LUNG CANCER
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Lung cancer epidemiology
• Lung cancer is leading cause of cancer death and one of the most common cancer in male and female
  • 2008. 1.6 million people developed lung cancer (1.1 million male and 0.5 million female) – 12.7% of all new cancer cases
  • 1.38 million people died due to lung cancer
  • 5 year survival in Europe: male 11.2%, female 13.9% (European White Book on Lung Cancer 2014); in Estonia 10% (Eesti Arst 2013;92:437)
• Highest incidence is in middle-, east- and south Europe and in north America
• Prognosis is bad, because lung cancer is usually detected in a late stage

Age standardized lung cancer incidence in Europe among male and female in year 2008
• Highest incidence of lung cancer among male in EU:
  • Hungary (109.5 cases per 100 000)
  • Poland (104.5 / 100 000)
  • Estonia (91.5 / 100 000)
• female:
  • Denmark (49.5 / 100 000)
  • Hungary (39.8 / 100 000)
  • Great Britain (38.7 / 100 000)

(Cancer incidence in Estonia (Eesti Arst 2009;88:635-40)
• Each year 700-800 new lung cancer cases are diagnosed in Estonia!
• Data from Estonian Cancer Registry concerning last 15 years (1994-2008)
  • Data request date: 19.10.2012
  • Altogether in registry: 11 437 lung cancer cases
    • Male: 9240
    • Female: 2197

Lung cancer risk factors
• Smoking
  • risk is related to intensity and duration of smoking
  • risk is in average 20 times higher compared to general population
• Passive smoking
  • risk is 20-30% higher compared to general population
• COPD
• Previous tuberculosis
• Genetic predisposition
• Harmful substances
  • Air pollution
  • Asbestos, arsenic, radon (miners, environmental radon in homes)
  • Coal
  • Cooking fumes (bad ventilation in kitchens)
• Radiation
• Hormone replacement therapy in female
• Diet?
• Human papilloma virus?
Lung cancer screening

Why is survival so low?
- Lung cancer is asymptomatic in early stages
- Delayed diagnosis
  - Advanced stage at the time of first diagnosis!
  - Patient visits doctor too late?
  - Doctor does not recognise lung cancer?
  - Long waiting times to investigations!
- Late referral to surgical treatment
- No screening program in Estonia

Who we should screen?
- Male / female?
- Smokers only?
  - Duration of smoking?
- Age
- Other risk factors
  - COPD? Previous lung cancer?

Which investigations we should use?
- Sputum cytology
- Chest x-ray, CT
- Cancer markers in blood?
- Exhaled breath condensate?

- Number of lung cancers diagnosed in early stage increased
- Adenocarcinoma was predominantly found cancer type
- Diagnostics of SCLC did not improve
- Due to lung cancer died:
  - 356 patients in CT group
  - 443 patients in X-ray group
- The number needed to screen with low-dose CT to prevent 1 lung cancer death was 320
- Relative reduction in lung cancer mortality in CT screening group compared to X-ray screening was 20%

Several cancer organizations in US recommend lung cancer screening for high-risk patients:
- Age 55-74 years
- Current smoker with smoking history > 30 pack-year and ex-smokers who quit < 15 years ago

Lung cancer symptomatology
- Long time asymptomatic
- Symptoms are non-specific
- Different cancer types have somewhat different symptomatology and onset of symptoms
- Different cancer localization causes different symptoms
- Most lung cancers are diagnosed in late stages!
- Lung cancer should be suspected especially in risk group patients
  - older age
  - male
  - smokers
  - COPD patients
Symptomatology

- Bronchopulmonary symptoms
  - cough, hemoptysis, wheeze, stridor, dyspnea, symptoms of infection
- Extrapulmonary symptoms
  - pain, hoarseness, fluidothorax, dysphagia, superior vena cava compression syndrome, superior sulcus tumor (Pancoast syndrome), Horner syndrome
- Symptoms of distant metastases
- Paraneoplastic syndromes
- General symptoms

Bronchopulmonary symptoms

- Cough
  - most common symptom (common also in other lung diseases)
  - develops due to bronchial wall irritation
  - needs special attention when nature of cough changes (smokers!)
  - night-time cough
- Hemoptysis
  - always alarming symptom - 1/3 of cases the cause is lung cancer
  - further investigations are always needed:
    - X-ray, CT, bronchoscopy
- Wheeze, stridor
  - tumor which compresses or obstructs trachea or major bronchus
- Dyspnea
  - fluidothorax
    - pleural carcinomatosis
    - other fluidothorax
  - lobar or pulmonary atelectasis
  - paresis of n. phrenicus
  - co-morbidities (COPD, heart failure)
- Symptoms of infection
  - bronchial obstruction → mucus retention → inflammation → pneumonia → lung abscess
  - cough with purulent excretion
  - fever
  - chills
  - differentiate from pneumonia and lung abscess
    - bronchoscopy
    - evaluate x-ray changes!
    - surgical therapy

Figure 1. Chest x-ray of a patient with left-sided centrally located tumor causing dyspnea due to whole lung atelectasis
Extrapulmonary symptoms

- Hoarseness
  - paresis of n. laryngeus recurrens
  - direct invasion by cancer, lymph node metastases
  - sin>dex

- Chest pain
  - cancer with invasion to the chest wall, mediastinum, spine

- Fluidothorax
  - malignant pleuritis
  - atelectasis > fluidothorax
  - morphological confirmation of the diagnosis is important!

