17th Central European Lung Cancer Conference including Best of WCLC 2018

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Dear colleagues,

It is our pleasure to welcome you to the 17th Central European Lung Cancer Conference including Best of WCLC 2018. The Conference is organized by Institute for Pulmonary Diseases in Sremska Kamenica and Central European Lung Cancer Association – CELCA.

The aim of CELCC is to develop strategies for decreasing the burden of lung cancer in Europe. Therefore, we invite different specialists working in the field of lung cancer to participate at the CELCC 2018.

Thank you for your highly appreciated contribution to this Conference.

We wish you a pleasant and rewarding stay in Novi Sad!

On behalf of the Organizing Committee, sincerely,

Prof. Dr Ilija Andrijević	Prof. Dr Nevena Secen	Prof. Dr Robert Pirker
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INVITED LECTURES

IL1

TOBACCO CONTROL IN SERBIA: GUIDELINES FOR THE FUTURE

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The Republic of Serbia ratified the Framework Convention on Tobacco Control in 2005 whichentered into force on May 2006. In 2007, Strategy for Tobacco Control was adopted for the period 2007-2015. Currently, several important laws regulate different aspects of importance for tobacco control and these laws are under jurisdicition of three ministries, namely: Law on protection of citizens from exposure to tobacco smoke (under Ministry of Health); Law on Tobacco and Law on Excise Tax (under Ministry of Finance) and Law on Adertising and Law on Consumer Protection (under Minstry of Trade, Tourism and Telecommunications).
According to the WHO report on the global tobacco epidemic from 2017 the level of implementation of specific measures differs with Monitoring and Taxation being marked with best grades as shown in the picture below:

Summary MPOWER WHO assesment for Serbia

M	M	O	W		E	R
MONITORING	SMOKE-FREE POLICIES	CESSATION PROGRAMMES	HEALTH WARNINGS	MASS MEDIA	ADVERTISIN G BANS	TAXATION
4 (1-4)	3 (1-5)	4 (1-5)	3 (1-5)	2 (1-5)	4 (1-5)	5 (1-5)

Source: WHO report on the global tobacco epidemic, 2017

Several nationally representative surveys and expert opinions provide the basis for identification of the current challanges in tobacco control in Serbia and give guidelines for the future steps:

- The gap in current Law on protection of citizens from exposure to tobacco smoke.
  Smoking is banned in all enclosed public and workplaces and public transportation with anexemption for the hospitality (owners can decide if smoking is banned or permitted if premises is < $80m^2$, while for the permises> $80m^2$ –smoke free area must be providedat least 50%)
- Insuficcient complience with current legislation both in terms of smoking ban and ban on selling tobacco products to minors(i.e 81.2% of 13-15 years old students not prevented to buy tobacco product because of age)
- Tobacco control legislation is not aligned with EU legislation (i.e. there areno pictorial warnings)
- High exposure to tobacco smoke, high smoking prevalence among adults with significantly higher prevalence among vulnerable groups such as Roma Youth, sex workers (with prevalence reaching more than 90%), children without parental care.
- No national quit line
- Low coverage with smoking cessetion services
- Presence of new products (e-cigarettes, vape mods, Heated Tobacco Products)

Based on challanges, specific guidelines for tobcco control for the future are identified:

- Better implementation of current legislation
- Adoption of the new Strategy for Tobacco Control with Action Plan
- Implementation of Protocol to Eliminate Illicit Trade in Tobacco Products
- Aligment with EU tobacco control legslation (EU Tobacco product directive 2014/40, other recommandation for smoke free enviroment)
- The steady increase in resources for tobacco control
- Change of social norms
- Capacity building of health professionals for smoking cessetionand increasing their motivation for a more active role in smoking prevention and cessetion
- Urgent need for strenghtening smoking cessetion services
- Strenghtening evidence based interventions tailored to the different population groups
- Response to new challanges in tobacco control (wateripe, ecigarettes, Heated Tobacco Products)
- Support to further research (i.e. to assess needs of vulnerable groups; motives and bariers to smoking cessation; social norms; Global Adult Tobacco Survey; economic burden of tobacco use; the share of illicit trade; measurement of airborne nicotine levels at public places)
- Support to civil society
- Strenghtening international coopreation

