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MSD
Novartis
Olimpus
Pfizer
Providens
Pulmodata
Roche
Sonar

*Prispevki niso lektorirani in recenzirani.

Rare lung diseases (Katarina Osolnik)

20'	A1A genotype	Karmen Meško Meglič
20'	A1A phenotype	Katarina Osolnik
40'	Imaging features of IPF	James F. Gruden
10’	IPF- retrospective analysis of our patients	Tina Jerič

Alpha-1 antitrypsin – the genotypes, their laboratory detection and genetic counselling

Karmen Meško Meglič, Matija Rijavec, Mira Šilar, Katarina Osolnik, Peter Korošec, University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a hereditary genetic disease with an incidence in the Caucasian population similar to cystic fibrosis, affecting approximately 1 in 2000 to 5000 individuals. Severe AATD carries a high risk of developing early pulmonary emphysema or chronic obstructive pulmonary disease. In some cases liver inflammation with eventual liver cirrhosis or carcinoma can develop. AATD is still an under-recognised clinical condition and recent guidelines from both the World Health Organization and the American Thoracic Society/European Respiratory Society recommend the establishment of screening programs for the detection of AATD in patients with COPD. The detection of coexisting AATD in these patients can lead to family screening, appropriate management, including lifestyle changes such as quitting smoking and replacement therapy in selected cases. Also specific genetic counselling for these patients and families is mandatory. AATD can be suspected by quantitative serum analysis for AAT, however only detection of gene mutations confirms exact diagnosis.

AAT and the gene

AAT is a circulating serine proteinase inhibitor (PI) secreted into the plasma by the liver as a mature glycoprotein. AAT permeates most body tissues acting as an inhibitor of a range of proteolytic enzymes thereby protecting tissues from self-degradation by these enzymes. The main target of AAT is neutrophil elastase released in the lung, which is irreversibly bound and inactivated during a process that consumes the AAT molecules as well.

AAT is encoded by the *SERPINA1* gene, and mutations in these gene lead to abnormally reduced serum AAT concentration. *SERPINA1* is the only gene in which mutations are known to cause AATD, and to date mutations in this gene are not known to be associated with other genetic diseases.

Two co-dominant alleles (gene copies, one received from the mother and the other received from the father) determine the AAT PI phenotype. Phenotypes are classified by a PI coding system, and designated by a two capital letter name of the inherited alleles e.g., PI*MM for individuals homozygous for the normal M allele and PI*ZZ for individuals homozygous for the Z allele.

AAT mutations and genotypes

Currently more than 120 mutations in the gene are known, but about 30 of them are of clinical relevance. Based on the serum concentration and the biochemical function of AAT genetic variants, the proteinase inhibitors (PI) are classified into three major categories:

1) The ***normal*** AAT phenotype M is determined by two normally functioning genes in a homozygous state, named PI*MM genotype. In this case the concentration of AAT is normal, in the range of 0.9 to 2.0 g/L, with the mean concentration of 1.3 g/L.

2) The ***deficient*** alleles are characterised by reduced but detectable AAT plasma levels, usually with genotypes PI*ZZ, and PI*ZS. The most prevalent severe deficiency phenotype Z consists of two copies of the *SERPINA1* gene with the same

mutation (Glu342Lys) and is determined by the genotype PI*ZZ. Also most of the pathology related to AAT deficiency is linked to the PI*Z allele, and in clinical practice, 96% of AATD patients have a homozygous genotype PI*ZZ.

Z-type AAT molecules polymerize within the hepatocyte, precluding secretion into the blood and causing low serum AAT levels. Only about 15% of Z protein is actually secreted into the plasma. One important circumstance that needs to be noticed is that children with the PI ZZ genotype and liver disease can have a plasma concentration of AAT that is as high as 40% of normal, thereby importantly influencing the threshold value which leads to the decision to test for the genotype.

Polymerization of the Z-type AAT also results in retention of aggregates of AAT in hepatocytes, leading to liver cirrhosis.

Cigarette smoking induces oxidation of Z-type AAT in the lung thereby promoting the adverse effect.

The second most prevalent is the PI*S allele, a deficiency allele characterized by the Glu264Val mutation. The S allele is characterized by accelerated degradation within the hepatocyte. The homozygous state for the S allele (so-called PI*SS) is not associated with clinical disease and a minority (~10%) of double heterozygotes with the Z allele (PI*SZ) have serum levels below the protective threshold value and are therefore at risk for developing COPD, especially if they smoke.

Other deficiency alleles include PI*Mmalton (p.Phe52del), PI*Siiyama (p.Ser53Phe), although these variants are rarely seen in the clinical practice.

3) In the ***dysfunctional*** group of phenotypes are alleles like PI*F and PI* Pittsburg, which lead to a normal serum concentration of AAT but with reduced function, thus leading to functional deficiency; e.g., with decreased binding to neutrophil elastase, as in the F variant, or with thrombin inhibitory activity, as in Pittsburgh variant. These variants are rare and correct figures of their frequency do not exist.

4) The ***null*** alleles, currently designated Q0, are characterized by absent circulating AAT due to transcriptional or translational errors that interrupt protein synthesis. The patients with these genotypes, which are extremely rare, have no detectable plasma levels.

AAT serum levels and their importance

The deficient, dysfunctional and null variants are related to clinically manifested disease, but actual development of disease and clinical severity of the disease mainly depends on the serum concentration of AAT.

The usual serum levels of AAT with regard of the genotype, as determined by an population based survey conducted on 6057 Caucasians of Swiss nationality (SALPADIA), are for PI*MM in the range of 1.050 to 1.640 g/L, for PI*MS between 0.880 to 1.369 g/L, for PI*SS 0.730 to 1.060 g/L, for PI*MZ 0.660-0.997, and for PI*ZZ between 0.490 and 0.660 g/L. An empirically determined serum AAT level of 0.8 g/L represents the protective threshold value below which the risk of emphysema is believed to increase. This threshold has not been evaluated since the SAPALDIA study published in 2012. The cut-offs determined by individual laboratories, bellow which samples should be selected for genotyping, currently ranges between 0.90 and 1.30 g/L. At our clinic we have a cut-off of 0.9 g/L.

SALPADIA suggested to set the cut-off at 0.92 g/L to avoid the loss of PI*Z and PI*S alleles as well as include cases where the inflammation status could increase serum AAT levels thus potentially leading to miss PI*MZ genotypes. The correct diagnosis of patients with the PI*MZ genotypes is crucial for different reasons. First,

these genotype leads to the so-called intermediate deficiency, where carriers indicate a slightly increased risk of developing COPD. This group of patients can be very well managed with just preventive measures like quitting smoking and change of unfavourable working environment. The second reason is that these patients are carriers of deficiency alleles which can be further transmitted to offspring thus being important for genetic testing and counselling of the whole family.

AATD epidemiology

AAT deficiency is still an underdiagnosed condition worldwide. Some studies indicate an about 8 year delay between first symptom and initial AATD diagnosis.

The prevalence of AATD is estimated to be in the range of 1 in 2000 to 1 in 5000, and every tenth European is a carrier of one of the most prevalent deficient alleles (PI*Z and PI*S). Approximately 4% of the north European population carries a PI*MZ genotype. The PI*Z prevalence is higher in northern and western European countries, whereas the PI*S prevalence is higher in south-western European countries.

No population based epidemiology data exists for Slovenia until now. The analysis of our hospital database revealed that in the period from beginning of 2005 when the genetic test was introduced until end of September 2013, in total 192 patients were genotyped. Among them 10.4% carried the PI*ZZ genotype and additional 1% was diagnosed as PI*SZ. Altogether 47% of the patients were carriers of the intermediate deficiency genotype PI*MZ. The finding of a deficient allele was followed by 34 family based surveys of carrier testing of relatives, which represents 53.6% of the analysed cohort. In the first three quarters of this year we noticed a 63% increase of sample submission for genetic analysis, compared to the average 21.5 samples sent in the last eight years.

Laboratory diagnosis of AATD and interpretation of genetic mutations

Testing for AATD should begin with determining the serum level of AAT. In the case that the serum level is below 0.9 g/L, the patient should be sent for genotyping, which provides the definitive diagnosis of AATD.

Important issues that need to be considered are that there are other conditions associated with low plasma concentration of AAT, which include: respiratory distress syndrome in newborns, severe protein loss, terminal liver failure, and cystic fibrosis. On the other hand, since AAT is an acute-phase reactant, its plasma concentration can be elevated into the normal range in PI*MZ heterozygotes. Up to fourfold increase were observed in inflammatory conditions, cancer, and liver disease. Therefore, only the detection of the involved genotypes can resolve the aetiology.

Patients with a borderline normal AAT serum level (0.9 – 1.1 g/L) and their first-degree relatives also should undergo genotyping, because these levels may correspond to an intermediate level phenotype (PI*SZ, PI*SS, PI*MZ), likely leading to identification of asymptomatic or misdiagnosed AATD family members.

In the Laboratory for Clinical Immunology and Molecular Genetics at the University Clinic Golnik, genotyping is routinely performed by allele-specific amplification using The Amplification Refractory Mutation System (ARMS™) ELUCIGENE™ AAT (Tepnel Diagnostics, Abingdon, Oxfordshire, UK), which detects the PI*M, PI*S and PI*Z alleles. This way we are detecting 95% of all deficient genotypes involved in AATD, since 95% of AATD results from presence of the PI*S and PI*Z variants. Targeted mutation analysis that is specific for detecting PI*Z and PI*S does not detect other rare deficiency alleles.

Sequence analysis detects rare and null alleles in *SERPINA1* that are not detected by targeted mutation analysis, but is rarely indicated. Sequence analysis is useful if targeted mutation analysis reveals only one disease-associated allele in an individual who meets diagnostic criteria for AATD; however, identification of both disease-associated alleles is not required for diagnosis.

The genetic test results should always be interpreted in the context of a clinical picture and family history, therefore we introduced a questionnaire (available on http://www.klinika-golnik.si/dejavnost-bolnisnice/klinicna-dejavnost/laboratorijska-dejavnost/datoteke/2013_vprasalnik_aat.pdf) which needs to be filled out and sent together with the sample to ensure the best possible interpretation of the reported result. This data point us to possible involvement of rare deficiency alleles.

Our laboratory is included in the external quality assessment scheme of INSTAND (Germany) and is successfully performing since the inclusion in year 2009.

Clinical genetics and genetic counselling

Genetic counselling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions and is an integrative part of every genetic testing. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible once the disease-causing mutations have been identified in the affected patient.

AATD is inherited in an autosomal recessive manner. When both parents are heterozygotes (e.g. PI*MZ), each child has a 25% chance of being affected (PI*ZZ), a 50% chance of being a carrier (PI*MZ), and a 25% chance of being unaffected and not a carrier (PI*MM). In the rare instance in which one parent is homozygous (PI*ZZ) and one parent is heterozygous (PI*MZ), the risk to each sibling of being affected is 50% and their offspring will be obligate heterozygotes (carriers; PI*MZ) for the disease-causing mutation.

Prenatal testing is possible but conflicting because of a small incidence of grave clinical manifestations in the form of hepatic failure in about 2% of children with detected PI*ZZ genotype. Also effective preventive measures and effective treatment is available.

Conclusions

Major gaps in understanding AATD still persist, including the precise mechanism and risk factors for liver disease, clarification of determinants of emphysema beyond cigarette smoking and occupational risk, the role of genetic modifiers of disease expression, and optimal therapy. We need to be aware of the disease since normal life span with good health can be assured for patients with AATD and possible carriers if the disease is diagnosed early and simple and cost effective preventive measures are implicated. The increase of samples submitted to our laboratory for genotyping in the last year shows us, that we are starting to be aware of the disease and that our patients can benefit the most from preventive measures.

Take home messages

1. Think of AATD in a patient with early onset COPD / emphysema and / or chronic liver inflammation, cirrhosis or hepatic carcinoma and test for AATD deficiency.
2. First line screening test is the determination of the serum level of AAT. In the case it is below 50% of the normal value (threshold 0.9 g/L), send for genetics.

3. Serum levels of AAT are not enough for a definitive clinical diagnosis, the genotype must be determined. Some other conditions can be associated with low plasma AAT level and other conditions, especially acute inflammation, can be associated with higher plasma AAT concentration, probably leading to no further testing of the genotype, thus missing the diagnosis of AATD.
4. The genetic test does not cover all variants responsible for the AATD. The mutation detection rate for AATD of our routinely used genetic test is 95% of all deficiency alleles leading to clinical manifestations.
5. For the appropriate interpretation of the genetic test result we need clinical information, including AAT serum level, lung and / or liver manifestation and current inflammation status.
6. In the case a patient has been recognised to carry a deficiency allele, the whole family can be affected, since AATD is a hereditary genetic disease. Therefore good pedigree data of family members with possible similar clinical manifestations is needed, to suggest further testing of these family members. Genetic testing for mutation carrier state is here performed for preventive reasons and possible family planning. For every carrier testing, the genotype of the affected patient needs to be determined first.
7. Genetic counselling should be an integrative part of the genetic test, to give the possible carriers an opportunity to make informed decisions regarding genetic testing.

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Retrospective analysis of our patients with idiopathic pulmonary fibrosis

Tina Jerič, Katarina Osolnik, University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia

Background: Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occuring primarily in older adults, limited to the lungs, and associated with the histopatological and/or radiologic pattern of UIP (usual interstitial pneumonia). It is a fatal disease with variable natural history. Median survival time is 2-3 years from the time of diagnosis.