- Dysphagia
  - esophageal invasion or compression by cancer of enlarged lymph metastatic nodes
  - rarely tracheoesophageal fistula

- Horner syndrome
  - ptosis, miosis, anhydrosis
  - invasion of stellate ganglion by tumor

- Pancoast syndrome (superior sulcus tumor)
  - shoulder and upper arm pain, weakness of arm muscles
  - invasion of thoracic inlet, brachial plexus and spine by tumor

- Compression of superior vena cava
  - Obstruction of superior vena cava by invasive tumor or metastatic lymph nodes
  - Blocked venous return from head, neck and arms
  - Development of edema
  - Headache, din in the ear
  - Morphological diagnosis of lung cancer should be confirmed
  - Chemo-radiotherapy
  - Very occasionally surgical therapy

Figure 2. Chest MRT of a patient with left-sided Pancoast tumor invading chest wall

Figure 3. Chest CT scan of a patient with right upper lobe tumor invading the mediastinum and causing compression of superior vena cava
Symptoms due to distant metastases
- Often asymptomatic
- Symptomatology depends on location and size of metastases
- Brain
  - headache, nausea, visual disturbances, intellectual disturbances, palsy
- Bones
  - pain, pathological fractures
- Liver, adrenals, kidneys
  - asymptomatic

Paraneoplastic syndromes
- Endocrine-metabolic
  - excessive production of ADH
  - Cushing syndrome from excessive production of ACTH
- Musculoskeletal syndromes
  - proliferative periostitis
  - finger clubbing
- Neuromuscular syndromes
  - sensory neuropathies, retinopathy, dementia, ataxia, hand tremor, balance disorders
- Haematological manifestations
  - anemia, thrombocytosis

Diagnostic steps of lung cancer
- History
  - complaints
  - smoking history, contact with other toxic substances, family history of cancer etc.
  - previous malignancies
- Physical examination
  - palpation
    - enlarged lymph nodes, direct tumor growth through chest wall, skin and subcutaneous metastases
  - percussion
  - fluidothorax
  - auscultation
    - bronchial obstruction, concomitant infection, atelectasis, fluidothorax

Localization of lung cancer
- Peripheral tumor
- Central tumor

Figure 4. Chest x-ray of a patient with right upper lobe peripheral tumor
Lung cancer morphology
- Non-small cell lung cancer NSCLC
  - squamous cell cancer
  - adenocarcinoma
  - large cell cancer
- Small cell lung cancer - SCLC
- Carcinoid

Adenocarcinoma
- Most common type of lung cancer, especially in female
- Incidence is increasing
- Usually peripheral
- Locoregional and distant metastases are common
- Various growth speed and patterns:
  - solitary pulmonary nodule
  - multifocal
  - infiltrate
  - dissemination
  - ground glass opacity
  - “scar cancer” - postTB

Squamous cell cancer
- Second common type of lung cancer
- Incidence is decreasing
- Central location
  - bronchial obstruction
- Peripheral
  - often with central cavity
- Slow progression
- Can be large tumor without metastases

Small cell lung cancer
- Most malignant type of lung cancer
- 15-35% of lung cancers
- Usually centrally located
- Local and distant metastases are very common already at the time of initial diagnosis
- Surgical treatment rarely possible
- Sensitive to chemotherapy
- Prognosis is very poor

Figure 5. Left lung necrotizing squamous cell carcinoma
Carcinoid
• Rare type of neuroendocrine lung tumor
• Often is diagnosed in young adults
• Best prognosis
• Typical and atypical carcinoid
• Central location
  • endobronchial > atelectasis (pneumonia), hemoptysis
• Peripheral
  • solitary pulmonary nodule
• Metastases are rare

Molecular diagnosis of lung cancer
• Adenocarcinoma has many mutations
  • mutations are usually exclusive
  • most common is KRAS
  • targeted therapy according to mutations
  • EGFR mutation is most common target for therapy

Spread of lung cancer
• Lung cancer spreads along bronchial tree
  • macroscopic margin
  • microscopic margin
• Invasion to other organs
  • mediastinum
    • trachea, pericardium, large vessels
  • diaphragm
  • chest wall
  • Pancoast tumor
  • n. laryngeus recurrens
  • n. phrenicus