IL2
IMPLEMENTATION OF LUNG CANCER SCREENING: THE HUNGARIAN EXPERIENCE

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Lung cancer is the cause of death of around 8000 Hungarian citizens each year. The HUNCHEST study launched in 2014 as pilot project examines the possibilities of a lung cancer screening program in Hungary utilising low-dose CT (LDCT) screening. As of July 2018, 1600, patients were screened, and recruitment is still ongoing. COPD is a recognised risk factor of lung cancer; therefore, patients are divided in four subgroups to analyse the relation of smoking and COPD to screening results. We will present the organizational tasks of setting up a screening program, and preliminary results as of November 2018.

IL3
NOVEL MOLECULAR LANDSCAPE OF NSCLC

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The completion of the Human Genome Project in 2003 allowed the implementation of genomic medicine in clinical practice. Cancer was shown to be a disease of the genome with different hallmarks including genome instability and an accumulation of somatic mutations. Non–small cell lung cancer (NSCLC) has become a prominent example of precision medicine among solid tumor malignancies,

Comprehensive genomic profiling of lung cancers revealed their genetic heterogeneity and complexity and identified numerous targetable oncogenic driver alterations. These molecular profiling efforts have made it possible to exploit the potential of molecularly targeted therapies. Selection of patients for targeted therapies is becoming biomarker-driven, where the oncogenic drivers in patient tumors are first identified, and subsequently patients bearing drug-sensitizing genetic aberrations are matched to the appropriate targeted therapy. Success of this design of clinical trials and practice was first demonstrated in EGFR inhibitor trials in lung cancer and has since been incorporated into subsequent targeted therapy trials including ALK-, ROS1-, and BRAF V600E-targeted therapies.

As molecular testing becomes increasingly important, preserving tissue for this purpose while rendering an accurate histologic diagnosis becomes a key consideration, especially in advanced-stage NSCLC, in which small biopsy samples are often the only specimen available. Next-generation sequencing panels are a powerful method of providing information relevant for both standard-of-care and investigational treatment options. However, taking advantage of the abundance of information gathered from these panels requires careful annotation, prioritization, and reporting of molecular findings and their clinical significance. Although molecular profiling has traditionally relied on direct sampling of tumor tissue, blood-based diagnostics (liquid biopsy), now offer the potential to provide some clinically useful information noninvasively.

