or in combination with capecitabine and sometimes bevacizumab, has demonstrated clinical benefit.

No randomised trial evidence is available for chemotherapy, and its role for bronchopulmonary carcinoids continues to be debated

Study/year	n: primaries	ORR	m duration
Moerdel/1991 CDDP+VP16	27: GI lung well-differentiated NET	7%	4–6 months
Mitry/1999 CDDP+VP16	12: well-differentiated lung/mid gut	Only 1, pt 1/12 (9%)	8 months
Fjallskog/2001 CDDP+VP16	32: lung/thymus, pancreas/ileum	34%	9 months
Bajetta/2007 XELOX	27: well-differentiated GEP, 5 pts lung	3 pts PR (60%) 1 pt SD (20%) 1 pt PD (20%)	20 months
Ekeblad/2007 TEMOZOLOMIDE	36: well-differentiated NETs, 13 bronchial NETs (10 TCs and 3 ACs), 7 thymic	Lung NETs PR (31%) SD (31%)	7 months
Spada/2016 CAPOX, FOLFOX-6, GEMOX	70: GEP, 15 bronchial	13%	8 months
Walter/2016 FOLFOX, GEMOX	32 bronchial NETS (8 TCs and 24 ACs)	PR (20%) SD (64%)	15 months

Fig. 14.7

AC, Atypical carcinoid; CDDP, cisplatin; CAPOX (or XELOX), capecitabine/oxaliplatin; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin; GEMOX, gemcitabine/oxaliplatin; GEP, gastroenteropancreatic; GI, gastrointestinal; NET, neuroendocrine tumour; ORR, overall response rate; PD, progressive disease; PR, partial response; pt, patient; SD, stable disease; TC, typical carcinoid.

In the RADIANT-4 trial, 31% of patients in the experimental group and 28% in the control group were diagnosed with lung NETs

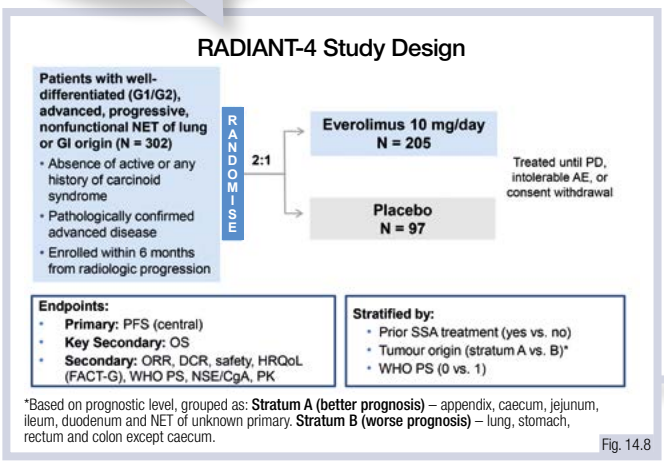


Fig. 14.8

AE, Adverse event; CgA, chromogranin; DCR, disease control rate; FACT-G, functional assessment of cancer - general; GI, gastrointestinal; HRQoL, health-related quality of life; NET, neuroendocrine tumour; NSE, neuron-specific enolase; ORR; overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; SSA, somatostatin analogue; WHO PS, World Health Organization performance status.

RADIANT-4 evaluated the impact of the oral mammalian target of rapamycin (mTOR)-inhibitor everolimus vs placebo.

Treatment with everolimus in lung NETs was associated with longer progression-free survival (PFS) – 9.2 months compared with 3.6 months in the placebo group.

Everolimus improved PFS by 6 months and reduced tumour progression risk by 50% in patients with advanced, progressive, non-functional lung NETs compared with placebo (hazard ratio [HR]= 0.50; 95% confidence interval [CI], 0.28-0.88).

For low proliferating tumours, treatment with somatostatin analogues might be an option in functional tumours with clinical symptoms.

The PROMID trial showed antitumour efficacy of octreotide long-acting release (LAR) in small intestinal NETs and it is now widely accepted for non-functioning tumours.

Lung NETs are typically under-represented in clinical trials of NET treatments. RADIANT-4 has reported results specific to lung NETs.

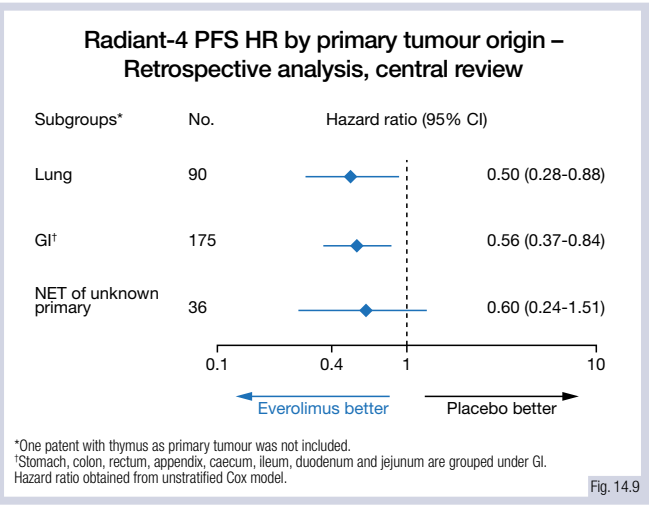


Fig. 14.9

CI, Confidence interval; GI, gastrointestinal; HR, hazard ratio; NET, neuroendocrine tumour; PFS, progression-free survival.

REVISION QUESTIONS

1. Which drug has demonstrated clinical benefit?
2. Which drug would you prescribe for functional tumours?
3. Which result has been shown by the RADIANT-4 trial?

Summary: Neuroendocrine tumours of lung origin

- NETs of the lung are rare (1% of all lung malignancies)
- Diagnosis is challenging and requires a specialised pathologist
- Proper distinction should be made between well- or moderately differentiated forms
- TCs and ACs or poorly differentiated forms (LCNEC and SCLC) have very different prognoses
- Nodal involvement is an important prognostic factor
- Imaging techniques: radiolabelled peptide scintigraphy is useful in well-differentiated forms
- In addition to CT scan, somatostatin receptor scintigraphy or ^{68}Ga-PET/CT is preferred for well-differentiated forms
- For LCNEC and SCLC, a PET scan is more informative
- The main therapy is surgical resection and systemic nodal dissection
- The role of chemotherapy for bronchopulmonary carcinoids continues to be debated. Temozolomide, alone or in combination with capecitabine and sometimes bevacizumab, has demonstrated clinical benefit
- In the RADIANT-4 trial, everolimus improved PFS by 6 months and reduced tumour progression risk by 50% in patients with advanced, progressive, non-functional lung NETs compared with placebo (HR= 0.50; 95% CI, 0.28-0.88)

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15 Immunotherapy for thoracic malignancies: Part B – Small cell lung cancer and mesothelioma

Immune checkpoint blockade in small cell lung cancer

In the phase III study CA184-156, 1132 patients were randomised to receive chemotherapy (ChT) with platinum/etoposide plus ipilimumab 10 mg/kg or placebo.

Patients without disease progression received maintenance ipilimumab at 10 mg/kg or placebo every 12 weeks, until disease progression or unacceptable toxicity for a maximum of 3 years.

The investigational arm did not prolong overall survival (OS) (11.0 vs 10.9 months, p = 0.3775) or progression-free survival (PFS) (4.6 vs 4.4 months, p = 0.0161).

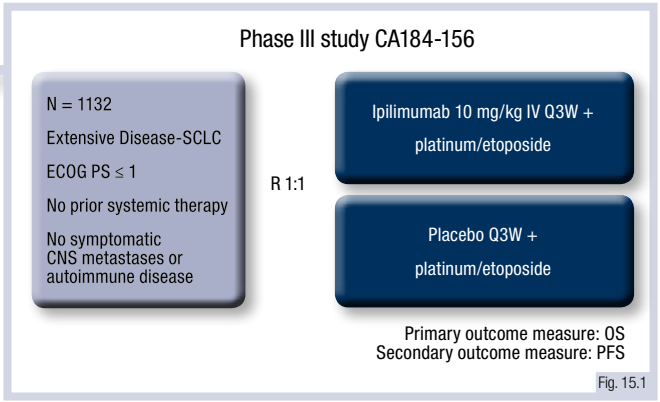


Fig. 15.1

CNS, Central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenously; OS, overall survival; PFS, progression-free survival; R, randomised; SCLC, small cell lung cancer.

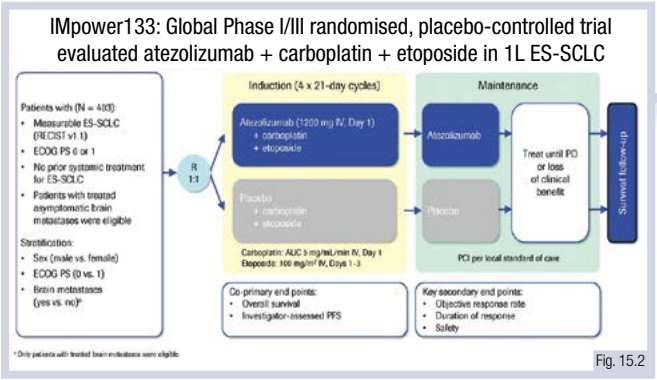


Fig. 15.2

AUC, Area under the curve; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ES-SCLC, extensive-stage small cell lung cancer; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours.

IMpower133 is a double-blind, placebo-controlled, phase III trial to evaluate atezolizumab plus carboplatin/etoposide in patients (pts) with extensive-stage (ES) small cell lung cancer (SCLC) who had not previously received treatment.

The addition of atezolizumab to ChT resulted in significantly longer OS and PFS than ChT alone.

At a median follow-up of 13.9 months:
The median OS was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (hazard ratio [HR] for death, 0.70; 95% confidence interval [CI], 0.54–0.91; p = 0.007).
The median PFS was 5.2 months and 4.3 months, respectively (HR for disease progression or death, 0.77; 95% CI, 0.62–0.96; p = 0.02).

The phase I/II study CheckMate 032 evaluated the safety and efficacy of nivolumab either alone or in combination with ipilimumab in pts with pretreated SCLC unselected for programmed death-ligand 1 (PD-L1) expression. Durable responses and clinical activity were found in both the nivolumab monotherapy and the combination therapy arms.

The safety profiles for both treatment strategies were manageable and consistent with these agents in other tumour histologies.

The combination of nivolumab and ipilimumab induced an overall response rate (ORR) of 46% in patients with recurrent SCLC with high tumour mutation burden (TMB), according to an exploratory analysis from the phase I/II CheckMate 032 study.

The phase III trial, CheckMate 331, evaluated nivolumab vs the current standard of care, topotecan or amrubicin (where approved), in pts with SCLC who relapsed following platinum-based ChT. The study did not meet its primary endpoint of OS.