Lymph node metastases
• Very common in lung cancer
  1. SCLC (most common)
  2. Large cell cancer
  3. Adenocarcinoma
  4. Squamous cell cancer

Figure 6. Bronchoscopic view of endobronchial carcinoid tumor in right main bronchus
• Order of metastases
  • bronchopulmonary lymph nodes
  • hilar lymph nodes
  • mediastinal lymph nodes
  • skip metastases

IASLC map of intrathoracic lymph nodes
Lymph node regions:
• N1
• N2
• N3

Lymph node metastases in T1 NSCLC (<3cm)
• Mediastinal metastases N2
  • primary tumor < 1 cm ~0%
  • primary tumor 1.1-2.0 cm 12%
  • primary tumor 2.1-3.0 cm 25%
• Extrathoracic lymph node metastases N3
  • Supraclavicular
  • neck lymph nodes
  • axillary lymph nodes (very rare)

Hematogenic (distant) metastases
• Very common in lung cancer
• Primary tumor 1-3 cm has in 4-5% of cases distant metastases
• May be asymptomatic
• Most common locations:
  • Liver, lung, pleura, brain, bones, adrenals
• Less common:
  • Kidneys, pancreas, skin, subcutaneous tissue, myocardium, thyroid gland, spleen

Lung cancer radiological diagnostics
• X-ray findings of lung cancer
  • solitary pulmonary nodule (diameter < 3 cm)
  • larger mass in lung
  • hilar enlargement
  • lung cavity
  • atelectasis of lung segment, lobe or entire lung
  • lung infiltrate
  • dissemination
  • fluidothorax
• Cancers with different morphology have somewhat different radiological findings!

Chest X-ray
• posterioranterior and lateral view
• usually primary investigation
• to evaluate tumor growth
• to evaluate treatment effect
• follow-up

• X-ray finding is caused by:
  • cancer itself
- distal changes - atelectasis, pneumonia
- metastases - lymph nodes, lung, pleura

**Computed tomography - CT**
- Detailed description of tumor:
  - Size
  - Lobulation
  - Margins
  - Speculation
  - pleural retraction
  - contrast enhancement > 30 HU
  - cavitation
  - calcifications (excentric / small dots)
- Exact localization of the tumor
- Evaluation of invasion
  - Mediastinum
  - large vessels
  - chest wall
- Size of mediastinal lymph nodes
  - diameter > 1 cm - predominantly malignant
- Diagnostics of distant metastases
  - Major investigation to establish cTMN stage
  - morphological diagnosis is also very important
  - to evaluate tumor growth and treatment effect
  - follow-up
- Virtual bronchoscopy

**Magnetic resonance imaging - MRI**
- detection of soft tissue invasion (chest wall, mediastinum)

**Ultrasonography - US**
- detection and evaluation of pleural effusion
- detection of intraabdominal metastases

**Positron emission tomography - PET**
- solitary pulmonary nodule - malignant / benign?
- detection of metastases
  - regional (lymph node metastases)
  - distant (hematogenic)
- detection of recurrences

![Figure 7. PET-CT of a patient with left upper lobe lung cancer](image)
Lung cancer morphological diagnostics

(Sputum cytology)

Bronchoscopy

• Fiberoptic videobronchoscopy
  • description of endobronchial findings
  • localization of the tumor
  • proximal extension
  • infiltration of the bronchial wall
  • bronchial obstruction
  • external compression
  • morphology
    • biopsy
    • transbronchial biopsy (X-ray)
    • cytology
    • bronchoalveolar lavage

Endobronchial ultrasound - EBUS

• Endobronchial ultrasound transbronchial fine needle aspiration (EBUS-TBNA) allows to evaluate tracheobronchial lymph nodes or tumor which is in contact with trachea or main bronchi
• Aspiration biopsy

Bronchoscopic navigation system

Esophagoscopy

• Endoesophageal ultrasound - EUS
  • allows to investigate lymph nodes or tumor which is in contact with esophagus
  • aspiration biopsy
  • it is possible to use bronchoscope for both EBUS and EUS

Transthoracic lung biopsy

• peripheral tumor
• solitary pulmonary nodule

• Biopsy is performed under CT, sonography or X-ray
• Local anesthesia

• Indications
  • confirmation of malignancy preoperatively
  • establishment of morphological diagnosis in case of inoperable tumor
  • confirmation of benign diagnosis to avoid futile operation
• Complications
  • hemoptysis
  • pneumothorax
  • pleural empyema
  • iatrogenic pneumothorax

Mediastinoscopy

• Indication
  • Establishment of N stage
    • Mediastinal lymph nodes > 1cm according to CT
    • PET-CT positive lymph nodes
    • Left lower lobe lung cancer
• Establishment of morphological diagnosis
  • One investigation gives morphological diagnosis and cancer stage
• Accessible lymph nodes (N2-3)
  • Main bronchi
  • Subcarinal
  • Bilateral para- and pretracheal

Videothoracoscopy - VATS
• Indications
  • solitary pulmonary nodule
  • unclear infiltrate, dissemination
  • suspicious pleural metastasis
  • unclear extent of mediastinal or chest wall invasion
  • enlarged lymph nodes not accessible by EBUS, EUS end mediastinoscopy
• Intraoperative frozen-section!