Methods: A retrospective analysis of patients' data from hospital's database Birpis. Patients diagnosed with IPF in University Clinic Golnik from 1993 till 2012 were included.

Results:

Analyzed parameters	**Results**
Patients	213 patients, 136 (64%) male, 77 (36%) female
Number of diagnosed patients	1-30 new patients per year, average 10,6
Age	36,8–90,6 years, median 72,1 years
Symptoms	200 (93,3%) patients complained about symptoms, 167 (78,4%) patients with dyspnea, 142 (66,7%) with cough
Duration of symptoms	2 days–20 years, average 14 months, median 4 months
Smoking	20 (9%) patients current smokers, 75 (35%) ex-smokers, 84 (40%) never smokers, 33 (16%) patients with no data about smoking history.
HRCT	Performed in 189 (88,7%) patients, in 152 (79%) patients UIP (usual interstitial pneumonia) pattern was present.
Bronchoscopy	Performed in 156 (72,2%) patients, diagnostic in 23 (14,7%) patients.
Surgical lung biopsy	Performed in 30 (14,1%) patients, in 27 (90%) patients UIP pattern was present.
Therapy	113 (53%) patients were treated, 54 (47,8%) patients with glucocorticoids, 21 (18,6%) with glucocorticoids and an immunomodulator, 16 (14,2%) with glucocorticoid, an immunomodulator and acetylcysteine, 16 (14,2%) with acetylcysteine, 6 (5,3%) patients with glucocorticoid and acetylcysteine
Survival	Median survival 2,7 years, 5-years survival 25,4%.

Conclusions: Median survival of our patients was 2,7 years, 5-years survival was 25,4% which is comparable with data from the literature. No statistically significant differences were found in survival of treated and untreated patients.

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An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med Vol 183. pp 788–824, 2011.

New technologies in interventional pneumology (Aleš Rozman)

20'	Contribution of EBUS to lung cancer diagnostics	Aleš Rozman
20'	Radiofrequency ablation of lung tumors	Igor Požek
20'	Bronchial thermoplasty	Aleš Rozman
30'	Endoscopic treatment of lung emphysema	Franz Stanzel (Hemmer)

Contribution of EBUS to lung cancer diagnostics

Aleš Rozman, University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia

Several techniques are available for diagnostic work-up in lung cancer, where major part play flexible bronchoscopy and guided transthoracic needle aspiration to some extent. In recent decade new techniques of guided biopsy were developed in order to improve accuracy and thus diagnostic yield of invasive procedures in lung cancer diagnostics. One of the most successful and widely used is endobronchial ultrasound guided fine needle aspiration (EBUS-FNA). This real-time guidance technique provides less invasive diagnosis of centrally located tumors and lymph nodes, which lie adjacent to trachea, main bronchi and esophagus.

Endobronchial ultrasound equipment

Two types of endobronchial ultrasound (EBUS) equipment are available for flexible bronchoscopy: the radial probe EBUS and the convex probe EBUS. The radial 20-MHz probe with water-inflatable balloon was introduced first. It allows visualization of surrounding structures of large airway as well as bronchial wall structure. However, it doesn't allow real-time biopsy guidance and blockage of central airways during balloon inflation limits its use especially in patients, which are not in general anesthesia and/or have borderline respiratory capacity. With exception of very limited range of indications (estimation of depth of tumor invasion) it was replaced by convex probe EBUS.

7,5 MHz convex probe EBUS is the integral part of dedicated flexible bronchoscope and allows real-time guided fine needle aspiration biopsy. The curved array of transducers scan in parallel to the long axis of the bronchoscope in range of 2 to 24 cm. Images are processed in dedicated ultrasound processor and displayed in B-mode or in the Color Power Doppler mode. The later feature allows clear differentiation between circular lesions and blood vessels, where we are in doubts (Figure 1). With freeze function lesions can be measured in two dimensions as well. There are two sizes of dedicated needles available to perform EBUS-FNA: 21 and 22-gauge. Needles are equipped with locking mechanism; safety adjuster knob and safety stop to prevent uncontrolled excessive protrusion. The length of the extruding part of needles is 40 mm. Needles are also equipped with internal stylet, which prevents contamination before needle insertion and facilitates removal of the biopsy specimen.

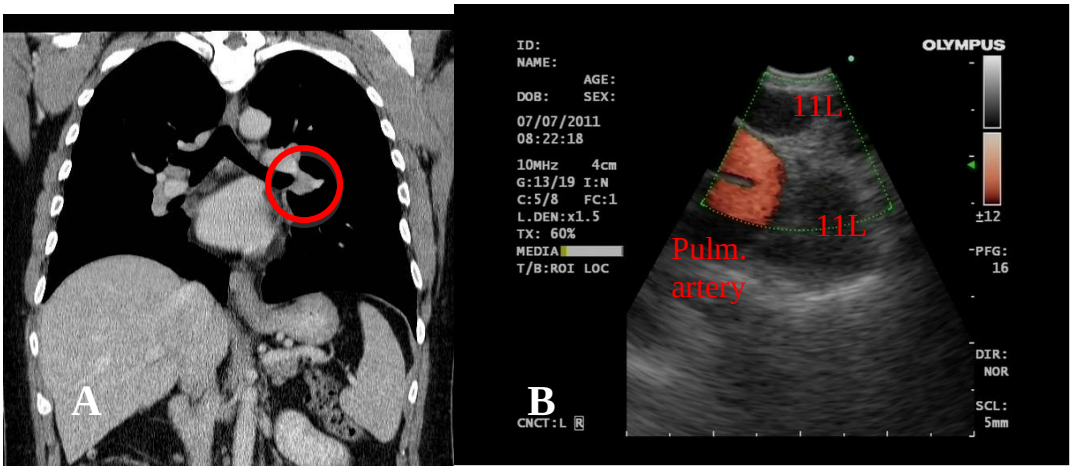

Figure 1. Lymph node in position 11L, adjacent to branching left pulmonary artery. A – CT scan, B – EBUS with Color Power Doppler.

Indications for EBUS-FNA

EBUS-FNA is indicated in diagnosis of suspected lung cancer or other mediastinal cancers, when the lesion is in the range of biopsy needle and no endobronchial abnormality is present. Moreover, it is advocated as one of the initial staging procedures in patients with non-disseminated lung malignancy. Biopsy provides sufficient cytological material for immunocytochemistry and DNA isolation, which may allow individualized treatment decisions according to specific tumor features (i.e. EGFR mutations, etc.). The lymph nodes, accessible by EBUS-FNA are in positions 2, 3p, 4, 7, 8, 9, 10 and 11, which extends the range of standard cervical mediastinoscopy.

The role of EBUS-FNA in mediastinal staging

The chest CT scan is an important first step to structure the subsequent staging of lung cancer patients. After exclusion of metastatic disease, patients can be separated into four categories with respect to primary tumor and mediastinal lymph node features.

- Radiographic group A (Figure 2): massive mediastinal infiltration, where discrete lymph nodes cannot be distinguished or measured. We recommend the classical “semi-blind” TBNA which has sufficient accuracy for diagnosis / staging.

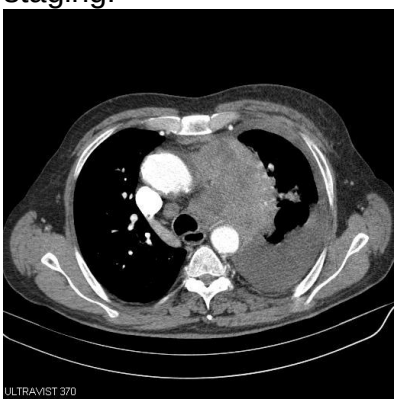

Figure 2. Radiographic group A.

- Radiographic group B (Figure 3): discrete lymph nodes, larger than 1 cm in short-axis diameter on transverse CT image (false-positivity rate cca. 40%). We recommend EBUS-FNA staging because of superb accuracy.

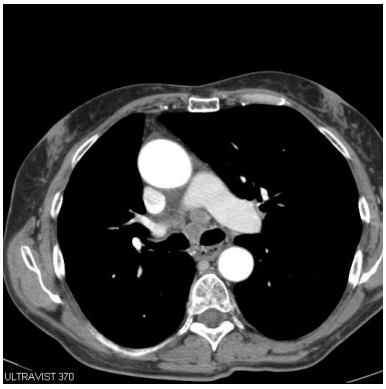

Figure 3. Radiographic group B.

- Radiographic group C (Figure 4): normal mediastinal lymph nodes but enlarged N1 lymph nodes or tumor within proximal one-third of the hemithorax (false-negativity rate 25 – 30%). We recommend EBUS-FNA staging because of superb accuracy.

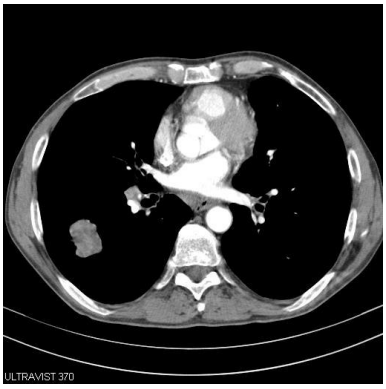

Figure 4. Radiographic group C.

- Radiographic group D (Figure 5): normal mediastinal and N1 lymph nodes, peripheral tumor. No invasive staging is required.

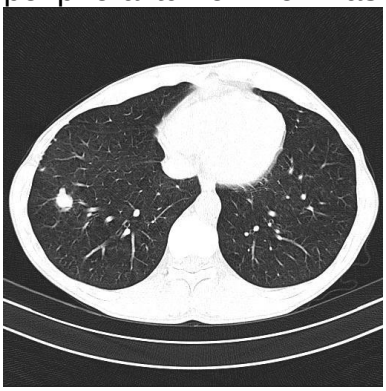

Figure 5. Radiographic group D.

Procedure description

EBUS-FNA is an advanced bronchoscopy technique, which requires additional training in order to develop required skills. Profound knowledge of mediastinal anatomy is of utmost importance for proper selection of biopsy targets and prevention of complications. EBUS-FNA can be performed as an outpatient procedure under local anesthesia and moderate level of sedation. The bronchoscope can be inserted nasally or orally, but some prefer insertion through endotracheal tube or rigid bronchoscope. The insertion through tube limits the contact with upper part of the trachea and accessibility of lymph nodes at position 2. After insertion of the bronchoscope we recommend systematic examination of the mediastinum by pressing the tip of the probe onto the airway. Balloon on the EBUS probe can be filled with saline in order to improve contact with bronchial wall and visualization of mediastinal structures. Once the lymph is found, the FNA needle is attached onto the working channel and its length adjusted. When the puncture is made and the tip of the needle is visible in the lymph node, the stylet is removed and syringe with negative pressure is attached on the external part of the needle. Several back and forth excursions within the lymph node are made to sample larger area of the node. Than negative pressure is detached and needle removed. Aspirated specimen is removed and smeared onto glass slides, air-dried and stained for rapid on-site evaluation or processed for further analysis. EBUS-FNA should be performed from distal (N3) to proximal (N1) lymph nodes to avoid upstaging in the case of contamination. After endobronchial staging, the bronchoscope can be gently introduced into esophagus and lymph node positions 8 and 9 checked for additional staging (Figure 6).

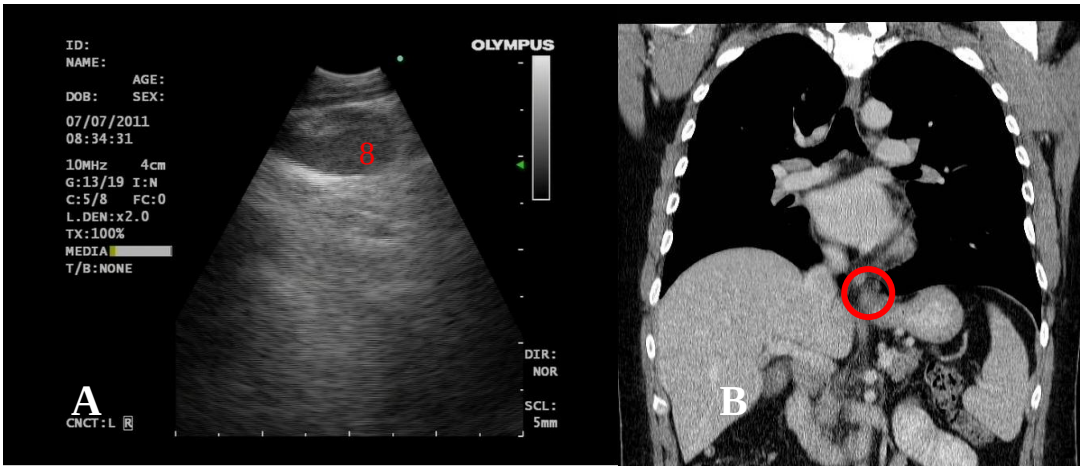

Figure 6. Lymph node position 8. A – EBUS, B – CT scan.

Results

Current large metaanalysis (Chest / May 2013) of EBUS-FNA for mediastinal staging revealed overall median sensitivity 89% and median negative predictive value 91%. In combination with lower mediastinal staging both values rise to 91% and 96% respectively. Two studies were published, where EBUS-FNA was also used for lower mediastinal staging (Hwangbo B, et al. Chest 2010, Herth FJ, et al. Chest 2010) with similar success as with EUS-FNA.