Key words: NSCLC, somatic mutations, next generation sequencing, liquid biopsy

IL4

ACQUISITION OF LUNG CANCER GENOMIC TISSUE BY EBUS- AND EUS-GUIDED METHODS

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A personalized approach can reduce lung cancer (LC) mortality. Molecular tests identifying genetic mutations in nonsmall cell lung cancer (NSCLC) can lead to more effective and personalized treatment targeted to mutations. Adequate tissue is required to diagnose, subcharacterise and genotype NSCLC by morphological, immunohistochemical and molecular techniques. Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA), transesophageal ultrasound-guided fine needle aspiration (EUS-FNA) and radial-probe endobronchial ultrasound (RP-EBUS)-guided diagnostic methods have proved to be reliable in diagnosis and staging LC. *But are they sufficient for molecular analysis?* The aim of this lecture is to review the current role of EBUS- and EUS-guided methods in molecular analysis and to recommend *a rational approach for optimal specimen acquisition and processing with regards to personalized care in LC*. In advanced NSCLC, using the least invasive technique is prudent. EBUS-TBNA, RP-EBUS-guided methods, or EUS-FNA is a minimally invasive technique. Cell blocks and smears of EBUS specimens Cekićare smaller than surgical specimens. However, EBUS/EUS-guided methods are advantageous (vs surgical methods) regarding sedation, safety, patient comfort, cost-effectiveness, comorbidies, poor performance. RP-EBUS-guided brushing, TBNA, forceps biopsy and bronchial washing increase diagnostic yield from 36% to 58-70% using a guide sheath, and from 63-69% to 84-90% using electromagnetic/virtual bronchoscopic navigation. EBUS-TBNA -widely accepted and minimally invasive for intrathoracic lesions- has replaced mediastinoscopy as first-line approach in diagnosis/staging with a sensitivity of 93-96% as it can access bilateral paratracheal and hilar, prevascular and subcarinal lymph nodes. EUS-FNA or EUS-FNA with EBUS scope (EUS-B-FNA) can access aortopulmonary, left paratracheal, subcarinal, paraesophageal and pulmonary ligament nodes and has comparable diagnostic performance to EBUS-TBNA. Both methods are complementary to surgical methods, not a substitute. Confirmatory surgical staging is required if they are negative/nondiagnostic. They can also be used for restaging after chemotherapy, surgery and radiotherapy besides rebiopsy on change of tumor behavior, relapse or metastasis. Combined endosonographic approach (EBUS-TBNA + EUS-FNA / EUS-B-FNA) has higher sensitivity than surgical staging and decreases unnecessary thoracotomies. EBUS-TBNA / EUS-FNA have high but variable adequacy for molecular analysis (70-99%) owing to heterogeneity of pathological techniques and sample sizes. In this era of personalized therapy, management depends on specimen phenotype and genotype. Thus, specimen collection and processing should be optimized. Bronchoscopist and cytologist must collaborate for ensuring adequate quality, quantity and processing of the specimens. Adequacy for biomarker testing is 70-95% with EBUS-TBNA or EUS-FNA and 71% with RP-EBUS-guided methods. Smears or cell blocks can provide high diagnostic yield (>90%) and adequacy for molecular analysis (72-98%); they are complementary to each other. Rapid onsite evaluation (ROSE) by a cytologist increases accuracy and adequacy (70-95%) for reliable molecular analysis of EBUS-TBNA / EUS-FNA specimens. ROSE decreases number of needles passes and sampled stations and obviates transbronchial biopsy. *"NSCLC not otherwise specified" (NSCLC-NOS)* means presence of

identified tumor cells but histological subtyping is not possible by morphology and staining. This occurs in 4-50% of cases and no active treatment can be done in 50-70% but cell blocks and immunohistochemistry can differentiate adenocarcinomas and squamous cell carcinomas in 73-95%. There is no strong evidence on superiority of 21-G EBUS needle over 22-G needle in diagnostic and molecular analysis. In acquiring and processing EBUS-TBNA /EUS-FNA/ RP-EBUS specimens, ROSE- together with cell block preparation- optimizes diagnostic performance by repeat aspirations from diagnostic sites and enables allocation of additional specimens for processing by priority and in appropriate triage for cytological, histological and molecular analysis. Several tissue particles should be available for cell block on "adequate ROSE". Bronchoscopist and ROSE cytologist together can decide whether sufficient specimen is obtained for cytological study and cell blocks for immunohistochemical and molecular analysis. Furthermore, implementation of local institutional strategies are required for diagnostic modalities, molecular analyses, cost-effectiveness, quality control, monitoring for safety and efficiency.