Tumour response			
	Nivolumab 3 mg/kg (n=98)	Nivolumab 1 mg/kg plus Ipilimumab 3 mg/kg (n=61)	Nivolumab 3 mg/kg plus Ipilimumab 1 mg/kg (n=54)
Objective response; 95% CI	10 (10%; 5-18)	14 (23%; 13-36)	10 (19%; 9-31)
Best overall response			
Complete response	0	1 (2%)	0
Partial response	10 (10%)	13 (21%)	10 (19%)
Stable disease	22 (22%)	13 (21%)	9 (17%)
Progressive disease	52 (53%)	23 (38%)	29 (54%)
Unable to determine	12 (12%)	8 (13%)	6 (11%)
Not reported	2 (2%)	3 (5%)	0
Time to objective response (IQR), months	2.0 (1.3-2.8)	2.1 (1.4-2.8)	1.4 (1.3-2.7)

Data are n (%) unless otherwise stated. All patients were enrolled at least 90 days prior to database lock.

CI, Confidence interval; IQR, interquartile range.

Fig. 15.3

Immune checkpoint blockade in small cell lung cancer (continued)

The phase Ib multicohort study KEYNOTE-028 evaluated the safety and efficacy of pembrolizumab in pts with SCLC who failed platinum-based ChT.

All pts enrolled were PD-L1 positive (>1%) as evaluated by immunohistochemistry (IHC) using the Merck 22C3 antibody.

Pembrolizumab demonstrated a promising response rate of 33% with median duration of response (DoR) of 19.4 months and 1-year survival of 37.7%.

Sixty-seven percent of pts had an adverse event with the most common being fatigue, rash, diarrhoea and arthralgia.

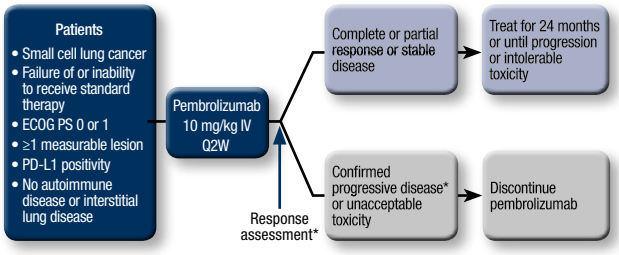
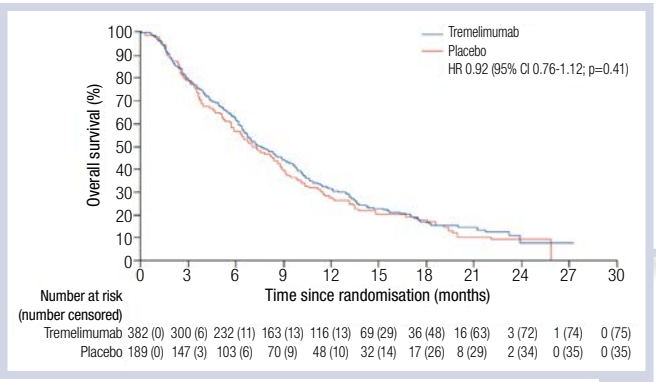


Fig. 15.4

ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenously; OS, overall survival; ORR, overall response rate; PD-L1+, programmed death-ligand 1-positive; PFS, progression-free survival; RECIST, Response Evaluation in Solid Tumours.

Immune checkpoint blockade in mesothelioma



CI, Confidence interval; HR, hazard ratio.

Fig. 15.5

Single-arm phase II trials of tremelimumab (MESOT-TREM-2008; MESOT-TREM-2012) achieved a partial response (6.9% and 13.8%, respectively) and durable disease control (31% and 52%, respectively).

The DETERMINE study evaluated tremelimumab or placebo as second-/third-line treatment for pts with unresectable pleural or peritoneal mesothelioma. Tremelimumab did not demonstrate superiority to placebo for the primary endpoint of OS. Preliminary safety data are consistent with the known safety profile of tremelimumab.

The single-arm, phase II DREAM trial combined durvalumab, cisplatin and pemetrexed as first-line therapy in malignant pleural mesothelioma. 57% of pts achieved PFS for at least 6 months, while median PFS was 6.9 months and median DoR, 6.5 months.

In the NIBIT-MESO-1 open label phase II trial evaluating durvalumab and tremelimumab as first- or second-line treatment for pleural or peritoneal mesothelioma, the ORR was 25% and DoR 16.1 months.

The MAPS2 trial randomised pts to either nivolumab or nivolumab and ipilimumab. Response rates were 17.5% vs 24.2% and grade ≥3 toxicities 9.5% vs 21.3%, respectively.

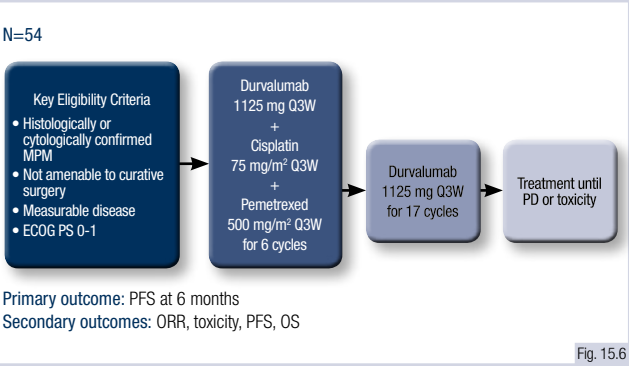


Fig. 15.6

ECOG PS, Eastern Cooperative Oncology Group Performance Status; MPM, malignant pleural mesothelioma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

REVISION QUESTIONS

1. In SCLC, when using anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) and anti-PD-L1 or anti-PD-1 in combination, does the response rate correlate with PD-L1 expression?
2. In SCLC, was ChT with platinum/etoposide plus ipilimumab 10 mg/kg vs placebo superior in OS?
3. Did tremelimumab demonstrate superiority to placebo for OS as second/third-line treatment for patients with unresectable pleural or peritoneal malignant mesothelioma?

Summary: Immunotherapy for thoracic malignancies Part B – Small cell lung cancer and mesothelioma

- Although combination ChTs continue to be the standard of care for SCLC, high rates of recurrence and limited long-term response are common
- Durable response in first-line cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockade and ChT combination strategies, as well as second-line PD-1 and CTLA-4 blockade combination strategies, support the idea of bringing either dual-targeted immunotherapies or other targeted therapy combinations to first-line treatment strategies in SCLC
- Optimal patient selection for immune checkpoint-directed therapies remains a challenge
- Further research on immune checkpoint pathways and associated therapeutic antibodies will be necessary to improve outcomes for patients with SCLC
- Early-phase studies with immune checkpoint inhibitors in pre-treated malignant mesothelioma patients have shown promising results. Results from ongoing trials are eagerly awaited

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Emerging targets and new agents in lung cancer

Human epidermal growth factor receptor 2 (*HER2*) exon 20 mutations

HER2 is a receptor tyrosine kinase of the ERBB family with no known identified ligand, functioning as a preferred dimerisation partner.

Activating *HER2* mutations in non-small cell lung cancer (NSCLC) were identified in 2004, occurring in up to 2%–4% of cases, mutually exclusive to other oncogenic drivers, predominantly observed in adenocarcinomas.

Mutations usually map to exon 20, are in-frame insertional and are homologous to epidermal growth factor receptor (*EGFR*) exon 20 insertions. Over 80% of cases harbour the A775_G776insYVMA insertion/duplication.

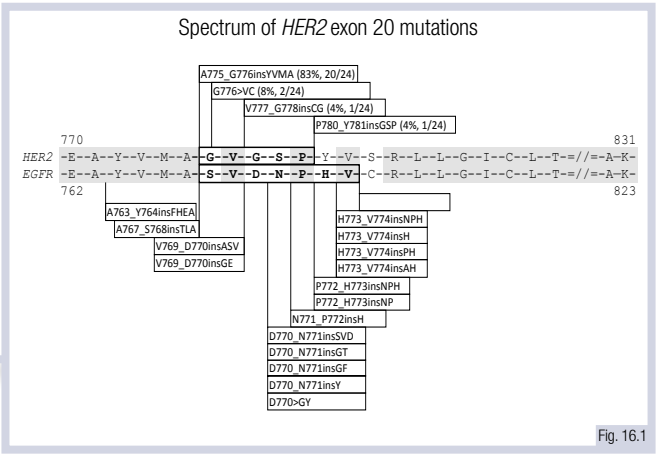


Fig. 16.1

EGFR, Epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2.

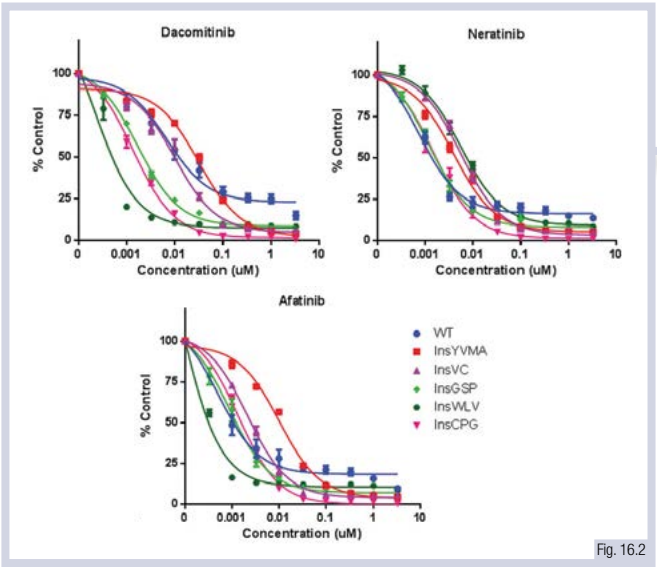


Fig. 16.2

WT, Wild type.

Afatinib and dacomitinib are pan-HER irreversible tyrosine kinase inhibitors (TKIs). TKI activity is poor in most patients with 1/13 responders to afatinib from the European Thoracic Oncology Platform (ETOP) NICHE trial and 3/26 responding in a phase II trial of dacomitinib.

Some patients may retain TKI sensitivity (e.g. dacomitinib responders are noted to harbour a general secretory pathway [GSP] insertion, an afatinib responder V777_G778ins GSP and *in vitro* data identifying sensitive mutations containing Gly700).

Several cases responding to weekly pulsed dosing of afatinib (280 mg weekly) have been reported.

Ado-trastuzumab emtansine (T-DM1) was trialled in a phase II study presented at the 2017 ASCO (American Society of Clinical Oncology) annual meeting, identifying responses in 8/18 cases and a median progression-free survival (PFS) of 4 months.

All responders had 0-2+ *HER2* expression and no amplification. Patients responding to chemotherapy (ChT)/trastuzumab combinations have been reported.

The mutation-specific irreversible TKI AP32788 is in development for NSCLCs with *HER2* mutations.

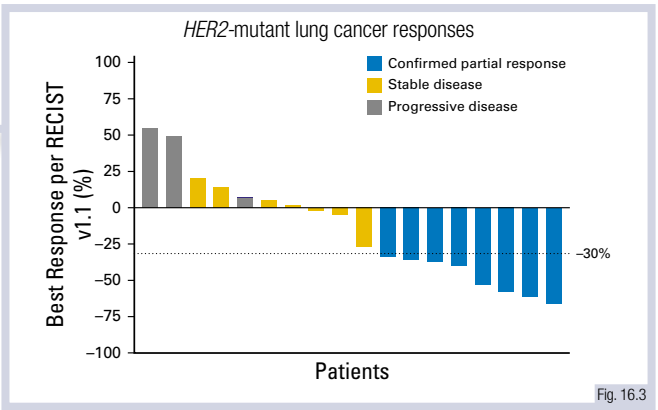


Fig. 16.3

HER2, Human epidermal growth factor receptor 2; RECIST, Response Evaluation Criteria In Solid Tumours.