Conclusion

EBUS-FNA may be the preferred method for staging and, perhaps, initial diagnosis of patients with lung cancer, limited to the chest. It is superior to non-invasive staging modalities (CT, PET) and may be similar to mediastinoscopy. For the time being the accepted strategy for mediastinal staging is EBUS-FNA, followed by mediastinoscopy if the first one is negative.

Further reading

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Radiofrequency Ablation (RFA) of Malignant Lung Tumors

Igor Požek, University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia

Introduction

Over the last 10 years percutaneous thermal ablation has increasingly been performed on solid tumors of the liver, kidney, mammary and adrenal glands. It is also increasingly being used for lung tumors, with the aim of local tumor control. Radiofrequency ablation (RFA) is the procedure for which there is the most clinical experience to date; new thermal procedures that are particularly promising for the treatment of lung tumors are cryoablation, microwave ablation, and laser-induced thermal therapy.

Indications

The standard of care for stage I nonsmallcell lung carcinoma (NSCLC) is generally accepted to be surgical resection. In patients who are deemed not to be candidates for surgery as a result of high comorbidity or reasons relating to pulmonary function, various treatment strategies are available, including observation, conventional fractionated radiotherapy, stereotactic body radiotherapy and RF ablation. It is generally accepted that observation and conventional radiotherapy offer survival rates that are inferior to the other therapeutic strategies. According to the American College of Chest Physician (ACCP) either stereotactic radiation therapy or RF ablation should be offered to patients who are medically inoperable. RF ablation can be a reasonable therapy even for selected patients with more advanced cancer. Such patients would include those with stage IIIb disease (based on a second nodule within the same tumor lobe) or stage IV disease based on a satellite nodule within another lobe. Additionally, patients with advanced stage disease who may be treated with RF ablation include those who have responded to definitive radiation and chemotherapy but have a persistent solitary peripheral focus of cancer, and those who present with a recurrent isolated cancer after previous lung resection. RF ablation can be considered when the tumor is ≤3 cm in diameter, the tumor is located at least 1cm from trachea, main bronchi, oesophagus.
Selected patients with limited pulmonary and hepatic colorectal metastatic disease, may qualify for percutaneous treatment provided that extrapulmonary disease is deemed curable. RF ablation has also been found to be useful for patients presenting with recurrent metastatic disease after a previous thoracotomy because it avoids some of the morbidity of a redo thoracotomy. Most centres preferentially treat patients with five or fewer lesions. In patients with lung metastases from other primary cancers, promising initial results have been reported in the treatment of metastases from renal cell carcinoma and sarcoma.

Contraindications

Absolute contraindications for ablation procedures are severe coagulation disorders and life expectancy of less than three months. A relative contraindication is central tumor location and proximity to large blood vessels. Thermal dissipation due to the vascular blood flow results in a high risk of recurrence and increased risk of hemorrhage.

Procedure

Radiofrequency ablation (RFA) is currently the most widely used procedure for interventional treatment of malignant lung tumors, usually performed under CT

guidance. Ablation is performed under sedation analgesia, local anesthesia of the needle track, or general anesthesia. High-frequency sine wave alternating current (375 to 460 kHz) is applied to the tumor. For monopolar RFA, the current must be diverted through large grounding pads on the thighs; for bipolar RFA it flows between the poles at the tip of the RF probe. The resulting friction (at temperatures of 60 to 100 °C) gives rise to protein denaturation and coagulative necrosis. If the site is close to the broncho - vascular bundle, pulmonary veins, mediastinal organs, or chest wall, this must be taken into account when planning the procedure: In these cases the cooling effect of perfusing pulmonary vessels close to the zone of ablation reduces the local effect of tissue heating. Inclusion of the bronchovascular bundle in ablation can lead to infarction and favor postinterventional cavity or fistula formation. Central tumors are therefore problematic, whereas peripheral foci and foci surrounded on all sides by the pulmonary parenchyma are suitable for percutaneous ablation. A small amount of contact with the pleura has no substantial effect on current flow but in approximately 20% of cases can lead to postinterventional pleurisy with pleural effusion. In order to increase local effectiveness, particularly for larger tumors the impedance of the treated tumor tissue can be reduced by introducing concentrated saline solution through the RF probe.

Results

In stage I NSCLC following RFA (as a result of functional ineligibility for surgery), small case series report one-year survival of 67% to 97%, two-year survival of 35% to 74%, and five-year survival of 20% to 61%. No significant long-term deterioration in pulmonary function parameters (VC, FEV1) following RFA has been reported to date. No prospective randomized trials comparing ablation to other local procedures (stereotactic radiotherapy, limited surgical resection) are available. A retrospective comparative study found no significant difference in survival between patients who underwent limited resection as a result of functional limitations and those who received RFA.

In the setting of colorectal cancer lung metastases, survival rates provided by RF ablation in selected patients, are substantially higher than those obtained with any chemotherapy regimens and provide indirect evidence that RF ablation therapy improves survival in patients with limited lung metastatic disease.

Complications

Peri-interventional or postinterventional pneumothorax is described as being the most common complication following percutaneous tumor ablation (30%), but chest drainage is required in only approximately 10% of patients. Smaller alveolar hemorrhages are relatively common. In individual cases, hemorrhagic pleural effusion or hemothorax has occurred after ablation. A productive cough may be slightly tinged with blood two to four weeks after ablation. Pain, which can begin up to two weeks after ablation, is usually caused by pleural irritation if a peripheral tumor has been ablated. Postinterventional reactive effusions may require drainage. Cavity formation as result of tumor colliquation or of postinterventional pneumonia following RFA are reported in up to 30% of cases. Only rarely do they induce further complications but in individual cases infection or hemorrhage may occur.

Conclusion

Percutaneous thermal ablation broadens the range of treatment options for patients who are not candidates for surgery. Tumor ablation should always be indicated on

the basis of interdisciplinary consensus through a tumor board (including pulmonologists, oncologists, thoracic surgeons, radiotherapists and radiologists).

Our experience

We have treated 11 patients since february 2006. All patients had NSCLC stage I (9 patients stage IA and 2 patients stage IB). They were not suitable for surgical resection of lung tumor due to accompanied cardiac and lung diseases, poor lung function or very old age.

All ablations were technically successful, with correct placement of the ablation device into the target tumour and completion of the planned treatment protocol. Local anesthesia to the skin and pleura was given at the needle entry site. Thoracic epidural anesthesia was used in 7 patients and conscious sedation or brief anaesthesia in others.

During the procedure all patients were stable and pain-free. In two patients pneumothorax occurred during the procedure, for which we have not stopped the ablation.

After the procedure most of treated patients (8/11) felt some pain. In three patients pleural effusion developed, which resolved spontaneously after one to two months. Two patients got pneumonia, which was successfully treated with antibiotics and in two exacerbation of COPD with transient respiratory insuficiency.

Follow up with contrast enhanced CT was performed 1, 3, 6 and 12 months after the treatment and in yearly intervals after that. In one patient PET/CT scan was done 2 months after the procedure.

In both tumors larger than 3 cm local recurence was seen on the edge of ablation after 6 months. Both tumors were not ablated with a safety margin, due to unfavorable location. In one patient satelite nodules around ablated tumor developed after one year in the same and also in other lobes. Three patient were lost to follow up, one died a year after ablation and one more than three years after ablation for other medical reasons. The rest are so far without evidence of local tumor recurence.

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Bronchial thermoplasty

Aleš Rozman, University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia

Asthma is chronic inflammatory airway disease, where patients typically experience recurrent episodes of dyspnea, wheezing, chest tightness and cough. Many cellular elements are involved in the initiation and propagation of inflammation, including mast cells, eosinophils, lymphocytes, macrophages etc. The appearance of symptoms is associated with airflow obstruction, which is reversible with treatment or spontaneously. The inflammation causes bronchial hyperresponsiveness to various stimuli and is the cause of airway remodeling with time. Airway remodeling refers to structural changes of airway wall with epithelial changes, subepithelial fibrosis, goblet cell metaplasia, blood vessel hyperplasia and hypertrophy of airway smooth muscles. The consequence of airway remodeling is irreversible airway obstruction.
Current asthma treatment includes anti-inflammatory (controller) and bronchodilator (reliever) medications. Anti-IgE antibody is the first treatment based on modulation of pathophysiologic characteristics of asthma. No pharmacologic treatment exists, which could be effective against increased smooth muscle cell mass, which is also an important factor in asthma pathophysiology.
At the moment we are mostly not able to treat asthma with curative intent. The major goals of treatment are to establish good control over asthma symptoms, to normalize exercise performance of patients, to prevent exacerbations and to prevent or to slow down airway remodeling and thus transition to irreversible obstruction of the airways.

Bronchial thermoplasty

Bronchial thermoplasty is a novel interventional method for asthma treatment, designed to reduce the amount of airway smooth muscle mass. The goals of such treatment are: decreased bronchoconstriction, reduced frequency and reduced severity of asthma symptoms. Bronchial thermoplasty is a part of complex interventional bronchoscopy procedure and should be therefore performed by an experienced bronchoscopist.
The therapeutic effect of bronchial thermoplasty is achieved by controlled heating (to 60 deg. C in duration of 10 s) of the airway wall, but all mechanisms are not yet fully elucidated. Thermal energy, induced by radiofrequency electrical energy from probe denaturates actin-myosin complexes and interactions within them. The immediate loss of muscle cell function (manifested by reduced hyperreactivity) is followed by reduced smooth muscle cell mass in the bronchial wall.

Procedure

Bronchial thermoplasty is performed by flexible bronchoscopy on patients under at least moderate level of sedation and topical anesthesia. Specially designed catheter with expandable electrode array is inserted through working channel of the bronchoscope (Figure 1).

Figure 1. Catheter with expandable electrode array for bronchial thermoplasty.

Catheter is attached to controller, which delivers electrical energy in the correct intensity and duration. All bronchi with diameter between 3 and 10 mm with exception of the middle lobe bronchi are treated in tree separate sessions with at least 3 weeks apart from each other. Divided treatment minimizes the risk of diffuse airways edema that might affect the entire bronchial mucosa in the case of single-session treatment. During the first session we usually treat right lower lobe, during second left lower lobe and during the last session both upper lobes. Middle lobe is avoided because of long, narrow lobar bronchus, where might treatment in theory induce middle lobe syndrome. Bronchi of selected lobe are treated systematically, from distal to proximal. Electrode is placed at the target region, 4 electrode wires are expanded until in contact with the airway wall and controller is activated by a footswitch. After 10 s cycle, during which the energy is delivered to the bronchial wall, electrode array is collapsed and repositioned for 5 mm proximally (Figure 2). This process is repeated until all bronchi in the selected lobe are treated.

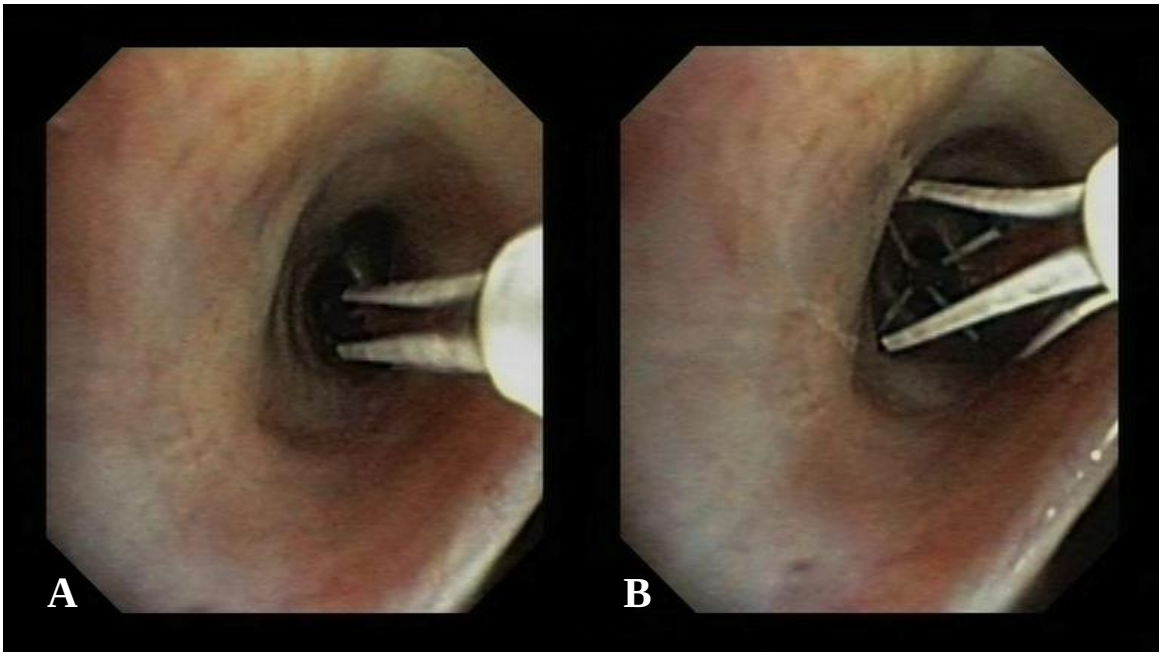

Figure 2. A – catheter for bronchial thermoplasty with collapsed electrode array. B – electrode array expanded, in position for delivering energy.