IL 5
IMMUNOTHERAPY FOR LUNG CANCER

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Lung cancer is among the tumours which are most studied as the targets of immune-based therapies in oncology. A variety of approaches have been investigated, including active immunisation with therapeutic vaccines, nonspecific immunotherapies (cytokines, inhibition/activation of regulatory factors like anti-CTLA-4 and anti-PD-1/PD-L1), and transfer of activated immune cells with antitumor activity. High interest in therapeutic vaccines decreased dramatically after failure of three well-known randomised phase III trials – MAGRIT, START and STOP, altogether with more than 4 000 participants (1, 2, 3). Nevertheless, there are two vaccines used in advanced NSCLC (non-small-cell lung cancer) in some countries outside of the EU, mostly like a switch maintenance. CIMAvax-EGF was developed in Cuba and the phase III international trial is ongoing also in the EU (4, 5). Racotumomab was developed in Cuba and Argentina. Large international phase III trial was completed, and the results are expected (6, 7). Recently, the new knowledge about the synergistic effect of vaccines and immune check-point inhibitors have again changed the view of vaccines, and the promising clinical research on this area is ongoing not only in lung cancer (8, 9, 10, 11). The immune checkpoint inhibitors anti-PD-1/PD-L1 monoclonal antibodies are the most successful nonspecific immunotherapies for lung cancer. Nivolumab, pembrolizumab (anti-PD-1), and atezolizumab (anti-PD-L1) were approved by EMA for the second-line treatment of advanced NSCLC after failure of the previous systemic therapy. All phase III trials leading to these approvals showed better overall survival (OS) and better toxicity profile than docetaxel (12, 13, 14, 15). A systemic review and meta-analysis aimed on comparative effectiveness of these drugs in previously treated NSCLC confirmed the positive dose-response relationship between PD-L1 expression and survival benefit, and little evidence of survival differences between nivolumab, pembrolizumab and atezolizumab (16). Only pembrolizumab is registered in the EU for the first-line treatment of advanced NSCLC, based on the phase III trial KEYNOTE-024 comparing pembrolizumab against chemotherapy in patients with high PD-L1 expression - TPS, tumour proportion score, 50% and more (17). Recently, similar study (KEYNOTE-042) has confirmed benefit of pembrolizumab against chemotherapy in patients with PD-L1 TPS 1 and more (18). The results were still better in the subgroup of patients with high PD-L1 expression (TPS 50% and more). However, the results of other positive phase III trials aimed on combination of chemotherapy with PD-1/PD-L1 inhibitors were published in 2018. These trials open new prospects both for patient with advanced squamous NSCLC (19, 20) and non-squamous NSCLC (21, 22). In addition, the published results of phase III trial aimed on the combination of anti-CTLA4 and anti-PD1 drugs (ipilimumab and nivolumab) indicate that the combination is especially effective in patients with high tumour mutation burden (23, 24). Immune check-point inhibitors are studied in all stages of NSCLC. The first successful trial in stage III NSCLC compared the anti–PD-L1 antibody durvalumab as consolidation therapy with placebo in patients who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy (25). Finally, there is good news also for patients with extensive small-cell lung cancer. The phase III IMpower133 study, comparing atezolizumab plus standard chemotherapy (carboplatin, etoposide) against standard chemotherapy, recently met its coprimary

endpoints of overall survival (OS) and progression-free survival (PFS) at its first interim analysis (26). Extensive research of immunotherapy in lung cancer continues in all imaginable combinations and settings, so the title of the recent article covering ASCO 2018 Conference "*End of an Era" for chemotherapy in non-small-cell lung cancer* (27) is not so far from reality.

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IL 6
EGFR-MUTATED NON-SMALL CELL LUNG CANCER MANAGEMENT

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The epidermal growth factor receptor (EGFR, ErbB1, HER1) belongs to the ErbB family of proteins, which is composed of four structurally related receptors – ErbB1 to ErbB4. EGFR is a monomer located in the cell membrane. It consists of extracellular, transmembrane and intracellular domains. If ligand binding occurs (EGF and TGF-α), a conformational change occurs that causes homo- and hetero-dimerization of the receptors. The dimeric EGFR becomes catalytically active and is capable of phosphorylation of a large number of tyrosine ends of the molecules. Activation of tyrosine kinase activity triggers a signaling pathway towards the cell nucleus. The effect of EGFR activation has been linked with increased cell proliferation, angiogenesis and invasiveness of the tumor cell, increase in its metastatic potential, and decreased apoptosis.

Activation mutations of the EGFR gene occur in about 40% of NSCLC patients in the Asian population and about 10-15% in the Caucasian population. These mutations are present in exons 18-21 that encode receptor kinase activity. The most common mutations are deletions in exon 19 (deletions 746 - 750) and a point mutation in exon 21 (L858R). EGFR mutations are more common in Asians, women, and in adenocarcinomas.
For the treatment of advanced NSCLC manifesting these mutations, first- and second-generation tyrosine kinase inhibitors (TKIs) of this receptor are used in the Czech Republic (afatinib, erlotinib, gefitinib). The presence of EGFR mutations is being examined in the Czech Republic in adenocarcinomas, non-squamous NSCLC, adenosquamous carcinoma, and in non-otherwise specified non-small cell lung cancers. The use of EGFR-TKIs in the first line leads to a significant prolongation of progression-free survival and to an increase in objective response compared to standard chemotherapy
However, despite the initial response and a prolonged remission, most patients treated with EGFR-TKIs develop resistance within about 12 months, leading to progression of the disease. T790M mutation is the most common cause (up to 60%) of the acquired resistance to EGFR-TKIs. This mutation is located in EGFR gene's exon 20 and leads to the exchange of threonine for methionine at the 790 position of the receptor kinase domain. Osimertinib was developed to overcome the resistance, and efficacy was also demonstrated in rociletinib, nazartinib, and avitinib (third-generation EGFR-TKIs).
Even during the treatment with third-generation EGFR-TKIs, resistance develops. Point mutation C797S in exon 20 was identified as the most common cause of resistance in third-generation TKIs.
In this paper, we will look at the results of treatment with EGFR-TKIs of the first, second and third generation.