REVISION QUESTIONS

1. Are all somatic *HER2* mutations in exon 20?
2. What is the most common *HER2* exon 20 genotype?
3. Which drugs have demonstrated potential sensitivity in *HER2* exon 20 mutations?

HER2 trans-membrane domain mutations

Table 1. Clinicopathologic Features of HER2 TMD Mutations in NSCLC

Case	Age	Sex	Stage	Smoking Status	TMD Protein Alteration	Codon Change	Nucleotide Change	Concurrent HER2 Amplification	MAF	TMB (mutations/Mb)	Response to HER2 TKI [a]
1	62	F	4	Never-smoker	V659E	GTT / GAA	1976_1977TT > AA	N	0.42	7.19	First-line afatinib, PR, 5 mo
2	54	M	4	Never-smoker	V659E G660R	GTTG GC / GAACGC	1976_1977TT > AA 1978G > C	N	0.16	3.99	Second-line afatinib, PR, 18 mo, ongoing
3	73	M	4	Never-smoker	V659E	GTT / GAG	1976_1977TT > AG	N	0.09	3.99	Third-line afatinib, 5 mo of symptomatic improvement and metabolic response
4	53	M	4	Positive history	G660D	GGC / GAC	1979G > A	N	0.14	3.19	Second-line afatinib, PD, 10 weeks
5	52	F	NR	Light smoker	V659E	GTT / GAA	1976_1977TT > AA	N	0.70	10.81	Second-line afatinib, not yet evaluable
6	59	F	4	Minimal remote smoking history	V659D	GTT / GAT	1976T > A	N	0.13	6.60	NA
7	69	M	4	NR	V659D	GTT / GAT	1976T > A	Y (30 copies)	0.94	6.60	NA
8	47	F	4	Never-smoker	V659D	GTT / GAT	1976T > A	N	0.14	5.50	NA
9	51	F	NR	NR	V659E	GTT / GAG	1976_1977TT > AG	Y (14 copies)	0.45	2.20	NA
10	59	F	2	NR	V659E	GTT / GAG	1976_1977TT > AG	N	0.11	1.10	NA
11	74	F	NR	NR	V659E	GTT / GAG	1976_1977TT > AG	N	0.27	7.19	NA
12	48	F	NR	NR	V659E	GTT / GAA	1976_1977TT > AA	N	0.46	7.99	NA
13	47	F	4	Minimal remote smoking history	V659E	GTT / GAA	1976_1977TT > AA	N	0.08	2.70	NA
14	33	F	NR	NR	V659_660VE	GTG / GGGTTGAAG	1976_1979TG > GGTTGAAG	N	0.2	2.20	NA
15	66	F	NR	Never-smoker	G660D S310F	GGC / GAC TCT / TTT	1979G > A 929C > T	N	0.12	3.30	NA

Note: Bold text indicates nucleotide changes.
[a]Follow-up cutoff was October 1, 2016.
HER2, erb-b2 receptor tyrosine kinase 2 gene; TMD, transmembrane domain; MAF, mutant allele frequency; TMB, tumor mutational burden; TKI, tyrosine kinase inhibitor; F, female; N, no; PR, partial response; M, male; PD, progressive disease; NR, not reported; NA, not applicable; Y, yes.

Fig. 16.4

HER2 mutations usually map to the kinase domain. *HER2* trans-membrane domains (TMDs) are important for receptor activation and can affect downstream activity independent of kinase domain mutations.

The G660D mutation in exon 17 was identified in the germline from a Japanese kindred and subsequent screening of HER TMDs identified the *HER2* TMD mutation *V659E* (analogous to the *V664E* driver mutation in rats).

A single case of *HER2 V659E* with Li-Fraumeni responded to combination lapatinib/paclitaxel, with *in vitro* sensitivity to lapatinib.

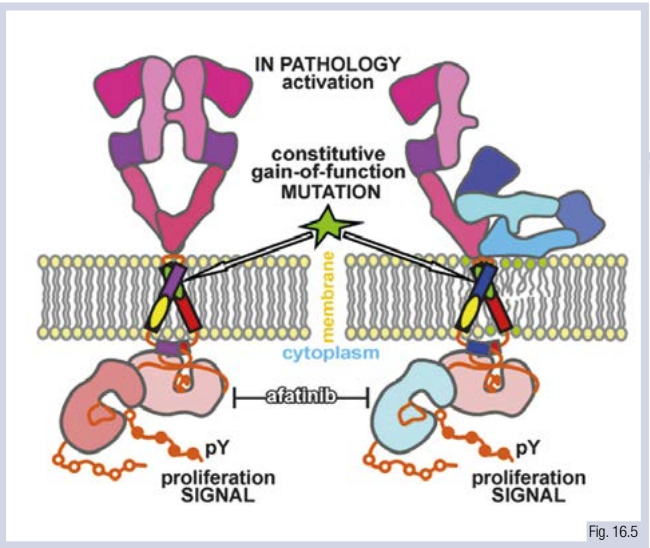


Fig. 16.5

Several other TMD mutations have been identified (*V664F*, *V665M*, *I675M*).

Treatment with afatinib identified responses in patients with *V659E* and the compound *V659E/G660R* mutation.

In additional screening of 8551 genotyped adenocarcinomas by Foundation Medicine, 2% were identified to harbour *HER2* 659/660 variants (*V659E*, *V659D*, *G660D*, *V659_660VE*, *V659E/G660R* compound).

REVISION QUESTIONS

1. How do *HER2* TMDs transform cells?
2. What are the most common *HER2* TMD genotypes?
3. Which drug has induced durable responses in some patients with *HER2* TMDs?

EGFR exon 20 insertions & MET copy number gain

Exon 20 insertions in the *EGFR* gene account for around 5% of all *EGFR* mutations in NSCLC, usually between residues Glu762 and Cys775, and typically occur in never/light-smokers.

Exon 20 insertions are usually resistant to erlotinib or gefitinib with poor activity *in vitro* and in case reports/series, although some genotypes (e.g. A763_Y764insFQEA) are sensitive.

The pan-HER irreversible second-generation TKI afatinib has demonstrated minimal activity against exon 20 insertions (8.7% responses, median PFS 2.7 months) from analysis of the LUX-Lung 2, 3 and 6 trials, although genotypes with distal insertions (e.g. a common Gly770) may retain sensitivity.

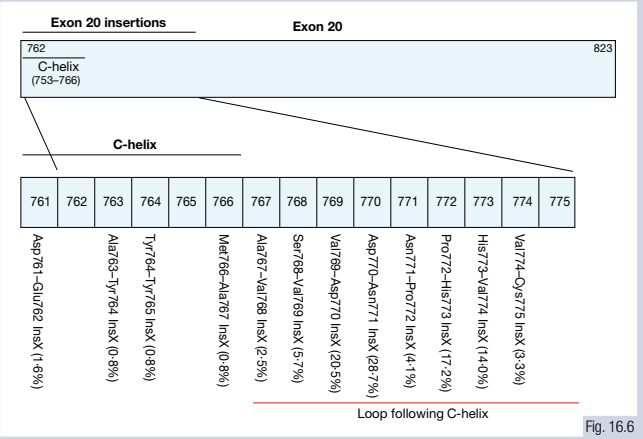


Fig. 16.6

Encouraging *in vitro* data suggest potential sensitivity to osimertinib. AP32788 is an *EGFR* wild-type sparing, irreversible *EGFR/HER2* inhibitor in development against *EGFR* and *HER2* exon 20 mutations (NCT02716116).

Dysregulation of the MET pathway in lung cancer occurs through a variety of mechanisms, including gene mutation, amplification, rearrangement and protein overexpression.

MET copy number gains arise from polysomy or amplification. The appropriate numbers of *MET* copies and relationship to centromere copy number status to best predict response from *MET*-directed therapy are poorly understood and continue to be evaluated.

MET/CEP7 ratio and classification of *MET* amplification

MET/CEP7 ratio	*MET* amplification classification	Percentage of total
<1.8	Negative	92.6
≥1.8 to ≤2.2	Low	3.6
>2.2 to >5.0	Intermediate	3.0
≥5.0	High	0.8
Total	–	100.0

Fig. 16.7

CEP7, Centromeric portion of chromosome 7; *MET*, mesenchymal epithelial transition receptor.

To date, the highest level of *MET* amplification (*MET*/CEP7 ratio ≥5) has been associated with response to crizotinib.

De novo *MET* amplification occurs in 1%–5% of NSCLCs and overlap exists between *MET* exon 14 genotype status.

In contrast, up to 30% of patients with *EGFR* mutation progressing on osimertinib have *MET* amplification as a potential resistance mechanism.

Several agents are in development against dysregulated *MET* including: multi-kinase MET TKIs (crizotinib, cabozantinib, MGCD265, AMG208, altiratinib, golvatinib), selective MET TKIs (capmatinib, tepotinib, tivantinib), anti-MET antibodies (onartuzumab, emibetuzumab) and anti-HGF antibodies (ficlatuzumab, rilotumumab).

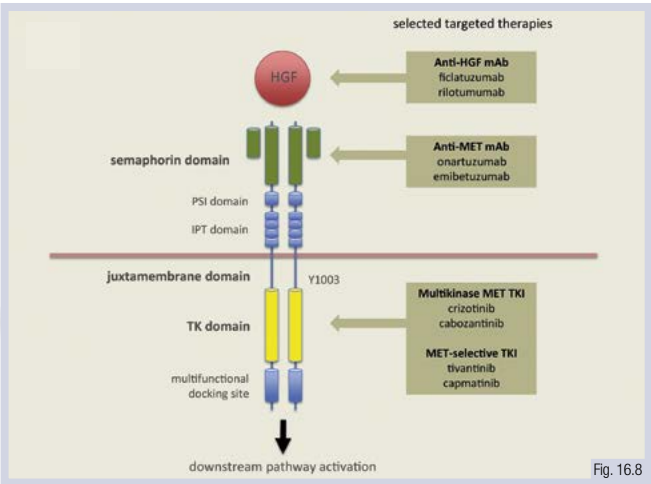


Fig. 16.8

HGF, Hepatocyte growth factor; mAb, monoclonal antibody; PSI, plexin semaphoring integrin domain; TK, tyrosine kinase; TKI, tyrosine kinase inhibitor.

REVISION QUESTIONS

1. How frequent are *EGFR* exon 20 insertions?
2. Are *EGFR* exon 20 insertions usually associated with sensitivity to erlotinib/gefitinib?
3. Which assays can be used to detect increased *MET* copy number?

Neurotrophic tyrosine receptor kinase (*NTRK*) & *NRG1* fusions

Gene fusions in *NTRK1*, *NTRK2*, *NTRK3* are rare oncogenic drivers in NSCLC. Fusion partners include the genes *CD74*, *MPRIP*, *BCAN* and *ETV6*.