Patient selection

To assure the proper selection of patients for bronchial thermoplasty a medical team of asthma specialist and experienced bronchoscopist should consider all indications and contraindications. Patient is appropriate candidate for procedure when selected on the basis of patient populations that have been studied in clinical trials and meets criteria for the safe bronchoscopy.

Minimal criteria are:

1. Adults with documented diagnosis of asthma
    - documented reversible decrease in FEV1 or
    - airway responsiveness by metacholine challenge
2. Nonsmoker for 1 year or more (if former smoker, < 10 pack years)
3. Symptomatic despite treatment with stable maintenance medication (fluticasone > 500 mcg/d or equivalent with or without LABA)
4. Prebronchodilator FEV1 at least 60% predicted
5. Stable with respect to asthma
    - no current respiratory tract infection
    - no severe asthma exacerbation within last 2 weeks
    - FEV1 within 10% of the best value
6. Able to safely undergo bronchoscopy
7. No known sensitivity to medications required to perform bronchoscopy
8. No known unstable comorbid conditions that would present a risk for bronchoscopy
9. No internal pacemaker or neurostimulator.

Side effects of treatment

After bronchoscopy with bronchial thermoplasty treatment there is an expected worsening in respiratory-related symptoms in the period of first few days after the procedure. Patients might experience breathlessness, localized wheezing, cough, chest discomfort, night awakenings and productive cough. These symptoms typically disappear within one week.

Clinical data

Data about safety and effectiveness of bronchial thermoplasty were obtained during several clinical studies. A feasibility study was a multicenter, single-arm, non-randomized study, designed to evaluate the long-term safety in stable asthmatic patients with mild to moderate asthma. AIR trial was a multicenter randomized controlled trial, designed to evaluate safety and efficacy in patients with moderate to severe asthma. RISA trial was designed to evaluate safety of bronchial thermoplasty in symptomatic, severe, persistent asthma patients, who were symptomatic despite treatment with high dose medications (inhalational and oral corticosteroids and LABA). AIR 2 was a pivotal study that contained majority of all treated patients. The study was multicenter, randomized, double-blind, sham-controlled designed to evaluate effectiveness and safety of treatment in a population of patients with severe asthma, who were still symptomatic despite conventional therapy with high-dose inhaled corticosteroids and LABA. Key findings were:

- improved asthma quality of life
- 32% reduction in severe exacerbations
- 84% reduction in emergency room visits for respiratory symptoms
- 73% reduction in hospitalizations for respiratory symptoms

- 66% reduction in lost time from work, school or other daily activities due to asthma
- 36% reduction in asthma (multiple symptoms) adverse events
- no deterioration of FEV1 over time.

High resolution CT scans didn't reveal bronchial dilation, bronchiectasis, bronchiolitis obliterans or emphysema afre one year. There were no incidences of pneumothorax, intubation, mechanical ventilation, airway stenosis or focal narrowing, cardiac arrhythmias or death after bronchial thermoplasty. 5-year follow-up of patients treated with bronchial thermoplasty showed in comparison with pre-treatment year:

- 44% reduction in severe exacerbations
- 78% reduction in emergency room visits for respiratory symptoms
- no deterioration of FEV1 over time, despite a 18% reduction in average daily inhaled corticosteroid dose
- HRCT showed no structural abnormalities that could be attributed to bronchial thermoplasty.

Conclusions

Bronchial thermoplasty is a novel treatment for patients with severe asthma who remain symptomatic despite adherence to high levels if inhaled corticosteroids or/and LABA. Treatment may improve the quality of life of asthma patients and reduce the rate of severe exacerbations and emergency department visits. There is significant decline in lost days from work and school because of asthma symptoms. It seems, that the effect is quite durable and complication rate low. However, patients with most severe asthma were not included and the method is not tested in patients with severe and frequent exacerbations and low FEV1. Proper selection of the patients and optimal pre- and post-operative management is of great importance for successful results.

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Metabolic and nutritional aspects in COPD (Mitja Lainscak, Annemie Schols (Maastricht, NL))

20	Many faces of malnutrition and metabolic issues in COPD	Annemie Schols
20'	Pulmonary rehabilitation: referral and nutritional implications	Frits Franssens
10'	Facts and numbers	Mitja Lainscak
40’	Panel discussion: Timing the intervention: when, how, and in whom	Mitja Lainscak, Annemie Schols, Frits Franssens,

Obstructive lung diseases (Sabina Škrgat, Mitja Košnik)

30'	Asthma endotypes	Stanislav Šuškovič
30'	COPD phenotypes	Wisia Wedzicha
15'	Occupation asthma: pitfalls and diagnostic approach	Matjaž Fležar
15'	Occupation asthma: view of occupational medicine	Metoda Dodič

Endotypes in asthma

Stanislav Šuškovič, University Clinic of Respiratory and Allergic Diseases Golnik

Asthma is a common chronic inflammatory disorder of the lung with variable airway obstruction, wheeze/cough, bronchial hyperresponsiveness and progressive airway remodeling. It was clearly confirmed, that wide heterogeneity exists within the population of patients with asthma ("asthma symptoms"). Asthma is generally recognized as a complex disease with variable severity, natural history, and response to treatment. Such heterogeneity in the disease clearly suggests a personalized approach in the treatment of asthma. But how? Treating asthma based on **phenotypes**[1] , which are observable characteristics with no direct relationship to disease mechanisms, demonstrated some successes yet remains suboptimal, given the variability in treatment response. There are many ways for defining different asthma phenotypes. For example 3 most relevant clinical phenotypes are the following:

(a) Frequent severe exacerbations with periods of relative stability between exacerbations (asthma with frequent severe exacerbations)

(b) Irreversible airway obstruction (asthma with fixed airflow obstruction)

(c) Asthma requiring systemic corticosteroids for its routine control (glucocorticoid-dependent asthma).

However, when combined with **endotypes**[1], which describes subpopulations of a disease with similar molecular mechanisms based on cellular and molecular mechanisms, including the reactivity of structural cells or treatment response, it is to be expected to produce more effective treatment responses.

Inhaled glucocorticoids (ICS) are the basics of asthmatic medications because of their relatively nonspecific and wide anti-inflammatory actions Glucocorticoid acts by binding to glucocorticoid receptors in the cytoplasm, and histone acetyltransferase acetylates glucocorticoid–glucocorticoid receptor a complex and facilitates the translocation into the nucleus. Where suppresses inflammation by regulating the expression of several immune genes. However, ICS are not effective in all asthmatics. For asthmatics with steroid hyporesponsiveness advanced airway remodeling is common. Steroid nonresponsiveness - resistance in asthma on the other hand mostly relates to glucocorticoid receptor dysfunction and deregulation of histone acetylation and deacetylation. In short: obviously many asthmatics need other therapeutic modalities.

Asthma has been traditionally viewed as an eosinophilic airway inflammatory disorder[2] as a manifestation of the Th2 response, which is characterized by the of Th2 cytokines such as IL-4, IL-5, IL-9, IL-13, and IL-33. However, in severe asthma, increased expression of other cytokines including interferon-gama, IL-8, IL-18, and IL-17 has been found in bronchial biopsies, and it have been found non-Th2 genes to be associated with severe asthma. Also, neutrophils and mast cells are appearing to be important effector cells in some severe asthmatic individuals. Again, these observations are clearly indicative of the vast heterogeneity in severe asthma, which clearly differs from mild-moderate asthma[3].

Variability in clinical characteristics, inflammatory profiles and responses to treatment has made it increasingly clear that severe asthma is not a single disease. Treating asthma based on phenotypes has been shown to be suboptimal in contrast to endotyping groups of asthmatics on the basis of underlying molecular mechanisms or treatment responses seems to be more therapeutically rewarding . At present, some

successes have been achieved in clinical trials when treatments are tailored to endotypes.
In order to differentiate between the various endotypes, 7 different parameters have been identified as most clinically relevant. Six endotypes that meet at least 5 of the 7 suggested parameters (clinical characteristics, biomarkers, lung functionalism, genetics, histopathology, epidemiology, and response to treatment) have been proposed. Endotypes of the PRACTALL[4] consensus are shown below.
Wenzel[5] proposed another classification of severe asthma endotypes.

Endotypes of Severe Asthma

PRACTALL Consensus[4]	Wenzel[5]
• Aspirin-sensitive asthma	• Early-onset allergic asthma
• Allergic bronchopulmonary mycosis	• Persistent eosinophilic asthma
• Allergic asthma (adults)	• Allergic bronchopulmonary mycosis
• Preschoolers with wheezing and positive asthma predictive indices	• Obese female
• Severe late-onset hypereosinophilic asthma	• Neutrophilic asthma
• Asthma in cross-country skiers	

Thus, personalized medicine has become the realm of future medicine. Physicians are getting closer to being able to 'tailor' a treatment scheme on the basis of the specific individual's biological data such as genomic, transcriptomic, and proteomic profiles, in addition to the traditionally defined asthma phenotypes.

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Cronic critical disease; Infections in immunocompromised patients (Franc Šifrer, Viktorija Tomič)

20'	Chronic critical illness- success or failure of medicine	Franc Šifrer
20'	Planning of comprehensive care of elderly	Gregor Veninšek
20'	End-of-life decisions in the Slovenian ICUs-a cross sectional survey	Grošelj U
20’	Value of microbiology in chronic critical illness	Viktorija Tomič

CHRONIC CRITICAL ILLNESS

Franc Šifrer, University Clinic of Respiratory Diseases and Allergy, Golnik

Introduction

Chronic critical illness (CCI) is a devastating condition for patients and their families. The hallmark of CCI is respiratory failure and ventilator dependency. Additional characteristics include profound weakness attributed to myopathy, neuropathy, and alterations of body composition including loss of lean body mass, increased adiposity, and anasarca; distinctive neuroendocrine changes; increased vulnerability to infection; brain dysfunction manifesting as coma or delirium that is protracted or permanent, incontinence and prolonged immobility. Symptoms include pain, thirst, dyspnea, depression, and anxiety. Managing CCI include ventilator weaning, nutritional support, rehabilitation, and palliative care. It is important to put efforts to prevent the transition from acute critical illness to CCI.

Pathophysiology

The hallmark of CCI is prolonged, rampant inflammation after acute critical illness that leads to progressive multi-organ dysfunction. In the acute phase of critical illness (which has a physiologically defined time frame to be 7-14 days after the acute injury or illness), the sympathetic nervous system, immune system and adrenal-endocrine systm all increase their activity to maintain cardiac output and organ perfusion. This is now reffered to as allostatic response., which can be summarized as an inflammatory response. In the acute phase these responses are adaptive. The allostatic response, if not turned off by resolution of the underlying problem, becomes maladaptive- this is referred to as allostatic load or burden. This change occurs between days 7-14 after the acute insult. The very chemicals designed for initial survival in acute critical illness lead to the issues of CCI. Persistent allostatic load leads to global tissue and organ damage. CCI is the price organs and tissues pay for persistent allostatic load and results in survival without recovery.

Epidemiology

Although advances in intensive care have enabled more patients to survive an acute critical illness, they also have created a large and growing population of CCI patients with prolonged dependence on mechanical ventilation and other intensive care therapies. Up to 10% of patients who require mechanical ventilation for acute conditions develop CCI. Patients from any type of medical or surgical intensive care unit can be affected. On the basis of data from foreign statewide databases, the mean age for adult patients is 65, for those in specialized weaning facilities it is in the eight decade. Patients are evenly divided according to sex, and comorbidities are common. Patients with trauma as an admitting diagnosis are ussually younger, more likely male, and have fewer comorbities. More than one-third of CCI patients receive care in teaching hospitals.

Clinical features

The hallmark of CCI is respiratory failure requiring prolonged dependence on mechanical ventilation. Although the term »prolonged mechanical ventilation« has been used in the literature to describe periods of ventilator dependency ranging from 2 days to 4 weks, this period is usually measured in weks for the chronically ill. Besides prolonged ventilator dependence, evidence suggests that CCI is a syndrome comprising additional characteristic features. These include profound weakness

attributed to myopathy, neuropathy, and alterations of body composition including loss of lean body mass, increased adiposity, and anasarca; distinctive neuroendocrine changes including loss of pulsatile secretion of anterior pituitary hormones, contributing to low target organ hormone levels and impaired anabolism; increased vulnerability to infection, often with multiresistant microbs; brain dysfunction manifesting as coma or delirium; skin breakdown associated with nutrional deficiencies, edema, incontinence, and prolonged immobility. Patients report significant distress from symptoms including pain, thirst, dyspnea, depression, and anxiety. Some of these features (e.g. brain dysfunction, symptom distress) may be present during acute critical illness but their prolonged duration and intensity in the chronic phase of critical illness are distinctive. Other features (e.g. changes in body composition and neuroendocrine patterns) have been described only in the chronic phase.

Although patients who remain ventilator dependent are at higher risk of death, successful weaning (between 30 and 53%) does not ensure long-term survival. Acute care hospital mortality for unselected patients is generally reported in the range of 20-49%. One-year mortality across study populations is 48-68% with little change over the past 20 years. Compared with patients requiring short-term ventilation, the risk of death in CCI patients remains particularly high between 60 and 100 days after initiation of mechanical ventilation. Nearly all patients with CCI leave the hospital with profound impairements of physical function, cognitive status, or both, and most therefore require institutional care. Patients discharged to extended care facilities who cannot be sufficiently rehabilitated for return to home by 6 months usually remain institutionalized until death. Fewer than 12% of CCI patients are alive and independent 1 year after their acute illness. So CCI also imposes heavy burdens on families, who experience high rates of depression and practical and financial hardships. Burdens for families are not limited to those who provide the care at home: depressive symptoms, caregiving overload, and physical deterioration may actually be more severe among families of patients who are institutionalized than of those who return home.