IL 7
ALK-POSITIVE NON-SMALL CELL LUNG CANCER MANAGEMENT

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ALK (anaplastic lymphoma kinase) is a tyrosine kinase target in several different cancers, including non-small cell lung cancer (NSCLC). In NSCLC, ALK is activated by chromosomal re-arrangement, leading to constitutive kinase activation and oncogene addiction. Frequency of this re-arrangement (named also fusion or positivity) is 3-7% of all NSCLC.

Re-arrangements in the gene encoding the ALK on chromosome 2p were first discovered as oncogene driver alterations in NSCLC in 2007, and first clinical results with ALK TKI crizotinib were reported already in 2010. Methods of detection today are immunohistochemistry, fluorescence in situ hibridisation and next-generation sequencing.

Three „generations“ of ALK TKI, defined by increasing „on target“ efficacy toward ALK exist today in clinical practice. Crizotinib belongs to the 1st generation, alectinib, ceritinib and brigatinib to the 2nd generation and lorlatinib to the 3rd generation. Crizotinib was superior in comparison to chemotherapy doublet, with PFS of 11months and became the standard of care in ALK-positive NSCLC. In last few years, ceritinib was also superior to chemotherapy in 1st line, with PFS of 16 months, and alectinib achieved far best results with PFS of 25 months, compared haed-to-haed to crizotinib. All three drugs are now available for 1st line treatment, but alectinib have one more advantage - much better CNS activity.

Brigatinib, and particularly lorlatinib are ALK-inhibitors of new generation capable to be effective in second and later lines, especially after failure to crizotinib. Spectrum of secondary mutations make the task of these drugs more complicated. Lorlatinib is, for example, active against most frequent secondary mutation, G1202R. Numerous ALK-independent mechanisms are responsible for resistance to ALK TKI therapy –activation of „bypass“ signaling pathways that circumvent the inhibited ALK fusion protein.

Combinations of ALK-inhibitors and MEK or CDK4/6 or even checkpoint inhibitors have been used in numerous clinical trials, mostly still ongoing. Combination of crizotinib and nibolumab is of limited efficacy but with unaceptable toxicity, and that study was early terminated.

As a summary, second generation ALK TKIs (alectinib, ceritinib) have shown superior clinical outcome, compared with first generation crizotinib. These, more potent inhibitors (to delay resistance development and reduce CNS involvement) are emerging as the new standard 1st line for metastatic ALK-NSCLC.

It is not clear how best to sequence ALK TKI therapy, or how to overcome acquired resistance that is not mediated by an ALK kinase domain mutation (still limited data about efficacy of next generation of ALK TKIs after progression on 1st line alectinib or ceritinib).

IL 8
THE ROLE OF SUPPORTIVE CARE IN LUNG CANCER MANAGEMENT

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Introduction: lung cancer (LC) is most common cancer and most frequent cause of cancer death in the world today. About 79% of LC patients were in stage III and IV at diagnosis. LC often presents at an advanced stage and result in a significant symptomatic burden. Supportive/ palliative care necessary to start at time of diagnosis and apply concurrently with disease-directed, life-prolonging therapies to improve quality of life.
Dyspnea: it is necessary to comprehensively assess the symptoms, educate patient/family on patient's condition and risk/benefits of treatment options.
Anorexia/cachexia: evaluate rate/severity of weight loss and associated symptoms. Focus on patient goals and preferences. Treat potentially reversible causes and conditions.
Pain: LC patients experience higher rates of pain than patients with other primary cancer diagnoses. All patients must be screened for pain at each contact. Select the most appropriate medication based on the pain diagnosis, comorbid conditions, and potential drug interactions. if necessary, include Interventional strategies.
Cough: cough predict a shorter overall survival in patients with LC. Disease-directed, symptom-directed and additional therapy are options.
Cancer-related fatigue: treatment strategies include: energy conservation, daily and weekly diary, nonpharmacologic and pharmacologic interventions.
Conclusion: The modern era of LC therapies includes an integrated emphasis on patient-centered care through the standard integration of supportive care services to improve value and patient well-being throughout the cancer care continuum, from diagnosis to survivorship or end-of-life care.
Key words: lung cancer, supportive, palliative, quality of life