The *NTRK1-3* genes encode the TRKA-C proteins and play roles in neuronal development, cell survival and cellular proliferation.

Activated fusions signal through RAS-RAF-MEK-ERK, PI3K-AKT-mTOR (mammalian target of rapamycin) and PLCγ-PKC pathways, driving and propagating malignancy. Tropomyosin receptor kinase (TRK) fusions occur in a number of solid tumours including NSCLC, colonic, head and neck, sarcomas and primary brain tumours.

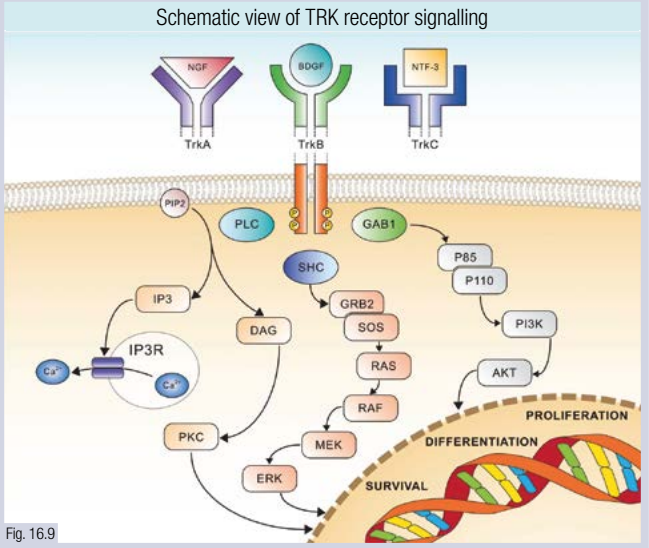


Fig. 16.9

TRK, Tropomyosin receptor kinase.

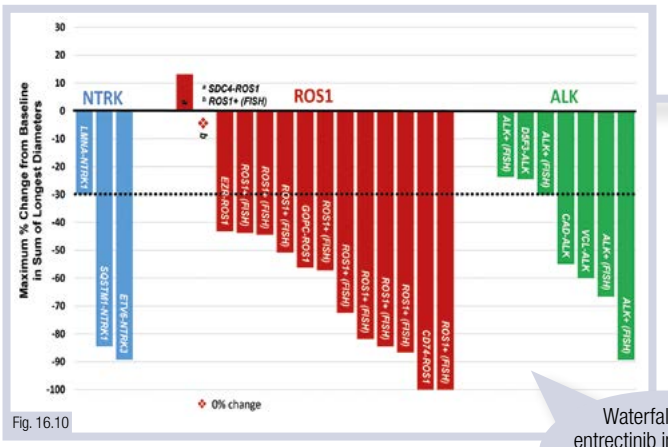


Fig. 16.10

ALK, Anaplastic lymphoma kinase; NTRK, neurotrophic tyrosine receptor kinase.

Waterfall plot of entrectinib in treatment naïve solid tumours with differing fusions

A number of pan-TRK inhibitors are in development, including entrectinib (RXDX-101), an adenosine triphosphate (ATP)-competitive TKI with sub-nanomolar enzymatic efficacy against *TRKA*, *TRKB*, *TRKC*, *ROS1* and *ALK*, designed to cross the blood–brain barrier.

Other TRK inhibitors include LOXO-101, MGCD516, TSR-011, PLX7486, DS-6051b and DCC-2701, as well as cabozantinib.

CD74-NRG fusions are rare, occurring in around 0.5% of NSCLCs. All cases identified from a larger cohort were identified as invasive mucinous adenocarcinomas.

CD74-NRG fusions lead to extracellular expression of the epidermal growth factor *(EGF)*-like domain of *NRG1* III β3, providing the ligand for *HER2-HER3* complexes.

Two patients with *CD75-NRG* fusions in invasive mucinous adenocarcinomas with durable responses to irreversible pan-HER TKI afatinib have been reported.

Schematic of NRG1-CD74 fusion protein and interactions with ERBB signalling

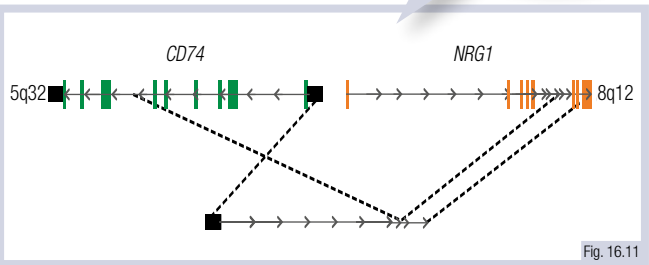


Fig. 16.11

REVISION QUESTIONS

1. Which proteins do *NTRK* genes usually encode?
2. Which drugs targeted against *NTRK* fusions are in development?
3. Which drug has demonstrated sensitivity against NSCLC with *NRG* fusions?

Indoleamine 2,3-dioxygenase (IDO)

IDO is an intracellular enzyme responsible for the first (and rate-limiting) step in tryptophan degradation in the kynurenine pathway.

Tryptophan is an essential amino acid and IDO overexpression reduces the availability of tryptophan. This induces immune tolerance through promoting inflammation in the tumour microenvironment and suppressing T and natural killer (NK) cell activity.

IDO inhibition is designed to overcome immune tolerance.

IDO catabolism along the kynurenine pathway

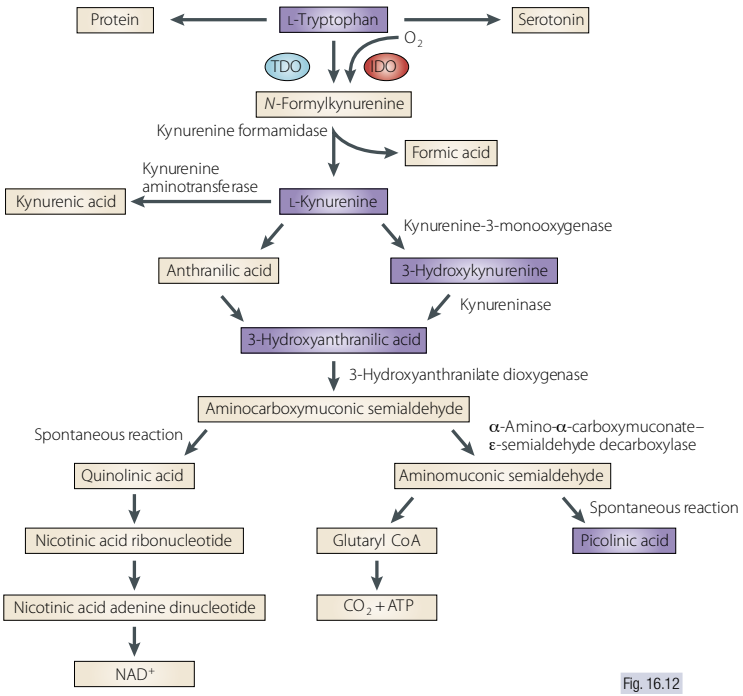
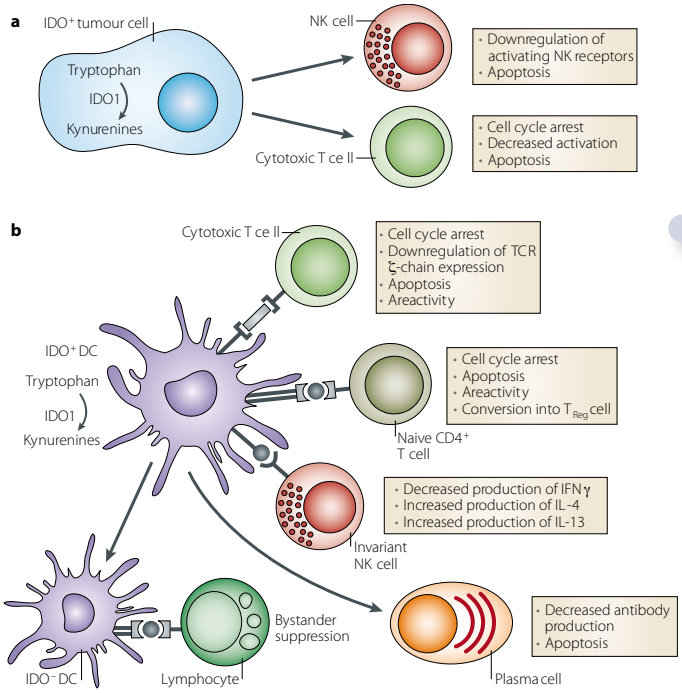


Fig. 16.12

ATP, Adenosine triphosphate; IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase.

Modulation of immune response by IDO-expressing cells



DC, Dendritic cell; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; NK, natural killer; TCR, T cell receptor.

Fig. 16.13

There are several IDO inhibitors in early phase development.

Epacadostat (Incyte) is the most advanced in these trials with phase I/II trials in both mono and combination therapy.

Epacadostat is a small molecule inhibitor of IDO1 and has been combined with pembrolizumab for patients with NSCLC. Encouraging response rates (overall response rate [ORR] 35%) and tolerable toxicities have led to an ongoing phase III study in NSCLC.

REVISION QUESTIONS

1. What is the function of IDO and in which pathway does it lie?
2. What impact does overexpression of IDO in tumour cells have on the immune response?
3. Which agent has been combined with pembrolizumab in NSCLC clinical trials?

4-1BB & Lymphocyte-activation gene 3 (LAG-3)

T cell activation requires antigen presentation and a balance between co-stimulatory signalling (e.g. CD80, CD86, CD40, OX40 and 4-1BB) to provoke T cell activation and inhibitory signalling (e.g. cytotoxic T-lymphocyte antigen 4 [CTLA-4], programmed cell death protein 1 [PD-1], LAG-3, T cell immunoglobulin and mucin domain 3 [TIM-3], Tigit and Vista) to limit overstimulation.

4-1BB (CD137) is a co-stimulatory member of the tumour necrosis factor receptor superfamily. T cell activation upregulates 4-1BB and its ligation by 4-1BB ligand (CD137L).

Early phase trials with anti-4-1BB monoclonal antibody (mAb) urelumab caused liver toxicity, potentially with one case of fatal hepatitis. This led to the early termination of a number of 4-1BB studies. Trials have since restarted as these toxicities seem mitigated through dose reduction (<1 mg/kg). Utomilumab (PF-05082566) is also an anti-4-1BB mAb in early phase trials.