Treatment challenges

Empirical research to define effective methods of treatment remains scant. Most data on specific therapeutic approaches derive from descriptive studies conducted in single centers, leaving clinicians to rely mainly on their own experience and extrapolation of evidence from studies of acutely critically ill patients, which may lack external validity in this setting.

Comprehensive care for the CCI patients includes multiple components with five key goals: ventilator liberation, nutritional support, cognitive and functional recovery, prevention of complications, and attention to paliative needs. Given the unique and complex challenges, a dedicated interdisciplinary team of professionals may be best equipped to provide this care.

Liberation from ventilator use protocol-driven approach to weaning and decannulation. For optimizing function and cognition it is important to iniatiate physical activity early and minimize use of deliriogenic medications. In providing nutritional support we use enteral route preferentially, give metabolic substrates without overfeeding. Vitamin D and bisphosphonate therapy should be considered. In preventing infection processes of care should be systematized to maximize use of essential preventive measures such as hand washing, isolation, removal of unnecessary indwelling catheters, restriction of antibiotic use, and best practices for

maintaining skin integrity. Source identification and control should focus first on possible line sepsis and pneumonia which account for the majority of infections.

Conclusion

The question whether we should attempt to save the chronically ill or let them die remains immediately relevant, but at present state of the evidence does not yet support a definite response. Pathobiology of chronic as distinct from acute critical illness deserve further investigation. Whereas existing evidence for optimal management strategies remains limited, data on long-term outcomes are available and clear. These data should not be ignored during discussions with patients and their families about appropriate goals of continuing intensive care therapies when critical illness becomes chronic.

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End-of-life decisions in the Slovene ICUs – a cross sectional survey

Urh Grošelj[1], Miha Oražem[2], Maja Kanič[2], Manca Stojan[2], Gaj Vidmar[3], Štefan Grosek[1]
[1] University Medical Centre Ljubljana, Ljubljana, Slovenia
[2] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[3] University Rehabilitation Institute, Republic of Slovenia, Ljubljana, Slovenia

Introduction

Ethical dilemmas in the intensive care medicine are frequently related to how intensively should be treated the patients, which critically depend on supportive therapy to maintain their vital functions and where no improvement is expected but just gradual worsening and end-organ failures (1-3). The decisions to terminate life-supporting treatment (TLST) mostly lead to death of such patients where the treatment was considered to be futile. These decisions could be emotionally very difficult for all the involved. Thus, the decision making process on TLST should be a balanced consideration for each individual patient, where the treatment is apparently futile – the expected effects and benefits of the treatment should be weighed against its harms and burdens. If the later exceed the former the most ethically sound action is to decide for TLST. From the ethical perspective, the process of TLST is crucially different from the active shortening of life of a patient with the intent to cause death of the patient (e.g. euthanasia, physician assisted suicide) (4). TLST could be divided into the withholding and the withdrawing of treatment. In the withholding of treatment no additional life support measures are introduced or the existing measures are not intensified; the illness is thus left to take its natural course while the palliative care measures are introduced. In the withdrawing of treatment the selected of the existing life support measures are discontinued (5). These could refer to the termination of medicamentous therapy (e.g. antibiotics, inotropes), of mechanical ventilation, of ECMO, of dialysis, etc.; in some cases even artificial hydration and nutrition could be terminated. Among the most widely accepted measures of TLST is the DNR (*do not resuscitate*) order, which is frequently considered as a form of the withholding of treatment (but some other argue it to be a form of the withdrawing of treatment). Most consider the withholding and the withdrawing of treatment not just both to be ethically acceptable but also to be ethically comparable decisions; of course, the primary intention should never be to actively shorten patients life. The mortality rate in the intensive care units (ICUs) is usually reported to be around 20%; in at least third of them the decision to TLST is made before death (the ratio somewhat varies among different countries and cultures; the data for Slovenia have not been published yet) (6). Many previous national and international studies in adult, pediatric and neonatal ICUs have dealt with the issue of TLST in futile patients (7-9). Unfortunately, Slovenia was not part of any of them. Our research group has made two studies on the issue in last three years. The first was the survey study on attitudes and experiences with ethical dilemmas at the end-of-life (EOL) of the Slovene ICU physicians. It was performed in the year 2012, showing that the Slovene ICU physicians frequently lack very detailed knowledge and also differ considerably on the issue of TLST (10). Furthermore, in beginning of the year 2013 we performed a three month prospective clinical study on the TLST decision making in the ICUs.

Methods

A cross-sectional survey among the Slovene ICU physicians and intensive care medicine residents from 35 different ICUs was performed using a questionnaire containing 43 questions about views on EOL decision-making. Fisher's exact test and

the Fisher-Freeman-Halton test were applied to cross-tabulated data; significance level was set at *P* ≤0.001 due to the large number of tested hypotheses.

Results

The response rate was 72.1% (267 questionnaires were returned out of 370 distributed), which represented roughly the same percentage of all the Slovene ICU physicians. Termination of futile treatment was assessed as ethically acceptable (*P* 0.001). The statement that there is no ethical distinction between withholding and withdrawing of treatment could not be confirmed (the answers 'there is a difference' and 'undecided' were less frequent, but not statistically significant; *P* = 0.216). A do-not-resuscitate order (DNR) was used more often than other withholding treatment limitations (*P* 0.001). A DNR was used most frequently in internal medicine ICUs (*P* 0.001; compared with paediatric and surgical ICUs). Withdrawal of inotropes or antibiotics was used more often than withdrawal of mechanical ventilation or extubation (66.7% vs. 12.0%; *P* 0.001). Withdrawal of mechanical ventilation or extubation was more often used in the paediatric ICUs (21.7%) as compared with the internal medicine ICUs (19.6%) and the surgical ICUs (3%) (*P* 0.001). Over two-thirds (70.6%) of the ICU physicians were against termination of hydration, which would be more often used in the internal medicine ICUs (*P* 0.001). Thirty-one percent of the Slovene ICU physicians used written DNR orders.

Conclusion

Termination of futile treatment was found to be ethically acceptable for the Slovene ICU physicians, although they were not convinced that withholding and withdrawing of treatment were ethically equal. A DNR would be used most often. Withdrawal of inotropes or antibiotics would be used more often than withdrawal of mechanical ventilation or extubation. Termination of artificial hydration would be rarely used in practice.

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Value of Microbiology in Chronic Critical Illness

Viktorija Tomič, University Clinic of Respiratory and Allergic Diseases, Golnik

Advances in intensive care have enabled more patients to survive an acute critical illness thus creating a large and still growing population of chronically critically ill patients. The universal definition of chronic critical illness (CCI) has not yet been agreed upon but the term »chronically critically ill« coined by Girard and Raffin in 1985 describes patients with prolonged dependance on mechanical ventilation and other intensive care treatments (1). The CCI patients and patients requiring prolonged mechanical ventilation often overlap which makes the epidemiologic, demographic, cost and outcomes estimation difficult. Nevertheless it's been estimated that CCI develops in 5% to 10% of patients who require mechanical ventilation during acute critical illness (2).

CCI is a syndrome comprising characteristic features such as profound weakness, neuroendocrine changes, increased vulnerability to infection, brain dysfunction, and skin breakdowns besides prolonged ventilator dependence. CCI patients are particularly susceptible to infections for many reasons. These patients have multiple indwelling devices, such as intravascular lines, urinary catheters, nasogastric tubes, tracheostomies, which represent additional portals of infections beside skin and mucosal breakdown. These patients also suffer from an immunologically deficient state usually reffered to as »immune exhaustion« (3). Prolonged stay in the ICU or long-term care facility greatly increases the risk of acquiring multidrug-resistant organisms (MDRO). Progression from colonisation to full blown infection with MDRO is an imminent threat postponing or preventing CCI patients' recovery. Infection prevention, timely and accurate microbiologic diagnostic procedure and appropriate antimicrobial treatment are an important part of a comprehensive, multidisciplinary approach to prevent and manage CCI. Depending on the facility the prevalence of different MDRO vary considerably and can be high. One 4-year prevalence study assessed patients on admission to long-term acute care hospital (LTAC) for colonisation with MDRO by collecting nasal, wound, rectal swabs, gastric tube aspirates and tracheal aspirates. After examining all culture sites, 69% of patients were found colonised with one MDRO, 23% had two MDROs, and 8% had three or more MDROs (4). Among rectal swabs, at least one MDRO was present in 50% of samples. The most common rectal swab pathogens were vancomycin resistant enterococci – VRE (38%) and extended spectrum beta-lactamase producing enterobacteria – ESBL-E (9%). Thirty-three percent of wound samples grew at least one MDRO and most prevalent were VRE (18%), methicillin-resistant *Staphylococcus aureus* – MRSA (7%) and carbapenem-resistant *Acinetobacter spp*. (7%). Fifteen percent of nasal cultures had MDROs, and of those 7% were Gram-negative bacilli, 6% were MRSA, and 4% VRE. In two other LTAC hospitals, monthly admission prevalence was as follows: VRE 26 – 61%, MRSA 33 – 61%, MDR *Acinetobacter spp*. 0 – 2% (3). Published data on transmission rates of MDROs in the LTAC hospitals are very limited but it's well established that implementation of admission screening, appropriate patient isolation, and comprehensive infection control practices allow control of MDROs. To be able to prevent as many healthcare-asspciated infections as possible an infection control education and good knowledge of all infection control policies and procedures is imperative for all healthcare worker caring for CCI patients. Hand disinfection and zero tolerance for non-adherence should be instituted.

Colonisation should not be treated and should be explicitly avoided where screening cultures are used. Only when infection arises should we use antimicrobial treatment. The most common infections are device-related infections, ventilator-associated pneumonia, catheter-associated urinary tract infections and blood stream infections. Rates of these infections can be positively influenced by implementation of effective healthcare-associated infection prevention strategies and procedure bundles. In case of infection the support of the microbiology laboratory capable of providing an accurate and rapid information is essential for appropriate antimicrobial treatment and for better chances of favourable outcome. Physicians should become familiar with all diagnostic possibilities of the microbiology laboratory as well as be aware of the importance of prudent use of antibiotics. Wide-spectrum antibiotics are obvious first choice for empirical treatment but de-escalation of antibiotics should occur as soon as the culture results and/or diagnosis is established. When in doubt about possibilities of microbiological diagnostic procedure or isolated microorganisms and their antimicrobial susceptibility traits consultation with a clinical microbiologist can be benificial.

Conclusion

CCI patients are very fragile and due to immune exhaustion extremely prone to acquire healthcare-associated infection. The implementation of infection prevention protocols and minimizing the use of indwelling devices can decrease healthcare-associated infection rates and keep them low. Also an antimicrobial stewardship programme has become indispensable to provide safe and quality care of these patients. Successful infection control, accurate microbiological diagnosis of infection and appropriate antimicrobial treatment need support of well organised and capable microbiology laboratory.

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Lung cancer (Nadja Triller, Tanja Čufer, Lučka Debevec)

15'	Delays in diagnosis and treatment of lung cancer in Slovenia	Katja Mohorčič, Nadja Triller
15'	Clinical register of lung cancer	Andraž.Jakel, Lučka Debevec, Katja.Mohorčič
10'	Side effets of systhemic treatment of lung cancer – The movie	Katja Mohorčič
20'	Multimodality treatment of non-small cell lung cancer	Lučka Debevec
20'	The role of pathologists in the era of personalized therapy	Izidor Kern
10’	Surgery for lung cancer- results from Pulmonary Clinic Golnik	Marko Bitenc

DELAYS IN THE DIAGNOSIS AND TREATMENT OF LUNG CANCER IN SLOVENIA IN 2012

Katja Mohorčič, Nadja Triller, University Clinic of Pulmonary and Allergic Diseases, Golnik

Background

Lung cancer (LC) is the fourth most common cancer among men and women in Slovenia accounting for almost 10% of all cancers. Approximately 1200 new patients (pts) are diagnosed every year. 5-year survival is 14.5% and at the time of diagnosis only 15% of patients have a curable disease (1). Prognostic factors in LC are age, sex, comorbidity, PS at the diagnosis, histology and stage of the disease (2). The most important factor affecting survival is stage at the diagnosis. Only pts with an early stage of lung cancer at the time of diagnosis have a favorable prognosis. We assume that delays in the diagnosis and treatment can result in diagnosing more advanced stages of LC. In theory shortening the interval between the first symptom of the disease and the beginning of its treatment could improve survival (3,4). Some studies showed that delays in the diagnosis and treatment can affect the stage at the diagnosis (5, 6), while others did not prove that (7,8,9,10,11,12).
The aim of our study was to determine the delays between the onset of symptoms and the first treatment in newly diagnosed LC pts in Slovenia in 2012 and to compare the delays between different regions in Slovenia.

Methods

Patients

We retrospectively analyzed records of 450 pts with newly diagnosed and microscopically confirmed LC in 2012 in four hospitals in Slovenia (UC Golnik, Topolšica, Novo Mesto, Institute of Oncology Ljubljana). Data were collected retrospectively using hospital information systems of all four hospitals. Where the data were insufficient, pts were subsequently contacted by the phone. Clinical staging was performed according to the latest 7th TNM classification (13). We filled out a questionnaire for each included patient with the information about the basic demographic data, region of residence, smoking, the diagnosis and stage of the disease and intervals in diagnostic procedures from the first symptom of LC to its treatment. Time intervals were compared between different Slovene regions.