(Diagnostic thoracotomy)
• Nowadays almost never need for diagnostic purposes

Lung cancer TNM classification
• 8th edition is implemented since Jan 1, 2017
• Used for all lung cancers incl. SCLC
• Proper TNM and cancer stage is needed for:
  • treatment planning
  • evaluating treatment efficacy
  • defining prognosis

Lung cancer treatment
• Surgical
• Chemotherapy
• Radiotherapy
• Targeted therapy
• Immunotherapy
• Palliative care
• Best supportive care
• Multimodality treatment!!
Selection of treatment modality depends on cancer morphology, mutations, stage, patients’ general status (ECOG), co-morbidities, lung function and previously used treatment methods.

Treatment options according to cancer stage:
• I stage: surgical treatment +/- chemotherapy stereotactic radiotherapy, radiofrequency ablation
• II stage: surgical treatment + chemotherapy chemoradiotherapy
• III stage: chemotherapy + radiotherapy targeted treatment occasionally surgical treatment preoperative downstaging
• IV stage: chemotherapy targeted treatment palliative treatment
Chemotherapy
- Survival is largely depending on patients’ general status at the time of diagnosis (Karnofski, ECOG; cancer stage; weight loss; gender)
- Platinum based chemotherapy prolongs survival, improves symptom control and quality of life
- Current results of NSCLC chemotherapy:
  - RR 25-35%
  - Prolongation of progression free survival 4-6 months
  - Median survival 8-10 months
  - 1 year survival 30-40%, 2 year survival 10-15%

Most commonly used chemotherapy drugs for NSCLC are Cisplatin, Carboplatin, Paclitaxel, Docetaxel, Vinorelbine, Gemcitabine, Etoposide

Lung cancer targeted treatment
- Pretreatment molecular diagnostics is mandatory
- EGFR activation mutation positive - Erlotinib, Gefitinib, Afatinib
  - Compared to chemotherapy:
    - Longer progression free survival (10.4 versus 5.5 months)
    - Less adverse effects
  - According to new treatment guidelines EGFR-TKI is indicated as first line treatment
- ALK fusion gene - Crizotinib

Lung cancer radiotherapy
- Indications for radiotherapy
  - Radical treatment (60-70 Gy)
  - Palliative treatment
  - Pre- and postoperative treatment
- 4D planning
- Stereotactic radiotherapy (SBRT, SABR)
- Prophylactic whole brain irradiation
- Brachytherapy (endobronchial)
- Chemoradiotherapy

Lung cancer surgery
- Most effective treatment option for lung cancer
- Prerequisites:
  - Completely removable tumor (R0 resection) incl. few T4 or even M1 cancers
  - Adequate lung function to tolerate planned resection
  - Acceptable surgical risk taking into account patient age, general status and comorbidities
- Surgical access: VATS / thoracotomy
- Anatomical lung resection
  - Lobectomy
  - Pneumonectomy
  - bronchial/arterial sleeve resection
  - extended lobectomy or pneumonectomy
  - en bloc resection of chest wall, spine, pericardium, superior vena cava, diaphragm
  - segmentectomy
  - (wedge resection)
- Lymphadenectomy
Advantages and disadvantages of VATS lobectomy
• Duration of surgery
• Intraoperative blood loss
• Postoperative pain
• Intra/postoperative complications
• Duration of postoperative pleural drainage
• Duration of postoperative hospital stay
• Postoperative lung function
• Cosmetic result
• Postoperative mortality
• Long term survival in cancer patients!

Adjuvant treatment
• Chemotherapy
• TKI?
• Immunotherapy?

Prognosis of NSCLC
• 5 year survival according to cancer stage:

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Summary
• Lung cancer is one of the most common cancers
• Major risk factor is smoking
• Symptomatology is various and symptoms develop at a late stage
• Lung cancer can be diagnosed with properly planned investigations (history, X-ray, CT, PET, BSK, TTB, MESK, VATS), hopefully in the future also by screening
• Lung cancer gives often regional (lymphogenic) and distant (hematogenic) metastases
• Planning lung cancer treatment requires proper diagnosis: morphology, stage, patient functional status and comorbidities
• Treatment of choice is surgery, preferably in a minimally invasive way
• In majority of cases multimodality treatment is used (chemo-, radio-, targeted-, immune- and palliative treatment)