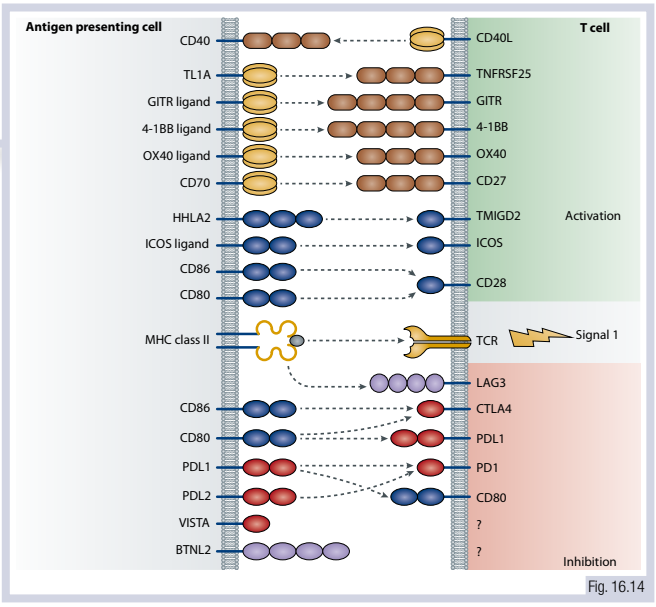


Fig. 16.14

CTLA-4, Cytotoxic T-lymphocyte antigen 4; LAG-3, lymphocyte-activation gene 3; MHC, major histocompatibility complex; PD-1/2, programmed cell death protein 1/2; PD-L1/2, programmed death ligand-1/2; TCR, T cell receptor.

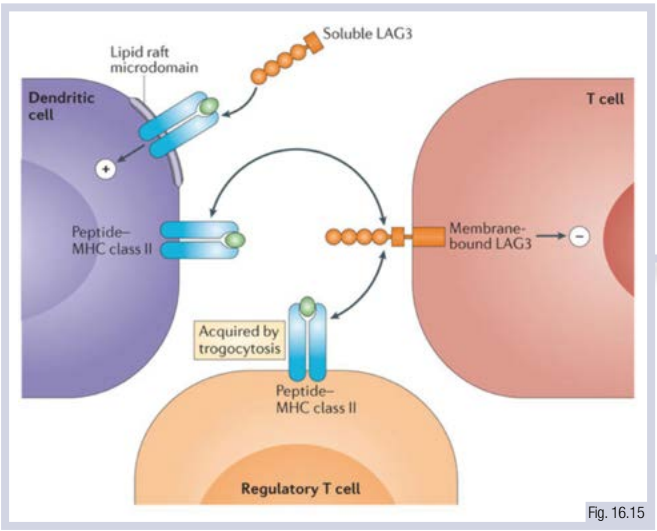


Fig. 16.15

LAG-3, Lymphocyte-activation gene 3; MHC, major histocompatibility complex.

LAG-3 is a negative co-stimulatory receptor and is upregulated on tumour infiltrating lymphocytes.

Blockade of LAG-3 results in increased T cell proliferation and enhanced anti-tumour T cell responses. It is frequently co-expressed with PD-1 on activated T cells.

Conversely, an alternatively spliced soluble form of LAG-3 (sLAG-3) acts as an immune adjuvant on other immune cells – enhancing their anti-tumoural effect.

A number of LAG-3-directed therapies are in development. These trials are in combination with anti-PD-1 agents (LAG525, BMS-986016) in solid organ cancers (including lung cancer).

Initial reports of LAG525 in combination with nivolumab in heavily pre-treated patients (including progression on prior immunotherapy) with malignant melanoma suggest a 16% ORR.

The LAG-3Ig fusion protein IMP321 is being tested in phase II trials in breast cancer in combination with ChT as an immune adjuvant.

REVISION QUESTIONS

1. Which cells in the immune system are affected by 4-1BB signalling?
2. What strategies are being utilised to manipulate the 4-1BB pathway therapeutically?
3. What is the physiological function of membrane-bound LAG-3 in the T cell?
4. What effect does antagonism of LAG-3 have in T cells in an activated T cell?

Chimeric antigen receptor (CAR) T cell therapy

CAR T cell therapy utilises patients' (or allogenic donors') T cells, which are activated and genetically modified *ex vivo* to recognise tumoural antigens.

Extracellular antigen-recognition domains are linked to intracellular signalling domains by genetic modification. The CAR T cells are then infused to induce an anti-tumoural effect.

Second- and third-generation CAR T cells are now in development where co-stimulatory domains like 4-1BB or CD28 enhance CAR T cell efficacy.

Some are engineered to include a 'suicide-gene' as a safety mechanism, activated in the event of severe toxicity or unresponsive to treatment. Serious adverse events include cytokine release syndrome (CRS).

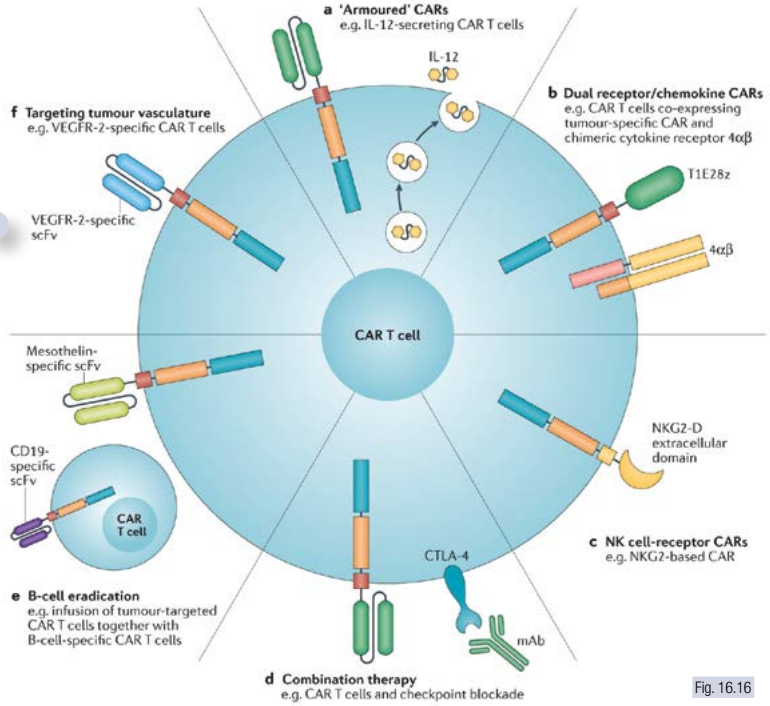


Fig. 16.16

CAR, Chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte antigen 4; IL-12, interleukin 12; mAb, monoclonal antibody; NK, natural killer; scFv, single chain fragment of variable region; VEGFR, vascular endothelial growth factor receptor.

CAR targets for the treatment of solid malignancies

Target	CAR structure	Malignancy	Institution	Reference
Mesothelin	CD3 and 4-1BB	Malignant pleural mesothelioma	UPenn	NCT01355965
		Pancreatic cancer	UPenn	NCT02465983
		Metastatic pancreatic (ductal) adenocarcinoma, epithelial ovarian cancer and malignant pleural mesothelioma	UPenn	NCT02159716
	CD3ζ and CD28	Mesothelioma and malignant pleural disease	MSKCC	NCT02414269
	CD3ζ, CD28 and 4-1BB	Mesothelioma, pancreatic and ovarian cancer	NCI	NCT01583686
FAP	CD3ζ and CD28	Mesothelioma	University of Zurich	NCT01722149

Fig. 16.17

CAR, Chimeric antigen receptor; FAP, fibroblast activation protein; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; UPenn, University of Pennsylvania.

In 2017, the first CAR T cell therapy tisagenlecleucel received USA Food & Drug Administration (FDA) approval targeting the CD19 antigen in patients with acute lymphoblastic leukaemia (ALL). CAR T challenges in solid organ cancers include identifying tumoural antigens that are specific.

CAR T cells directed at mesothelin, an antigen found on malignant pleural mesothelioma and some lung cancers, have been developed and are in early phase studies including third-generation CAR T cells (CD28/4-1BB).

Clinical trials with CAR T cells in lung cancer directed at mesothelin and FAP

REVISION QUESTIONS

1. In what way are T cells manipulated to generate a CAR T cell?
2. What antigens are being targeted in mesothelioma in CAR T cell clinical trials?
3. What is a 'suicide gene'?

Summary: Emerging targets and new agents in lung cancer

- Several new molecular drivers are being evaluated as drug targets in NSCLC
- Established molecular drivers previously deemed drug resistant are being evaluated to identify sensitive mutant genotypes
- *HER2* and *EGFR* exon 20 insertions may be sensitive to afatinib, contingent on specific genotype
- A number of different *HER2*-directed approaches for *HER2* exon 20 insertions or TMDs are being developed (e.g. the use of ado-trastuzumab emtansine and genotype-specific afatinib)
- A number of different *EGFR*-directed approaches for exon 20 insertions are being developed (e.g. genotype-specific afatinib and AP32788)
- *MET* aberrations remain a viable drug target. Efforts are ongoing to characterise *MET* amplification and genotypes that result in exon 14 skipping to predict sensitivity to MET inhibitors
- A number of rare fusions in NSCLC are being further developed as drug targets including *NRTK* and *NRG* fusions
- Manipulation of the immune system has become the focus of many new therapies
- Physiological overexpression of IDO in tumour cells induces immune anergy and its inhibition aims to overcome tolerance
- Therapies targeted at the immune checkpoint designed to either reduce co-stimulatory negative signalling (e.g. LAG-3) or enhance activating pathways (e.g. 4-1BB) are in trials in combination with established immunotherapies
- CAR T cell therapy demonstrates good response rates in ALL and, despite its expense and toxicity profile, the quest to identify specific antigen targets in solid cancers with effective CAR T cell design is underway

Further Reading

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Appendix 1: WHO 2015 Classification

Tumours of the lung

- Adenocarcinoma
  - Lepidic adenocarcinoma
  - Acinar adenocarcinoma
  - Papillary adenocarcinoma
  - Micropapillary adenocarcinoma
  - Solid adenocarcinoma
  - Invasive mucinous adenocarcinoma
    - Mixed invasive mucinous and non-mucinous adenocarcinoma
  - Colloid adenocarcinoma
  - Fetal adenocarcinoma
  - Enteric adenocarcinoma
  - Minimally invasive adenocarcinoma
  - Preinvasive lesions
    - Atypical adenomatous hyperplasia
    - Adenocarcinoma *in situ*
- Squamous cell carcinoma
  - Keratinizing
  - Non-keratinizing
  - Basaloid squamous cell carcinoma
  - Preinvasive lesion
    - Squamous cell carcinoma *in situ*
- Neuroendocrine tumours
  - Small cell carcinoma
  - Large cell neuroendocrine carcinoma
  - Carcinoid tumour
  - Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
- Large cell carcinoma
- Adenosquamous carcinoma
- Sarcomatoid carcinoma
  - Pleomorphic, spindle cell, and giant cell carcinoma
  - Carcinosarcoma
  - Pulmonary blastoma
- Other and unclassified carcinomas
  - Lymphoepithelioma-like carcinoma
  - NUT carcinoma
- Salivary gland-type tumours
  - Mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
  - Epithelial-myoepithelial carcinoma
  - Pleomorphic adenoma
- Papillomas
  - Squamous cell papilloma
  - Glandular papilloma
  - Mixed squamous cell and glandular papilloma
- Adenomas
  - Sclerosing pneumocytoma
  - Alveolar adenoma
  - Papillary adenoma
  - Mucinous cystadenoma
  - Mucous gland adenoma
- Mesenchymal tumours
  - Pulmonary hamartoma
  - Chondroma
  - PEComatous tumours
  - Congenital peribronchial myofibroblastic tumour
  - Diffuse pulmonary lymphangiomatosis
  - Inflammatory myofibroblastic tumour
  - Epithelioid haemangioendothelioma
  - Pleuropulmonary blastoma
  - Synovial sarcoma
  - Pulmonary artery intimal sarcoma
  - Pulmonary myxoid sarcoma with *EWSR1-CREB1* translocation
  - Myoepithelial tumours / myoepithelial carcinoma
  - Other mesenchymal tumours
- Lymphohistiocytic tumours
  - Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)
  - Diffuse large B-cell lymphoma
  - Lymphomatoid granulomatosis
  - Intravascular large B-cell lymphoma
  - Pulmonary Langerhans cell histiocytosis
  - Erdheim-Chester disease
- Tumours of ectopic origin
  - Germ cell tumours
  - Intrapulmonary thymoma
  - Melanoma
  - Meningioma
- Metastases to the lung