Definitions

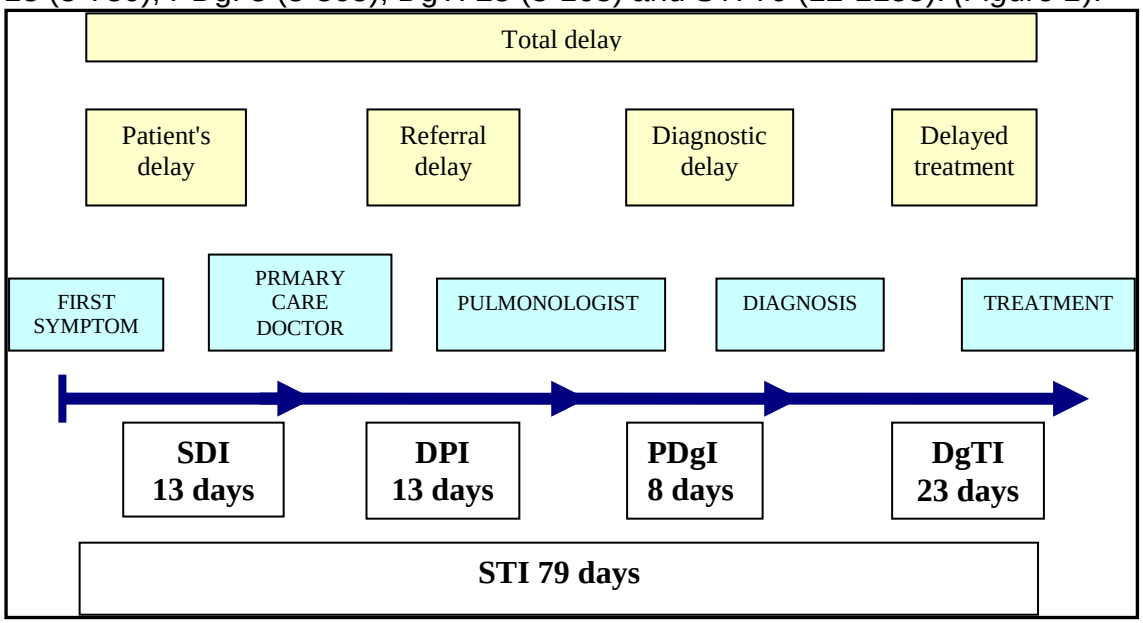
The following time intervals were determined:

- symptom to doctor interval (SDI) – the interval between the first symptom of lung cancer to the first visit to the doctor at the primary care,
- doctor to pulmonologist interval (DPI) – the interval between the first visit at the doctor to the first visit at the pulmonologist,
- pulmonologist to diagnosis interval (PDgI) – the interval between the first visit at the pulmonologist to the microscopically confirmed diagnosis of LC,
- diagnosis to treatment interval (DgTI) - the interval between the microscopically confirmed diagnosis of LC to the first treatment,
- and symptom to treatment interval (STI) – the interval between the first symptom of LC to the first treatment received.

The criteria about the time delays in our study were taken from the Turkish study of Yilmaz et al (11), which incorporates the recommendations of British Thoracic Society (14) and Canadian recommendations. Recommended intervals are <30 days for SDI, < 14 days for DPI, PDgI and DgTI, < 72 days for STI.

Results

Data of 450 pts (65% men, median age 66 years (range 30-90 years)) with newly diagnosed LC in 2012 were evaluated. 418 (92.9%) pts were diagnosed at UC Golnik. 86% of the pts were current or ex-smokers. 53% had stage IV disease at the diagnosis, 25% stage III, 43% stage II and 12% stage I. Most common histological type of LC was adenocarcinoma (43%). 31% of pts had squamous cell carcinoma and 16% small cell LC. Median intervals in days were as follows: SDI 13 (3-730), DPI 13 (3-730), PDgI 8 (3-365), DgTI 23 (3-163) and STI 79 (12-1155). *(Figure 1)*.



Mean times from the microscopically confirmed diagnosis of LC to the first treatment were as follows: to the operation 37.8 days, to systemic treatment 24.1 days and to the radiation 27.7 days.

The region of residence of our group of pts was mostly Gorenjska region or Osrednjeslovenska region (together 55% of our pts). That is why we decided to divide our pts in 2 groups according to the region of residence for the intent of comparing the results of the time intervals: Gorenjska region and Osrednjeslovenska region together on one side and all the other regions on another. We found no statistically significant difference between the intervals in those 2 groups of pts. *(Table 1).*

Mean (days)	SDI	DPI	PDgI	DgTI	STI
Osrednjeslov. + Gorenjska regions	42.1 (3-365)	26.6 (3-730)	16.0 (3-365)	25.1 (3-163)	79.0 (9-1098)
Other regions	41.8 (3-730)	33.5 (3-447)	22.4 (3-330)	27.1 (3-120)	94.2 (9-751)
p*	p=0.97	p=0.21	p=0.07	p=0.34	p=0.16

Conclusion

All the time intervals are in line with the British and Canadian recommendations except for the interval between the diagnosis and treatment and consequently total

delay. There are 3 centers in Slovenia for surgical and systemic treatment of LC pts: UC Maribor, Ljubljana (Institute of Oncology Ljubljana and Thoracic Surgery Department at UMC Ljubljana) and only one center for radiation therapy at Institute of Oncology Ljubljana. Almost all of our patients were treated at UC Golnik and in Ljubljana. Our analysis included more than 1/3 of all newly diagnosed LC pts in 2012. That is why we can assume that treatment delay found in our group of pts can reflect current organization of Slovenian healthcare system at least for the West part of Slovenia. The treatment delay to the surgery was the longest (almost 40 days) because pts usually need to perform more tests before surgery, and also because waiting time for PET CT in Slovenia is several weeks.
No difference in time intervals was found between Osrednjeslovenska + Gorenjska region and all the others Slovenian regions although the interval between the first symptom of LC and the diagnosis could be longer in regions where the access to pulmonologist is worse. As almost 93% of pts in our analysis were diagnosed at UC Golnik and treated at Golnik or Ljubljana, treatment delays were similar for all pts irrespective of the region of residence.

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KLINIČNI REGISTER PLJUČNEGA RAKA

Tanja Čufer, Andraž Jakelj, Univerzitetna klinika za pljučne bolezni in alergijo

ABSTRACT

Only registries and clinical databases can offer us adequate insight into cancer care. Precaution is needed when planning a registry or database since we do not wish to capture too much or too little information. Corrections after registry has come to life are difficult.

Cancer Registry of the Republic of Slovenia provides us with data on Slovenia's cancer incidence and mortality since 1950. The national registry does not include all the information regarding cancer that we might wish for, therefore since 2010 we have started collecting more extensive data on cancer patients who are diagnosed and treated in Clinic Golnik. Forming and managing the registry is extremely challenging and it requires a lot of work. However, it was worth our effort because today (after three years) the hospital's cancer registry provides us with priceless and detailed information on the demographic characteristics of the cancer patients, the anatomical stage and molecular biology of the disease and treatment outcomes. We also collect the data that the national registry does not collect.

Our future goal is to combine all data on lung cancer regardless of where in Slovenia the cancer has been diagnosed or treated.

UVOD

Zanimanje za zdravje prebivalstva se iz dneva v dan povečuje. V povezavi s tem se veča tudi želja/potreba po zbiranju zdravstvenih podatkov. Podatke lahko zbiramo povsem rutinsko, vendar se pri takem načinu zbiranja pojavijo velike omejitve, te pa so povezane s problemom točnosti in reprezentativnosti podatkov in analiz, nedosledne registracije obolenj, večkratne registracije obolelih, nejasnim namenom zbiranja podatkov in nepoznavanjem populacije. Pri tovrstnem načinu zbiranja podatkov tudi ni kontrole nad samim zbiranjem.

Omejitve pri uporabi podatkov rutinske zdravstvene statistike zožujejo možnosti analitičnega spremljanja obolevnosti, zato se za nekatera obolenja, ki so posebnega pomena, uvaja drugačen način registracije, in sicer registre bolezni. Ta način zbiranja podatkov je za ugotavljanje obolevnosti in epidemiološke študije zelo primeren, vendar ga ni mogoče uporabljati za vsa obolenja.

Registri v zdravstvu ne služijo le za spremljanje podatkov o bolezni, pač pa lahko povezovanje posameznih registrov služi kot osnova za raziskovanje etioloških dejavnikov ali dejavnikov, ki pospešujejo pojav bolezni. Oblikovanje registra je izredno zahtevno ter zahteva ogromno dela. Za njegovo vodenje je potrebno veliko časa in denarja, poleg tega pa vedno obstaja nevarnost, da bo prišlo do zlorabe osebnih podatkov.

Registre lahko razdelimo v dve glavni skupini. V prvi skupini so populacijski, druga skupina registrov pa so t. i. hospitalni/klinični registri (3).

KLINIČNI REGISTER PLJUČNEGA RAKA

Register raka Republike Slovenije je eden prvih populacijskih registrov v svetu, ki nam že desetletja nudi podatke o pojavnosti, prevalenci in umrljivosti za posameznimi raki v Sloveniji. S pojavom novih diagnostičnih in terapevtskih metod, predvsem pa z razmakom molekularne diagnostike in tarčnega zdravljenja raka se je pojavila potreba po dodatnem natančnem vodenju podatkov v okviru kliničnih registrov posameznih rakov. Ti registri omogočajo pridobivanje novih spoznanj o

učinkovitosti in varnosti posameznih diagnostičnih ter terapevtskih pristopov pri bolnikih oskrbljenih v okviru vsakodnevne klinične prakse. Zdravnikom in vodstvom bolnišnic pa nudijo neprecenljive podatke o učinkovitosti in kvaliteti njihovega dela (1).
Na Kliniki Golnik smo v letu 2010 vzpostavili klinični register raka pljuč. V ta register vpisujemo številne podatke o bolnikovem splošnem stanju, podatke o vrsti in obsegu raka pridobljene z diagnostičnimi postopki ter podatke o zdravljenju. Vključeni so podatki vseh bolnikov s pljučnim rakom, diagnosticiranih na Kliniki Golnik. Spremljamo podatke o simptomih bolezni, spremljajočih stanjih in boleznih, delovanju notranjih organov, anatomskem obsegu raka, patološki klasifikaciji in molekularnih označevalcih. Za bolnike zdravljene na Kliniki Golnik pa zbiramo tudi podatke o zdravljenju in izhodih zdravljenja (1).

Ker je za pridobitev zanesljivih in relevantnih podatkov iz kateregakoli registra potrebno najprej poskrbeti za dobro kvaliteto vnešenih podatkov (4), ki morajo biti točni in čimbolj popolni ter pravilno vnešeni smo pred začetkom dela registra pripravili ustrezne obrazce, predvsem konziliarni obrazec, iz katerega se vnaša velik del podatkov. Skupina zdravstvenih strokovnjakov naše klinike je v sodelovanju z računalniškimi strokovnjaki skrbno oblikovala in pripravila šifrant za vnos podatkov. Podatkovna baza in šifrant sta bila narejena v okviru ARRS projekta in v sodelovanju naše klinike z ljubljansko Fakulteto za računalništvo in informatiko. Zaenkrat podatke ročno vnašamo iz konziliarnih obrazcev, zapisov preiskav in zdravljenja. Glede na to, da je večina teh podatkov že v bolnišničnem informacijskem sistemu, smo že zastavili aktivnosti za direkten prenos teh podatkov v klinični register, kar pa ni enostavno. Klinični register zahteva po eni strani zelo natančen in definiran vnos podatkov, po drugi strani pa mora zagotavljati svobodo vpisa dodatnih informacij. Gotovo bo potrebno še veliko dela in sodelovanja zdravnikov, s skrbniki sistema ter informatiki preden bomo udejanjili neposreden prenos podatkov za večino podatkov (1).
Prva leta dela na kliničnem registru so povezana s številnimi težavami in pastmi, kar smo izkusili tudi na Golniku. Najprej se je postavilo vprašanje, kako obsežen naj bo zajem podatkov. Načeloma je najbolje zajeti čim več podatkov, kar pa je zamudno. Dodaten problem je relevantnost podatkov na konziliarnih listih in v bolnišničnem informacijskem sistemu. Zlasti to velja za podatke, ki so predmet subjektivne ocene zdravnika. Neustrezna ocena splošnega stanja bolnika s strani lečečega zdravnika ima za posledico neustrezen izsledek analize registra. Pomembno je bilo skrbno in premišljeno šifriranje podatkov in nato vnos glede v šifrant, kjer je bilo potrebno tesno sodelovanja zdravnikov, informatikov in osebja, ki vnaša podatke. V primeru nerazumevanja šifre je vnos podatkov lahko neustrezen. In nenazadnje, potrebno je bilo upoštevati zakonodajo glede varovanja osebnih podatkov in bolnikovih pravic. Veliko je nalog, za katere sta potrebna dodaten kader in sredstva. Pomanjkanje tako kadra kot sredstev pa je bila in je še vedno ena od naših največjih težav (1).

POROČILO REGISTRA ZA PRVO OBDOBJE

Rezultat skrbnega vnosa podatkov, zelo zahtevnega postopka preverbe zanesljivosti podatkov z dvojnimi vnosi in križnimi preverbami in poglobljene analize podatkov je prvo poročilo kliničnega registra raka pljuč Klinike Golnik (KG), ki zajema obdobje 2010 do julija 2013. To poročilo je razkrilo, da smo na KG v tem obdobju obravnavali 1787 bolnikov z rakom pljuč, 74 z mezoteliomom, 26 z karcinoidom in 4 bolnike s timomom. Poročilo tudi pove, da so demografske lastnosti bolnikov s pljučnim rakom

obravnavanim na KG primerljive z lastnostmi bolnikov drugje v razvitem svetu, srednja starost bolnikov je bila 66,5 let, 33% bolnikov je bilo žensk, 10,5% je nekadilcev. Pri večini (50,6%) je bila bolezen odkrita v razsejanem stadiju IV in kar 43,7% bolnikov je imelo adenokarcinom, delež bolnikov z drobnoceličnim rakom pljuč pa je znašal samo 14,7%. V primerjavi s podatki objavljenimi za leto 2006 je viden premik k večjemu deležu žensk med obolelimi, večjemu deležu adenokarcinomov (2) in žal tudi k višjemu stadiju ob diagnozi, kar je lahko posledica migracije stadijev zaradi natančnejših preiskovalnih metod, kot sta PET-CT in ultrazvočno vodena biopsija bezgavk (EBUS). EGFR mutacije so bile določene pri 83% bolnikov z adenokarcinomom in so bile pozitivne pri 16,8% bolnikov. To je vsekakor podatek, ki kaže na več kot zadovoljivo raven določanja molekularnih označevalcev raka pljuč na KG. Podatki o zdravljenju ter izhodih zdravljenja se še vnašajo in obdelujejo in bodo predvidoma na voljo konec tega leta.

KAKO DALJE

Prva tri leta pionirskega dela na kliničnem registru raka pljuč so nas pripeljala do določenih spoznanj in usmeritev za bodoče. Glede na velik obseg dela in omejene kadrovske možnosti je tako kot pri drugih registrih tudi v našem primeru potrebno zagotoviti direkten prenos čim večjega števila podatkov iz bolnišničnega informacijskega sistema v klinični register. Vzpostavili smo tudi že povezavo z Registrom raka Republike Slovenije, katero moramo še bolje definirati in formalizirati. Slovenija ima ponosno in dolgo tradicijo prvega populacijskega registra raka v centralni Evropi, ki nam bo vedno nudil neprecenljive epidemiološke podatke za vse rake v državi (1). Povezava kliničnega registra s populacijskim registrom v smislu izmenjave skupnih osnovnih podatkov ter preživetij izboljša kakovost podatkov in nudi možnost še boljših analiz in izsledkov (4).

Na Kliniki Golnik letno diagnosticiramo okoli 700 bolnikov z rakom pljuč, kar pomeni več kot polovico vseh bolnikov s tem rakom v Sloveniji. Idealno bi bilo, če bi se v kliničnem registru združili podatki vseh treh največjih centrov za diagnostiko in zdravljenje raka pljuč, Klinike Golnik, Onkološkega inštituta v Ljubljani in UKC Maribor. Takšen klinični register bi bil zaradi obsega podatkov in celostnih informacij o diagnostiki in zdravljenju posameznega bolnika, ki se pogosto izvaja na več mestih, velikega pomena in vrednosti. Dodatno bi tak klinični register omogočil zbiranje, analiziranje in vrednotenje izhodov zdravljenja pri bolnikih z določenimi molekularnimi označevalci, kar je v eri personificirane onkologije ne samo potrebno, ampak nujno (6).

ZAKLJUČEK

Populacijski registri so imeli vedno veliko vlogo pri spoznavanju same bolezni. Vedno bolj pa se kot orodje za učenje in pridobivanje novih znanj o boleznih uveljavljajo klinični registri, saj nudijo neprecenljive podatke o medicinski in stroškovni učinkovitosti naših pristopov k diagnostiki in zdravljenju raka. Bolnišnični registri so v onkologiji predpogoj za kontrolo kvalitete dela, omogočajo nam preverbo lastnega dela in boljše načrtovanje dela v bodoče. Klinični registri lahko dobro delujejo le, če se s podatki, ki jih vsebujejo, vsakodnevno ukvarjamo. Delo z njimi ne sme zastati niti nam delo z njimi ne sme postati rutina, saj lahko zelo hitro takšni registri postanejo arhiv neobvladljivih tabel brez koristnih izhodov.

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Multimodality treatment in lung cancer

Lučka Debevec Kodrič

Selecting the treatment for lung cancer (LC) patient the following should be considered:

1. The capacity of LC to early and frequent metastatic spread to regional lymph nodes and to distant organs.
2. Limited options for lung resection. Lung is life's important organ not suitable for any reduction or removal as breast, uterus or stomach. In lung cancer there should be always determined weather regional lymph node metastases or distant metastases are present. The selected treatment should influence also regional and/or distant metastases.
3. The capability of the patient for the selected treatment. Beside lung function, biological age and comorbidity definitely influence the preservation of other life's important organs. In the case of chemotherapy (ChT) mostly bone marrow capacity decisively influence dosage and duration of cytotoxic treatment. Calendar age itself is not an absolute contraindication for any treatment modality, but it is decisive for life expectancy that must be considered selecting aggressive treatment modalities in LC.
4. Histology of LC. During the last decades, treatment of small cell LC (SCLC) has become different from non-small LC (NSCLC) (Table 1). Therefore histology has to be determined. Flexible bronchoscopy and its biopsy techniques, CT guided needle biopsy, thoracoscopy and cervical mediastinoscopy offer many opportunities. Exploratory thoracotomy (ET) without previous verification of a suspected lung tumor is exceptional. During the decade 1990-1999 at Clinical Department for Thoracic Surgery, Clinical Centre Ljubljana, Slovenia, there were 169 ET (9.1%) among 1808 thoracotomized patients, but only one of them due to microscopic verification of previously unconfirmed lung cancer.

Table 1: Treatment of LC according to histology

Treatment modality	NSCLC	SCLC
Surgery	Stage I, II, selected IIIA	Adjuvant to ChT in selected LD
Radiotherapy	Inoperable stage I, II, IIIA and IIIB	Adjuvant to ChT in LD
ChT	Inoperable stage I-IV	Standard all patients
PCI	Exceptionally	Standard in LD Individually in ED
Biological treatment	Selected patients	Not used

Resection itself or combined with ChT or radiotherapy gives best hope for cure or long term survival in lung cancer patients. In NSCLC it can be the only treatment, but in SCLC adjuvant to ChT and radiotherapy [1]. This is confirmed by our experience: in 345 LC patients diagnosed in 1996 At Clinic Golnik, Slovenia, 5 years survived only 27 patients, among them 26 resected [2]. From 26 SCLC patients, resected from 1980 to 1987 at Clinical Department for Thoracic Surgery, Clinical Centre Ljubljana, Slovenia, consequently treated with ChT, some also with radiotherapy, one third survived 5 years [3]. Therefore selecting patients with LC limited enough for radical resection, i.e. removal of lung lobe, lobes or wing and regional lymph nodes. These

are patients stage I, II and selected stage IIIA. Generally, one quarter of all LC patients is eligible for surgery [4]. And in one half of NSCLC patients metastases out of the lungs are present and in 10-15% progresses unresectable primary tumor by the time of the diagnosis [5]. In our series of diagnosed 345 above mentioned LC patients the situation was similar: 77 pts. (22%) operated on and 62 pts.(18%) resected. Development of surgical techniques, progress of anesthesiology, perioperative care and postoperative rehabilitation decreased mortality after resection beyond 3%. In LC patients not eligible for surgery, radiotherapy and mostly systemic therapy come into play.

Radiotherapy: Development of modern equipment and more accurate radiotherapy techniques enables application of high radiation dose to relatively limited area of primary tumor and regional lymph nodes. But radiotherapy has also its limitations. Not all patients are eligible for radical radiotherapy, some even not for palliative radiotherapy. At Institute of Oncology Ljubljana, Slovenia, among 253 LC patients irradiated during one year, only 88 (35%) received radical dose (more than 50Gy) [6].

Chemotherapy was for a long time the method of selection only for SCLC. During the last decades, the development of more efficient and less toxic cytostatic drugs, enabled use of ChT in NSCLC. Not only better response rates, but also the desire of the patients for treatment, expectations of patient's family and hope of physicians to modify the course of the disease despite the fact that due the ChT quality of life and symptom control might decrease and the extension of life questionable.

Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells. Monoclonal antibodies and tyrosine kinase inhibitors are two types of targeted therapy being used in the treatment of non-small cell lung cancer.
Monoclonal antibody therapy is a cancer treatment that uses antibodies made in the laboratory from a single type of immune system cell. These antibodies can identify substances on cancer cells or normal substances that may help cancer cells grow. The antibodies attach to the substances and kill the cancer cells, block their growth, or keep them from spreading. Monoclonal antibodies are given by infusion.
By all these individual treatment modalities in LC, surgery, radiotherapy and ChT available at present, best possible results are already achieved. Better survival rates are not expected. Targeted therapy is developing, new substances are tested and there is hope for better achievements in future. For sure, more cured patients and better survival can be reached by combination of treatment modalities, i.e. multimodality treatments.

Small cell lung cancer
In SCLC the basic treatment is ChT. Radiotherapy can be adjuvant or concomitant to ChT. Radiotherapy before ChT is used rarely, mainly in severe cases of syndrome venae cavae superior or severe dysphagia. Because SCLC is very chemosensitive, improvement of symptoms is achieved by ChT before radiotherapy can be performed in practice. Concomitant chemo- and radiotherapy accelerates tumor regression, but can be difficult for the patient. Due to side effects, mainly bone marrow depression, such therapy might be prolonged.
In SCLC brain is often site of distant metastases not being detected by CT or MRI. Chemotherapy passes haemato-encephalic barrier badly. Therefore prophylactic

cranial irradiation (PCI) is used. After PCI brain metastases are less common and survival rates better than in patients irradiated for detected brain metastases.
With regard to resection, here are still different views in SCLC. It is not disputed that the basic treatment is ChT and surgery is supportive to it. The possibility of cure with surgery in some patients without ChT is allowed, mainly in rare cases in early stage SCLC, mostly in accidentally found and removed round lesions [7]. Randomized trials to determine the role of resection in SCLC are lacking. One of few is the LCSG (Lung Cancer Study Group): 328 SCLC patients resected after initial ChT, followed by adjuvant radiotherapy and PCI compared to equally treated patients without resection. Significant survival difference was not detected ($p = 0.78$) [8].
Whether resection followed by ChT or resection after ChT in all patients eligible or only in patients without complete response to ChT. In a trial of Karrer from Wiena, that included also our patients [1], patients were resected, ChT was administered postoperatively. Four-year survival rate of stage T1-3N0 was 58%, and of stage T1-3N3 33%.
Concerning surgery in SCLC, combined SCLC-SNCLC (adenocarcinoma, squamous cell, large cell carcinoma) less sensitive to should be considered.
Targeted therapies in SCLC. There has been a considerable amount of research in the understanding of the depth of biology of SCLC and utilizing this knowledge to develop targeted approaches. Several signaling pathways have been found to be activated in SCLC tumor cells, forming a rationale for blocking some of the drugable targets. Molecular changes and biological markers have been identified but remain to be validated. Novel and targeted agents have been evaluated but without much success. Increasing understanding of the biology and potential clinical evaluation of biomarkers will pave the way for more effective treatments.

Non-small cell lung cancer

Resection is the method of choice in all operable NSCLC. In doubtfully resectable cases the possibilities for radical resection can be improved by preoperative i.e. neoadjuvant ChT. Rarely, preoperative radiotherapy might be indicated. Neoadjuvant ChT affects also potential distant micrometastases. In some cases not only reduction of tumor size, but also complete pathologic response in some tumor-sites is observed. Postoperative radiotherapy is performed after incomplete resection of NSCLC. Routine postoperative radiotherapy of mediastinum does not prolong the survival [9]. Postoperative i.e. adjuvant ChT after complete resection of NSCLC increases five-year survival rate in stage II - IIIA [10].
NSCLC is less sensitive to ChT than SCLC. But in progressed inoperable NSCLC there is often no other option to influence on tumor growth and metastatic spread and to achieve symptom control.
The effect of ChT is evaluated by the rate of complete and partial responses according to RECIST (Response Evaluation Criteria In Solid Tumors) criteria.
From patient's perspective symptom control and quality of life are more important than objective response to therapy. Here is the trouble for a physician. If the patient tolerates ChT badly, probability of a good response limited, might be the expected survival despite the ChT short. »Primum nil nocere« applies also to LC patients. Despite the fact that the decision for giving up specific oncological treatment and care for the patient only symptomatically is difficult for the physician and disappointing for the patient and his family, ChT should not be performed »ut aliquid fieri videtur«.