Tumours of the pleura

- Mesothelial tumours
  - Diffuse malignant mesothelioma
    - Epithelioid mesothelioma
    - Sarcomatoid, desmoplastic, and biphasic mesothelioma
  - Localized malignant mesothelioma
  - Well-differentiated papillary mesothelioma
  - Adenomatoid tumour
- Lymphoproliferative disorders
  - Primary effusion lymphoma
  - Diffuse large B-cell lymphoma associated with chronic inflammation
- Mesenchymal tumours
  - Epithelioid haemangioendothelioma
  - Angiosarcoma
  - Synovial sarcoma
  - Solitary fibrous tumour
  - Desmoid-type fibromatosis
  - Calcifying fibrous tumour
  - Desmoplastic round cell tumour

Tumours of the thymus

- Thymomas
  - Type A thymoma, including atypical variant
  - Type AB thymoma
  - Type B1 thymoma
  - Type B2 thymoma
  - Type B3 thymoma
  - Micronodular thymoma with lymphoid stroma
  - Metaplastic thymoma
  - Other rare thymomas
    - Microscopic thymoma
    - Sclerosing thymoma
    - Lipofibroadenoma
- Thymic carcinomas
  - Squamous cell carcinoma
  - Basaloid carcinoma
  - Mucoepidermoid carcinoma
  - Lymphoepithelioma-like carcinoma
  - Clear cell carcinoma
  - Sarcomatoid carcinoma
  - Adenocarcinomas
  - NUT carcinoma
  - Undifferentiated carcinoma
  - Other rare thymic carcinomas
- Thymic neuroendocrine tumours
  - Typical and atypical carcinoids
    - Typical carcinoid
    - Atypical carcinoid
  - Large cell neuroendocrine carcinoma
  - Small cell carcinoma
- Combined thymic carcinomas
- Germ cell tumours of the mediastinum
  - Seminoma
  - Embryonal carcinoma
  - Yolk sac tumour
  - Choriocarcinoma
  - Mature and immature teratoma
  - Mixed germ cell tumours
- Germ cell tumours with somatic-type solid malignancy
  - Germ cell tumours with associated haematological malignancy
- Lymphomas of the mediastinum
  - Primary mediastinal large B-cell lymphoma
  - Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)
  - Other mature B cell lymphomas
  - T lymphoblastic leukaemia / lymphoma
  - Anaplastic large cell lymphoma and other rare mature T- and NK-cell lymphomas
  - Hodgkin lymphoma
  - B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma
- Histiocytic and dendritic cell neoplasms of the mediastinum
  - Langerhans cell lesions
  - Histiocytic sarcoma
  - Follicular dendritic cell sarcoma
  - Interdigitating dendritic cell sarcoma
  - Fibroblastic reticular cell tumour
  - Other dendritic cell tumours
- Myeloid sarcoma and extramedullary acute myeloid leukaemia
- Soft tissue tumours of the mediastinum
  - Thymolipoma
  - Lipoma
  - Liposarcoma
  - Solitary fibrous tumour
  - Synovial sarcoma
  - Vascular neoplasms
  - Neurogenic tumours
    - Ganglioneuroma, ganglioneuroblastoma, and neuroblastoma
  - Other rare mesenchymal tumours
- Ectopic tumours of the thymus
  - Ectopic thyroid tumours
  - Ectopic parathyroid tumours
  - Other rare ectopic tumours
- Metastasis to the thymus or mediastinum

Tumours of the heart

- Benign tumours and tumour-like lesions
  - Rhabdomyoma
  - Histiocytoid cardiomyopathy
  - Hamartoma of mature cardiac myocytes
  - Adult cellular rhabdomyoma
  - Cardiac myxoma
  - Papillary fibroelastoma
  - Haemangioma
  - Cardiac fibroma
  - Lipoma
  - Cystic tumour of the atrioventricular node
  - Granular cell tumour
  - Schwannoma
- Tumours of uncertain behaviour
  - Inflammatory myofibroblastic tumour
  - Paraganglioma
- Germ cell tumours
  - Teratoma, mature
  - Teratoma, immature
  - Yolk sac tumour
- Malignant tumours
  - Angiosarcoma
  - Undifferentiated pleomorphic sarcoma
  - Osteosarcoma
  - Myxofibrosarcoma
  - Leiomyosarcoma
  - Rhabdomyosarcoma
  - Synovial sarcoma
  - Miscellaneous sarcomas
  - Cardiac lymphomas
  - Metastatic tumours
- Tumours of the pericardium
  - Solitary fibrous tumour
  - Sarcomas
  - Malignant mesothelioma
  - Germ cell tumours
  - Metastatic tumours

Appendix 2: International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society Classification of Lung Adenocarcinoma in Resection Specimens

Preinvasive lesions
- Atypical adenomatous hyperplasia
- Adenocarcinoma in situ (≤3 cm, formerly BAC)
  - Nonmucinous
  - Mucinous
  - Mixed mucinous/nonmucinous

Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumour with ≤5 mm invasion)
- Nonmucinous
- Mucinous
- Mixed mucinous/nonmucinous

Invasive adenocarcinoma
- Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
- Acinar predominant
- Papillary predominant
- Micropapillary predominant
- Solid predominant with mucin production

Variants of invasive adenocarcinoma
- Invasive mucinous adenocarcinoma (formerly mucinous BAC)
- Colloid
- Fetal (low and high grade)
- Enteric

(BAC = bronchioloalveolar carcinoma)

Appendix 3: Selected treatment schedules

Non-small cell lung cancer

NON-SMALL CELL LUNG CANCER: STAGE I OR II				
Examples of acceptable chemotherapy regimens for adjuvant chemotherapy for stage I or II (goal to complete 4 cycles)				
Cisplatin	50 mg/m²	i.v.	d1 + d15	q 28 d [1, 2, 3, 4, 5, 6]
Vinorelbine	25 mg/m²	i.v.	d1 + d8 + d15 + d22	
OR				
Cisplatin	100 mg/m²	i.v.	d1	q 28 d [1, 2, 3, 4, 5, 6]
Vinorelbine	30 mg/m²	i.v.	d1 + d8 + d15 + d22	
OR				
Cisplatin	75-80 mg/m²	i.v.	d1	q 21 d [1, 2, 3, 4, 5, 6]
Vinorelbine	25-30 mg/m²	i.v.	d1 + d8	
OR				
Cisplatin	100 mg/m²	i.v.	d1	q 28 d [1, 2, 3]
Etoposide	100 mg/m²	i.v.	d1-3	
OR				
Cisplatin	75 mg/m²	i.v.	d1	q 21 d [7]
Gemcitabine	1250 mg/m²	i.v.	d1 + d8	
OR				
Cisplatin	75 mg/m²	i.v.	d1	q 21 d [8]
Docetaxel	75 mg/m²	i.v.	d1	
OR				
Cisplatin	75 mg/m²	i.v.	d1	q 21 d [7] (for non-squamous histologies)
Pemetrexed	500 mg/m²	i.v.	d1	
Patients with comorbidities or patients not able to tolerate cisplatin may alternatively use the following regimen				
Carboplatin	AUC 6	i.v.	d1	q 21 d [9, 10]
Paclitaxel	200 mg/m²	i.v.	d1	

NON-SMALL CELL LUNG CANCER: STAGE III: CONSOLIDATIVE IMMUNOTHERAPY AFTER CHEMO-RADIOTHERAPY				
Durvalumab	10 mg/kg	i.v.	d1	q 2 w (for PD-L1 ≥1%, up to 12 months) [11, 12]

NON-SMALL CELL LUNG CANCER: STAGE IV OR RECURRENT DISEASE: FIRST-LINE CHEMOTHERAPY				
Examples of drug regimens, including platinum-based doublets				
Cisplatin	75 mg/m²	i.v.	d1	q 21 d [13, 14]
Paclitaxel	175 mg/m²	i.v.	d1	
OR				
Cisplatin	100 mg/m²	i.v.	d1	q 28 d [14]
Gemcitabine	1000 mg/m²	i.v.	d1 + d8 + d15	
OR				
Cisplatin	60 mg/m²	i.v.	d1	q 21 d [15, 16]
Gemcitabine	1000 mg/m²	i.v.	d1 + d8	
OR				
Cisplatin	75 mg/m²	i.v.	d1	q 21 d [8, 14]
Docetaxel	75 mg/m²	i.v.	d1	
OR				
Carboplatin	AUC 6	i.v.	d1	q 21 d [14, 17]
Paclitaxel	175-225 mg/m²	i.v.	d1	
OR				
Carboplatin	AUC 6	i.v.	d1	q 28 d [18, 19, 20, 21]
Paclitaxel	90 mg/m²	i.v.	d1 + d8 + d15	
OR				
Paclitaxel protein bound	100 mg/m²	i.v.	d1 + d8 + d15	q 21 d [22]
Carboplatin	AUC 6	i.v.	d1	
OR				
Carboplatin	AUC 6	i.v.	d1	q 21 d [23]
Docetaxel	75 mg/m²	i.v.	d1	
OR				
Carboplatin	AUC 5	i.v.	d1	q 21 d [24, 25, 26]
Gemcitabine	1250 mg/m²	i.v.	d1 + d8	
OR				
Cisplatin	100 mg/m²	i.v.	d1	q 28 d [8]
Vinorelbine	25 mg/m²	i.v.	weekly	
OR				
Cisplatin	40 mg/m²	i.v.	d1	q 21 d [15]
Vinorelbine	25 mg/m²	i.v.	d1 + d8	
OR				
Carboplatin	AUC 5	i.v.	d1	q 21 d [27]
Vinorelbine	30 mg/m²	i.v.	d1 + d8	