Targeted therapies in NSCLC. Tyrosine kinase inhibitors are targeted therapy drugs that block signals needed for tumors to grow. Tyrosine kinase inhibitors may be used with other anticancer drugs as adjuvant therapy.
Tyrosine kinase inhibitors used to treat non-small cell lung cancer include erlotinib and gefitinib. They are types of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. Crizotinib is a type of tyrosine kinase inhibitor that is used to treat non-small cell lung cancer with a certain type of chromosome change that affects the anaplastic lymphoma kinase (ALK) gene.
Afatinib, an irreversible ErbB-family blocker, that could be of some benefit to patients with advanced lung adenocarcinoma who have failed at least 12 weeks of previous EGFR tyrosine-kinase inhibitor treatment.
Monoclonal antibodies used to treat non-small cell lung cancer include bevacizumab and cetuximab, both used in clinical trials. Bevacizumab binds to vascular endothelial growth factor (VEGF) and may prevent the growth of new blood vessels that tumors need to grow.

Conclusion

LC remains a deadly disease for majority of patients. Our task is to determine histology, biological characteristics and the extension of the disease and regarding to patient's capability for treatment to select the combination of treatment modalities that considering side-effects and risks gives best chances to cure. If curative treatment is not possible, treatments should be used to even temporary improve symptom control and if possible prolong the survival.
Lung cancer has to be determined in each individual patient as good as possible. Treatment for every patient should be carefully planned by the team of specialist dealing with diagnostics and treatment of lung cancer. Decisions should be based on experience of careful monitoring patients and regular determining the results of treatments. Unfortunately, the latter is lacking too often.

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Vloga patologa v dobi osebne medicine

Izidor Kern, Univerzitetna klinika za pljučne bolezni in alergijo Golnik

Uvajanje novih tarčnih zdravil v zdravljenje rakavih bolnikov je tesno povezano z odkrivanjem pravih fenotipskih in genotipskih lastnosti tumorja ter dokazovanju tarč, to je prijemališč za delovanje omenjenih zdravil. Prav patologija igra pri tem osrednjo vlogo, ker z različnimi laboratorijskimi metodami poskuša najti v bolnikovem vzorcu tumorja specifične lastnosti, na osnovi katerih se v multidisciplinarnem pristopu odloči za najbolj ustrezajoče zdravljenje prilagojeno bolniku (1). Na področju iskanja tarč in tarčnega zdravljenja pljučnega karcinoma smo priča velikim korakom napredka. V rutinskem delu in zdravljenju pljučnega karcinoma imamo vsaj dva para diagnostični test in z njim povezano zdravilo: aktivirajoče mutacije gena za EGFR in erlotinib ali gefitinib ter ALK genska preureditev in krizotinib. Patološka diagnostika pljučnega karcinoma podobno kot drugih tumorjev ni več preprosta, je kompleksna in opravljena mora biti v kratkem času skladno z mednarodnimi priporočili.

Zanesljivi diagnoza in klasifikacija pljučnega karcinoma

Kritična naloga patologa v smeri osebne medicine je postavitev zanesljive diagnoze, kar pomeni kar najbolj natančno tipizacijo tumorja. Pri tem se je potrebno zavedati določenih omejitev, ki jih prinesejo vrsta in velikost tumorskega vzorca na eni strani in zahteve po določanju napovednih dejavnikov. Z drugimi besedami gre za iskanje optimalne poti med čimbolj natančno histološko opredelitvijo tumorja in čuvanjem vzorca za testiranje napovednih dejavnikov. Ker se pri klasifikaciji pljučnih karcinomov soočamo s količinskimi problemi, je potreben zelo premišljen, robusten diagnostični pristop (2). Pri večini bolnikov s pljučnim karcinomom diagnoza in opredelitev njegovega tipa temeljita na majhnih vzorcih tumorskega tkiva ali celičnih vzorcih, v katerih je možen omejen nivo tipizacije tumorja. Ni presenetljivo, da je zaradi tega problema prišlo do oblikovanja prirejene klasifikacije pljučnih karcinomov (3). Uporabljamo tudi novo klasifikacijo pljučnega adenokarcinoma, ki opušča bronhioloalveolarni karcinom in mešani tip adenokarcinoma, uvaja pojem in situ adenokarcinoma in minimalno invazivnega karcinoma ter priporoča oceno prevladujočega vzorca rasti (3). Osnova je še vedno morfološka ocena, ki temelji na rutinsko obdelanih vzorcih tumorja. V malih tkivnih in celičnih vzorcih tako poznamo histološki tip nedrobnocelični pljučni karcinom. Če ne uporabljamo osnovnega panela protiteles za imunohistokemično metodo, znaša delež tako opredeljenih pljučnih karcinomov do 40%. S pomočjo dveh do štirih protiteles v imunohistokemiji (TTF1, napsin A, p40 ali p63, CK5/6; tabela 1), ta delež znižamo pod 10%. Določenih tipov pljučnega karcinoma ne moremo diagnosticirati v malih tkivnih in celičnih vzorcih (velikocelični karcinom, sarkomatoidni karcinom, adenoskvamozni karcinom). Preobširna uporaba protiteles v imunohistokemiji pomeni stroškovno neučinkovitost, ne izboljša zanesljivosti diagnoze in predvsem izgubo tumorskega vzorca.

Zamejitev bolezni

Patolog sodeluje v postopku klinične ocene razširjenosti pljučnega raka (klinični TNM stadij bolezni). Gre za obdelavo in pregled vzorcev plevralnega izliva, transbronhialnih igelnih biopsij s tanko iglo (slepih ali ultrazvočno vodenih), tankoigelnih aspiracijskih biopsij tipnih sprememb ali vodenih igelnih biopsij zasevkov v notranjih organih in mehkih tkivih. Razprava o bolniku v multidisciplinarnem pristopu zagotavlja optimalen izbor zdravljenja in zmanjšuje možnost napačnih odločitev (4). V primeru, da je bolnik kirurško zdravljen, patolog s pregledom

odstranjenega dela pljuč in mediastinalnih bezgavk določi patološki TNM stadij bolezni. Pri tem so pomembni tako makroskopski kot mikroskopski elementi: velikost tumorja, odnos do visceralne in parietalne plevre, lega tumorja, satelitski tumorski nodusi, oddaljenost tumorja od resekcijskih površin, tumorska zaseženost bezgavk, žilno in perinevralno tumorsko vraščanje, histološki tip tumorja, njegov podtip oziroma komponente, ki ga sestavljajo. Izvid mora biti standardiziran z vsemi ključnimi elementi pomembnimi za napoved bolezni in nadaljnje ukrepanje.

Določanje napovednih dejavnikov

Patolog pregleduje bolnikove vzorce tumorja, celične in tkivne. Pri bolnikih s pljučnim karcinomom pogosto sprejmemo v laboratorij različne vzorce tumorja istega bolnika v krajšem časovnem obdobju. Večina bolnikov s pljučnim karcinomom je bronhoskopiranih in pri tem posegu vzorčijo tumor ter eventuelno povečane mediastinalne bezgavke. V primeru prisotnega plevralnega izliva in tipnih vratnih bezgavk se opravi punkcija. Med prejetimi vzorci patolog izbere najbolj primerne za določene preiskave, s katerimi ugotavljamo prediktivne in prognostične dejavnike pljučnega karcinoma. Prav tako patolog izbere ustrezni test za potrjevanje določenega dejavnika. Za iskanje mutacij gena za EGFR so na voljo zelo različne metode, nekatere med njimi so priporočene in validirane. Pri določenih dejavnikih sta v proces iskanja vključena presejalni in potrditveni test. Takšen je pristop pri iskanju ALK genske preureditve, kjer je presejalna metoda validirana imunohistokemija, pozitiven rezultat pa potrdimo z metodo flurescenčne in situ hibridizacije ob uporabi ustreznih genskih sond. Rezultate opravljenih testiranj patolog interpretira skladno z ocenjeno količino in kakovostjo tumorskega vzorca. Rezultati testov so integralni del izvida, ki mora biti izdan v primernem času po odvzemu vzorca oziroma prejemu vzorca v laboratorij upoštevajoč za klinika razumljivo obliko in terminologijo. Zelo pomembno je, da je laboratorij s tovrstnimi testi, ki so ključnega pomena za odločitev o vrsti bolnikovega zdravljenja, vključen v zunanje, mednarodne sheme kakovosti. Tako za EGFR in ALK testiranje so objavljena priporočila (2, 5). Odgovornost patologa je ključnega pomena za upoštevanje in uveljavljanje priporočil v vsakodnevni praksi. Pri nas skušamo uveljaviti prakso rutinskega določanja EGFR in ALK statusa ob postavitvi diagnoze pljučnega karcinoma pri vseh bolnikih z adenokarcinomom in nedrobnoceličnim karcinomom brez natančnejše opredelitve. Pri tem uporabljamo stopenjski model, kjer najprej opravimo EGFR (in KRAS) testiranje (slika 1). Če sta oba testa negativna, izvedemo še ALK testiranje.

Skrben odnos do bolnikovih vzorcev tumorja

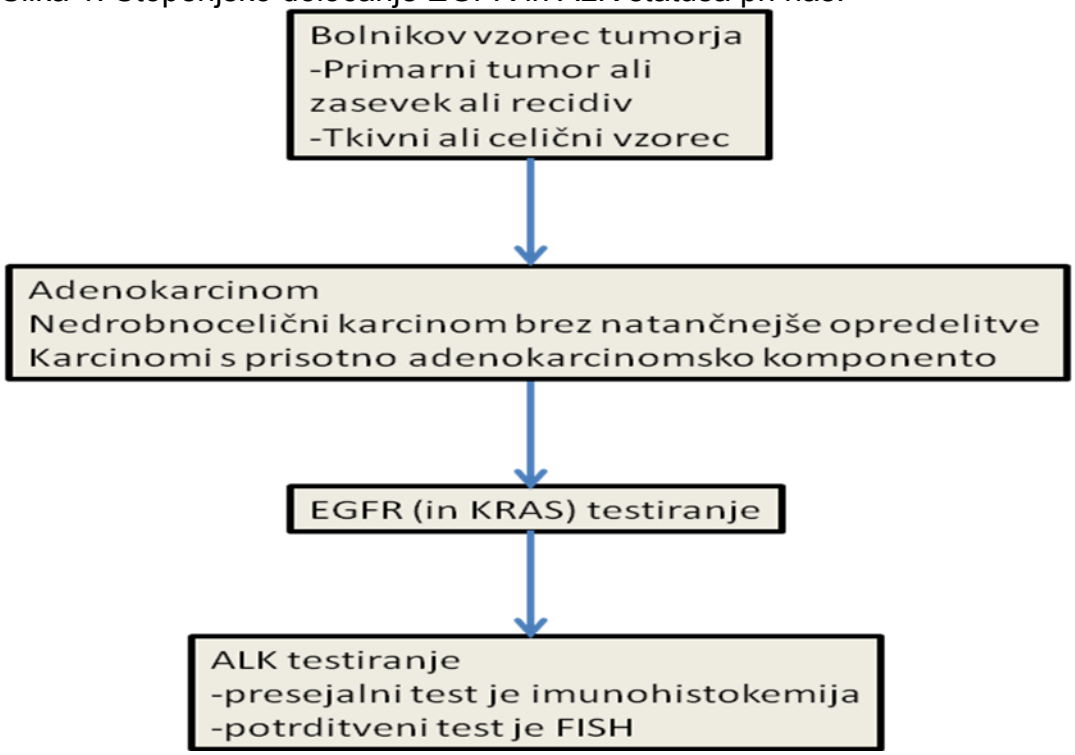
Zahteve po zanesljivi diagnozi pljučnega karcinoma, čimbolj natančni opredelitvi njegovega tipa in določitvi napovednih dejavnikov terjajo optimalno organizacijo dela v laboratoriju, stalnemu izboljševanju v predanalitski fazi in skrbi za ustrezno shranjevanje bolnikovih vzorcev tumorja (6). Optimalna diagnoza je možna le, če ima patolog na voljo optimalen vzorec. Optimalnost vzorca je določena z njegovo količino, visoko vsebnostjo viabilnega tumorja, hitro in ustrezno fiksacijo po odvzemu vzorca, pravilnim in pravočasnim transportom v laboratorij, izpolnjeno napotnico z vsemi zahtevanimi in pomembnimi podatki, identifikacijo vzorca v laboratoriju, sistemačnim sekundarnim vzorčenjem, dolžino fiksacije znotraj priporočenih časovnih okvirov in standardno obdelavo vzorca v laboratoriju prilagojeno vrsti tkiva/celic. Kirurške vzorce po možnosti sprejemamo sveže in takoj opravimo sekundarno vzorčenje. Tumor fiksiramo in shranimo na različne načine, kar omogoči izvedbo rutinske obdelave vzorca in različne molekularne teste. S takšnim pristopom je možno

ustvariti tumorsko banko in bolniku tudi kasneje omogočiti nova testiranja ter s tem dostop do novih oblik zdravljenja. Patolog mora vzbuditi v sodelavcih, ki imajo opravka v laboratoriju z obdelavo bolnikovih vzorcev tumorja, skrben in odgovoren odnos. Razumeti morajo pomen izvajanja laboratorijskih postopkov v kontroliranih in nadzorovanih pogojih.

Tabela 1. Diagnostični algoritem z uporabo osnovnega panela protiteles v imunohistokemiji za natačno tipizacijo nedrobnoceličnega pljučnega karcinoma.

	TTF1	Napsin A	P40	CK5/6
Adenokarcinom	+	+	-	-
Epidermoidni karcinom	-	-	+	+
Nedrobnocelični karcinom brez natančnejše opredelitve	-	-	-	-

Slika 1. Stopenjsko določanje EGFR in ALK statusa pri nas.



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