NON-SMALL CELL LUNG CANCER: STAGE IV OR RECURRENT DISEASE: FIRST-LINE CHEMOTHERAPY (continued)				
Bevacizumab-based chemotherapy for patients who meet eligibility requirements (non-squamous histology, treated brain metastases, no history of haemoptysis)				
Carboplatin	AUC 6	i.v.	d1	q 21 d (continue bevacizumab every 21 d after 4-6 cycles are completed: continue until disease progression) [28, 29]
Paclitaxel	200 mg/m²	i.v.	d1	
Bevacizumab	15 mg/kg	i.v.	d1	
OR				
Cisplatin	80 mg/m²	i.v.	d1	q 21 d (continue bevacizumab every 21 d after 4-6 cycles are completed): continue until disease progression [28]
Gemcitabine	1250 mg/m²	i.v.	d1 + d8	
Bevacizumab	7.5-15 mg/kg	i.v.	d1	
OR				
Carboplatin	AUC 6	i.v.	d1	q 21 d with pemetrexed and bevacizumab continued until disease progression (remember folate and B12 supplements along with dexamethasone premeds for pemetrexed) [30, 31]
Pemetrexed	500 mg/m²	i.v.	d1	
Bevacizumab	15 mg/kg	i.v.	d1	
Pemetrexed-based chemotherapy for patients who meet eligibility requirements (non-squamous histology)				
Cisplatin	75 mg/m²	i.v.	d1	q 21 d (remember folate and B12 supplements along with dexamethasone premeds for pemetrexed) [32]
Pemetrexed	500 mg/m²	i.v.	d1	
OR				
Carboplatin	AUC 5	i.v.	d1	q 21 d (remember folate and B12 supplements along with dexamethasone premeds for pemetrexed) [26, 33, 34]
Pemetrexed	500 mg/m²	i.v.	d1	
Treatment recommendations for patients with contraindications to carboplatin or cisplatin				
Gemcitabine	1100 mg/m²	i.v.	d1 + d8	q 21 d [35, 36]
Docetaxel	100 mg/m²	i.v.	d8	
OR				
Gemcitabine	1000-1200 mg/m²	i.v.	d1 + d8	q 21 d [27, 37, 38, 39]
Vinorelbine	25-30 mg/m²	i.v.	d1 + d8	

NON-SMALL CELL LUNG CANCER (WILD TYPE): STAGE IV or RECURRENT DISEASE: FIRST-LINE THERAPY				
Examples of drug regimen for non-squamous histology (Combination chemotherapy plus immunotherapy)				
Cisplatin or Carboplatin	75 mg/m² AUC 5	i.v. i.v.	d1 d1	q 21 d (continue pemetrexed + pembrolizumab every 21 d after 4 cycles are completed: continue up to a total of 35 cycles or disease progression) [40]
Pemetrexed	500 mg/m²	i.v.	d1	q 21 d
Pembrolizumab	200 mg flat dose	i.v.	d1	q 21 d
OR				
Cisplatin or Carboplatin	75 mg/m² AUC 6	i.v. i.v.	d1 d1	q 21 d (continue pemetrexed + atezolizumab every 21 d after 4-6 cycles are completed: continue until disease progression) [41]A
Pemetrexed	500 mg/m²	i.v.	d1	q 21 d
Atezolizumab	1200 mg flat dose	i.v.	d1	q 21 d
OR				
Carboplatin	AUC 6	i.v.	d1	q 21 d (continue bevacizumab + atezolizumab every 21 d after 4-6 cycles are completed: continue until clinical benefit) [42]A
Paclitaxel	200 mg/m²	i.v.	d1	q 21 d (175 mg/m² for Asian patients)
Bevacizumab	15 mg/kg	i.v.	d1	q 21 d
Atezolizumab	1200 mg flat dose	i.v.	d1	q 21 d
Examples of drug regimen for squamous histology (Combination chemotherapy plus immunotherapy)				
Carboplatin	AUC 6	i.v.	d1	q 21 d (continue pembrolizumab every 21 d after 4 cycles are completed: continue up to a total of 35 cycles or disease progression) [43]A
Paclitaxel protein bound or Paclitaxel	100 mg/m² 200 mg/m²	i.v. i.v.	d1 + d8 + d15 d1	q 21 d q 21 d
Pembrolizumab	200 mg flat dose	i.v.	d1	q 21 d
OR				
Carboplatin	AUC 6	i.v.	d1	q 21 d (continue atezolizumab every 21 d after 4-6 cycles are completed: continue until clinical benefit) [44]A
Paclitaxel protein bound or Paclitaxel	100 mg/m² 200 mg/m²	i.v. i.v.	d1 + d8 + d15 d1	q 21 d q 21 d (175 mg/m² for Asian patients)
Atezolizumab	1200 mg flat dose	i.v.	d1	q 21 d
Example of drug regimen for NSCLC with TMB ≥10 mutation/Mb (Combination immunotherapy)				
Nivolumab	3 mg/kg	i.v.	d1	q 2 w (continue up to two years or disease progression) [45]A
Ipilimumab	1 mg/kg	i.v.	d1	q 6 w
Example of drug regimen for NSCLC with PD-L1 ≥50% (Immunotherapy monotherapy)				
Pembrolizumab	200 mg flat dose	i.v.	d1	q 21 d (continue every 21 d up to two years or disease progression) [46]
Bevacizumab-based chemotherapy for non-squamous histology				
Cisplatin	75 mg/m²	i.v.	d1	q 21 d (continue bevacizumab+ pemetrexed every 21 d after 4-6 cycles are completed: continue until disease progression) [47,48]
Pemetrexed	500 mg/m²	i.v.	d1	q 21 d
Bevacizumab	7.5 mg/kg	i.v.	d1	q 21 d
Examples of drug regimen for squamous histology				
Cisplatin	75 mg/m²	i.v.	d1	q 21 d SQUIRE (114-115 – 116) (continue necitumumab every 21 d after 4-6 cycles are completed: continue until disease progression) [49]
Gemcitabine	1250 mg/m²	i.v.	d1	q 21 d
Necitumumab	800 mg flat dose	i.v.	d1 + d8	q 21 d

[A] Not EMA approved.

NON-SMALL CELL LUNG CANCER: STAGE IV OR RECURRENT DISEASE: EXAMPLES OF SECOND-LINE CHEMOTHERAPY				
Docetaxel	75 mg/m²	i.v.	d1	q 21 d (goal 4-6 cycles) [50, 51, 52, 53, 54]
OR				
Pemetrexed	500 mg/m²	i.v.	d1 (non-squamous histology)	q 21 d (goal 4-6 cycles; remember folate and B12 supplements along with dexamethasone premeds for pemetrexed) [54]
OR				
Erlotinib	150 mg	PO	daily	for patients with EGFR mutation or gene amplification; given until disease progression [7, 17, 55, 56, 57, 58, 59, 60, 61, 62, 63]

Erlotinib alone in second-line and third-line settings remains the standard of care.[64]

NON-SMALL CELL LUNG CANCER (WILD TYPE): STAGE IV or RECURRENT DISEASE: EXAMPLE OF SECOND-LINE REGIMENS				
Examples of regimens including immunotherapy				
Pembrolizumab	2 mg/kg	i.v.	d1	q 21 d (for PD-L1 ≥1%, continue until disease progression) [65]
Pembrolizumab	200 mg flat dose	i.v.	d1	q 21 d [46]
OR				
Nivolumab	3 mg/kg	i.v.	d1 + d15	q 2 w (any PD-L1, continue until disease progression) [66, 67]
Nivolumab	240 mg flat dose	i.v.	d1	q 2 w [68] (the actual schedule uses)
OR				
Atezolizumab	1200 mg flat dose	i.v.	d1	q 21 d (any PD-L1, continue until disease progression) [69]
Examples of regimen combining chemotherapy with antiangiogenic agents				
Docetaxel	75 mg/m²	i.v.	d1	q 21 d REVEL (improved efficacy was seen in non-responding patients to first-line or fast progressing tumours) [70, 71]
Ramucirumab	15 mg/kg	i.v.	d1	q 21 d
OR				
Docetaxel	75 mg/m²	i.v.	d1	q 21 d LUME-1 (for adenocarcinoma histology; improved efficacy was seen in non-responding patients to first-line or fast progressing tumours) [72,73]
Nintedanib	200 mg	PO	twice daily	q 28 d
OR				
Paclitaxel	90 mg/m²	i.v.	d1 + d8 + d15	q 28 d (continue both drugs until toxicity or disease progression) [74]A
Bevacizumab	10 mg/kg	i.v.	d1 + d15	q 28 d
OR				
Afatinib	40 mg	PO	daily	q 28 d (for squamous histology; an option for patients unfit for chemotherapy or immunotherapy) [75]

NON-SMALL CELL LUNG CANCER: STAGE IV OR RECURRENT DISEASE: THIRD-LINE CHEMOTHERAPY				
Erlotinib	150 mg	PO	daily	for patients with EGFR mutation or gene amplification; given until disease progression [7, 17, 55, 56, 57, 58, 59, 60, 61]

NON-SMALL CELL LUNG CANCER (WILD TYPE): STAGE IV or RECURRENT DISEASE: EXAMPLES OF THIRD-LINE REGIMENS				
Example of drug regimen after immunotherapy				
Docetaxel	75 mg/m²	i.v.	d1	q 21 d [8]
Example regimen (prospective trials) for ECOG-PS 0-2 patients treated with immunotherapy				
Nivolumab	3 mg/kg	i.v.	d1	q 2 w [76, 77]

NON-SMALL CELL LUNG CANCER: STAGE IV OR RECURRENT DISEASE: EXAMPLES OF SINGLE-AGENT THERAPY				
Paclitaxel	200 mg/m²	i.v.	d1	q 21 d [78,79]
OR				
Docetaxel	35 mg/m²	i.v.	weekly	for 3 wks q 4 wks [36, 50, 53, 80]
OR				
Docetaxel	75 mg/m²	i.v.	d1	q 21 d [50, 51, 52, 53]
OR				
Gemcitabine	1000 mg/m²	i.v.	d1 + d8 + d15	q 4 wks [81, 82]
OR				
Gemcitabine	1250 mg/m²	i.v.	d1 + d8	q 21 d [24, 37]
OR				
Vinorelbine	25 mg/m²	i.v.	weekly	[83, 84]
OR				
Vinorelbine	30 mg/m²	i.v.	d1 + d8	q 21 d [36, 85, 86]
OR				
Pemetrexed	500 mg/m²	i.v.	d1	q 21 d [54] (non-squamous histology)

Systemic chemotherapy is not indicated for patients with poor performance status (ECOG 3-4), except for erlotinib in patients who are EGFR-mutation positive. [7]

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: FIRST-LINE EGFR-mutated				
Examples of drug regimen EGFR TKI in monotherapy				
Gefitinib	250 mg	PO	daily	First-generation TKI (given until progression or clinical benefit) [87-92]
OR				
Erlotinib	150 mg	PO	daily	First-generation TKI (given until progression or clinical benefit) [93, 94]
OR				
Afatinib	40 mg	PO	daily	Second-generation TKI (given until progression or clinical benefit) [95-99]
OR				
Dacomitinib	45 mg	PO	daily	Second-generation TKI; in patients without CNS mets (given until progression or clinical benefit) [100, 101]A
OR				
Osimertinib	80 mg	PO	daily	Third-generation TKI, targeting both sensitizing and resistant mutation (exon 20 *T790M*) (given until progression or clinical benefit) [102, 103]

[A] Not EMA approved; patients with PS 3 – 4 may also be offered an EGFR TKI.

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: FIRST-LINE EGFR-mutated				
Examples of drug regimen: combination of chemotherapy + EGFR TKI*				
Carboplatin	AUC 5	i.v.	d1	q 21 d (continue gefitinib daily after 4-6 cycles are completed until progression or clinical benefit) [104]A
Pemetrexed	500 mg/m^2	i.v.	d1	q 21 d (remember folate and B12 supplements along with dexamethasone premeds)
Gefitinib	250 mg	PO	daily	

[A] Not EMA approved; *observed worse adverse event included neutropaenia, anaemia, thrombocytopaenia compares to single-agent TKI.

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: FIRST-LINE EGFR-mutated				
Example of drug regimen: combination of bevacizumab + EGFR TKI				
Bevacizumab	15 mg/kg	i.v.	d1	q 21 d (in these studies patients with CNS mets were excluded) [105-108]
Erlotinib	150 mg	PO	daily	

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: BEYOND FIRST-LINE EGFR-mutated				
Examples of drug regimen in pre-treated patients with EGFR TKI agent with exon 20 T790M acquired resistance (around 50% of patients)				
Osimertinib	80 mg	PO	daily	(until progression or clinical benefit) [109-111]
Example of drug regimen in pre-treated patients with EGFR TKI agent without exon 20 T790M mutation				
Cisplatin	75 mg/m^2	i.v.	d1	q 21 d (continue with pemetrexed every 21 d until progression) [112]
Pemetrexed	500 mg/m^2	i.v.	d1	q 21 d (remember folate and B12 supplements along with dexamethasone premeds)

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: FIRST-LINE ALK-rearranged				
Examples of drug regimen with ALK TKI				
Crizotinib	250 mg	PO	BID	First-generation TKI (given until progression or clinical benefit) [113-115]
OR				
Ceritinib	750 mg	PO	daily	Second-generation TKI (given until progression or clinical benefit) [116]
OR				
Ceritinib	450 mg	PO	daily	Second-generation TKI, recommended dose, less toxic with same efficacy (given until progression or clinical benefit) [117]
OR				
Alectinib	300 mg	PO	BID	Third-generation TKI, in Asian patients (given until progression or clinical benefit) [118]
OR				
Alectinib	600 mg	PO	BID	Third-generation TKI, in Caucasian patients (given until progression or clinical benefit) [119, 120]
OR				
Brigatinib	180 mg with a 7-day run-in at 90 mg	PO	daily	Next-generation TKI (given until progression or clinical benefit) [121]A

[A] Not EMA approved.

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: BEYOND FIRST-LINE for ALK-rearranged				
Example of drug regimen after first-line chemotherapy				
Crizotinib	250 mg	PO	BID	First-generation TKI, after first-line chemotherapy (given until progression or clinical benefit) [122]
Examples of drug regimen for patients who progressed after first-line crizotinib				
Ceritinib	750 mg	PO	daily	Second-generation TKI (given until progression or clinical benefit) [123]
OR				
Alectinib	600 mg	PO	BID	Third-generation TKI (given until progression or clinical benefit) [124, 125]
OR				
Brigatinib	180 mg with a 7-day run-in at 90 mg	PO	daily	Next-generation TKI (given until progression or clinical benefit) [126]
OR				
Lorlatinib	100 mg	PO	daily	Next-generation TKI (given until progression or clinical benefit) [127-129]

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: BEYOND SECOND-GENERATION RESISTANCE for ALK-rearranged				
Examples of drug regimens for patients who progressed after one or more ALK TKI				
Brigatinib	180 mg with a 7-day run-in at 90 mg	PO	daily	Next-generation TKI (given until progression or clinical benefit) [126] A
OR				
Lorlatinib	100 mg	PO	daily	Next-generation TKI (given until progression or clinical benefit) [127-129] A

[A] Not EMA approved; are recommended if available (e.g. such as compassionate use).

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: ROS1-rearranged				
Examples of drug regimens for first-line or pre-treated crizotinib-naïve patients				
Crizotinib	250 mg	PO	BID	First-generation TKI (given until progression or clinical benefit) [130-133]
OR				
Ceritinib	750 mg	PO	daily	Second-generation TKI (given until progression or clinical benefit) [134]A
Examples of drug regimen for patients treated with crizotinib in first-line				
Cisplatin	75 mg/m^2	i.v.	d1	q 21 d (continue with pemetrexed every 21 d until progression) [130-133]
Pemetrexed	500 mg/m^2	i.v.	d1	q 21 d (remember folate and B12 supplements along with dexamethasone premeds)
OR				
Lorlatinib	100 mg	PO	daily	Next-generation TKI (ongoing studies) [135]A

[A] Not EMA approved.

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: FIRST-LINE BRAF-mutated				
Example of drug regimen after BRAF/MEK inhibitors				
Dabrafenib	150 mg	PO	BID	BRAF-inhibitor [136-138]
Trametinib	2 mg	PO	Daily	MEK-inhibitor

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: SECOND-LINE BRAF-mutated				
Example of drug regimen for treatment-naïve for BRAF-V600E mutation				
Cisplatin	75 mg/m^2	i.v.	d1	q 21 d (continue with pemetrexed every 21 d until progression) [130-131]
Pemetrexed	500 mg/m^2	i.v.	d1	q 21 d (remember folate and B12 supplements along with dexamethasone premeds)

[A] Not EMA approved.

NON-SMALL CELL LUNG CANCER: STAGE IV or RECURRENT DISEASE: Other actionable oncogenic drivers				
Example of drug regimen for MET exon 14 mutation (as a resistance mechanism of EGFR or *de novo*)				
Crizotinib	250 mg	PO	BID	First-generation TKI (given until progression or clinical benefit) [139, 140]
Examples of drug regimens for *HER2* insertion exon 20 mutation				
Afatinib	40 mg	PO	daily	Inhibits *EGFR*- and *HER2*-mutant [141]A,B
OR				
Poziotinib	16 mg	PO	daily	Next-generation inhibitor of *EGFR*- and *HER2*-mutant [142]A,B
OR				
Ado-trastuzumab emtansine (TDM1)	3.6 mg	i.v.	d1	q 21 d targeting *HER2*-mutation and amplification or protein expression [143,144]A,B

[A] Not EMA approved; [B] not currently recommended.

Abbreviations: *ALK*, anaplastic lymphoma kinase; AUC, area under the curve; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; EMA, European Medicines Agency; *HER2*, human epidermal growth factor receptor 2; Mb, megabase; PD-L1, programmed death ligand-1, TKI; tyrosine kinase inhibitor; TMB, tumour mutational burden.

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Non-small cell lung cancer

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Small cell lung cancer

SMALL CELL LUNG CANCER: EXAMPLES OF TREATMENT REGIMENS RECOMMENDED FOR LIMITED-STAGE SCLC				
Concurrent chemotherapy recommendations with radiation for limited-stage disease				
Cisplatin	60 mg/m²	i.v.	d1	q 21 d for 4 cycles [1]
Etoposide	120 mg/m²	i.v.	d1-3	
OR				
Cisplatin	25 mg/m²	i.v.	d1-3	q 21 d for 4 cycles [1, 2, 3]
Etoposide	100 mg/m²	i.v.	d1-3	
OR				
Cisplatin	80 mg/m²	i.v.	d1	q 28 d for 4 cycles [4]
Etoposide	100 mg/m²	i.v.	d1-3	
OR				
Carboplatin	AUC 5-6	i.v.	d1	q 21 d [5]
Etoposide	100 mg/m²	i.v.	d1-3	
Note: Radiotherapy for limited-stage disease should start with cycle 1 or 2 of chemotherapy				

SMALL CELL LUNG CANCER: EXAMPLES OF FIRST-LINE CHEMOTHERAPY FOR EXTENSIVE-STAGE DISEASE				
Stage IV disease				
Cisplatin	60-80 mg/m²	i.v.	d1	q 21-28 d [6, 7, 8, 9, 10, 11, 12, 13]
Etoposide	80-120 mg/m²	i.v.	d1-3	
OR				
Carboplatin	AUC 5-6	i.v.	d1	q 28 d [13, 14, 15, 16]
Etoposide	80-100 mg/m²	i.v.	d1-3	
OR				
Cisplatin	60 mg/m²	i.v.	d1	q 28 d [8, 11, 12]
Irinotecan	60 mg/m²	i.v.	d1 + d8 + d15	
OR				
Cisplatin	30 mg/m²	i.v.	d1 + d8 (or 80 mg/m² d1)	q 21 d [7, 9]
Irinotecan	65 mg/m²	i.v.	d1 + d8	
OR				
Carboplatin	AUC 5	i.v.	d1	q 28 d [14, 16]
Irinotecan	50 mg/m²	i.v.	d1 + d8 + d15	
OR				
Carboplatin	AUC 4-5	i.v.	d1	q 21 d [17, 18, 19]
Irinotecan	150-200 mg/m²	i.v.	d1	
OR				
Cyclophosphamide	800-1000 mg/m²	i.v.	d1	q 21-28 d [20, 21, 22]
Doxorubicin	40-50 mg/m²	i.v.	d1	
Vincristine	1-1.4 mg/m²	i.v.	d1	

SMALL CELL LUNG CANCER: EXAMPLES OF FIRST-LINE THERAPY FOR EXTENSIVE-STAGE DISEASE				
Stage IV disease				
Carboplatin	AUC 5	i.v.	d1	q 21 d (continue with atezolizumab until disease progression or clinical benefit) [23]A
Etoposide	100 mg/m²	i.v.	d1,2,3	q 21 d
Atezolizumab	1200 flat dose	i.v.	d1	q 21 d
A Not EMA approved.				

SMALL CELL LUNG CANCER: EXAMPLES OF SECOND-LINE CHEMOTHERAPY FOR RELAPSED OR REFRACTORY DISEASE				
Stage IV disease				
Etoposide	50 mg/m²	PO	daily	for 3 wks q 4 wks [24]
OR				
Topotecan	2.3 mg/m²	PO	d1-5	q 21 d [25, 26, 27]
OR				
Topotecan	1.5 mg/m²	i.v.	d1-5	q 21 d [25, 26, 28]
OR				
Carboplatin	AUC 5	i.v.	d1	q 28 d [14, 16]
Irinotecan	50 mg/m²	i.v.	d1 + d8 + d15	
OR				
Carboplatin	AUC 4-5	i.v.	d1	q 21 d [17, 18, 19]
Irinotecan	150-200 mg/m²	i.v.	d1	
OR				
Cisplatin	30 mg/m²	i.v.	d1	q 28 d [29]
Irinotecan	60 mg/m²	i.v.	d1 + d8 + d15	
OR				
Cisplatin	60 mg/m²	i.v.	d1	q 28 d [8, 12]
Irinotecan	60 mg/m²	i.v.	d1 + d8 + d15	
OR				
Cisplatin	30 mg/m²	i.v.	d1 + d8 (or 80 mg/m² d1)	q 21 d [7, 9]
Irinotecan	65 mg/m²	i.v.	d1 + d8	
OR				
Paclitaxel	80 mg/m²	i.v.	weekly	for 6 wks q 8 wks [30]
OR				
Paclitaxel	175 mg/m²	i.v.	d1	q 3 wks [31]

Abbreviations: AUC, Area under the curve; EMA, European Medicines Agency; SCLC, small cell lung cancer.

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Small cell lung cancer

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Image sources

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