YOUNG DOCTORS SESSION (CASE REPORTS)

TREATMENT OF A PATIENT WITH METASTATIC EGFR WILD TYPE ADENOCARCINOMA -CASE REPORT

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BACKGROUND: The treatment of metastatic lung adenocarcinoma depends of availability of molecular testing and medicaments, patients age, performance status, and also depends of patient's preferences. The treatment algorithm for EGFR positive metastatic adenocarcinoma giving more opportunities for patients known as long survivors. In contrast, treatment options for EGFR wild type adenocarcinoma is very limited.

CASE PRESENTATION: A 47- year-old man, non- smoker. MSCT scan done in May 2014 showed tumor nodule, longest diameter 46mm, in the left lung lower lobe. June 2014, he underwent thoracotomy. Intraoperative there were metastasis on pericardium, diaphragm and in pleura. The operation was completed at the level of exploration. Histological finding was Adenocarcinoma pulmonis- EGFR wild type. Stage IV A (T2bN0M1a). Patient went through total of 6 cycles of Paclitaxel/ Platinum + Bevacizumab chemotherapy. February 2015 patient underwent VATS exploration and procedure of talc pleurodesis. He received 4 cycles of chemotherapy regime Pemetrexed/ Platinum + Bevacizumab, and then 2 cycles according to the protocol Gemcitabine/ Platinum. October 2015 treatment with Erlotinib started. February 2017 CT scan showed tumor in the left lung with longest diameter 46mm and 9 mm node in the left lung upper lobe. (RECIST v 1.1. SD). Chest MSCT scan in September 2018 showed tumor in the left lung lower lobe with longest diameter 48mm; 15 mm node in the left lung upper lobe; 10 mm node in the right lower lobe. (Recist v 1.1 PD). On visit in September 2018, patient had excellent general condition (PS 0) practiced bike and basketball. In summer and outumn 2018 riding a bike he exceeded 130km / day. What next?

CONCLUSION: In this case we have described administration of TKI -Erlotinib showed efficacy despite of wild type EGFR. This is an example of performance-based model treatment.

KEYWORDS: Adenocarcinoma; EGFR wild type; Erlotinib.

IS SURGICAL TREATMENT AN OPTION IN LIMITED-DISEASE SCLC? – 2 CASE REPORTS

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Small cell lung cancer (SCLC) is characterized by high malignant potential and poor prognosis. Stage I-IIA SCLC is diagnosed in less than 5% of patients with SCLC. Patients most likely to benefit from surgery are those with SCLC in clinical stage I-IIA (T1-2, N0,M0). Prior to surgery standard staging evaluation must be done (CT of the chest and upper abdomen, brain MRI and PET/CT imaging). Also, prior to surgical resection, all patients should undergo mediastinoscopy or other surgical mediastinal staging procedures so occult nodal disease can be excluded. For patients who are undergoing definitive surgical resection, the preferred surgical resection is lobectomy with mediastinal lymph node dissection. Here we report 2 cases of limited disease SCLC. The first case is women with limited diseases SCLC (T2aN0M0) who was treated first with chemotherapy (2 cycles – cisplatin and etoposide - PE) and after that was assessed with standard preoperative evaluation. During preoperative evaluation the dissemination of SCLC was not noted. However, mediastinoscopy revealed metastases in lymph nodes position 4 right and 7 so no further surgery was done. After that, patient was treated with additional 2 cycles of chemotherapy (PE), but soon liver metastases were discovered, and she was treated with second line chemotherapy (CAV protocol). After only two cycles, she did not tolerate any further chemotherapy and in a very near future she passed away. The second case is women also with initially limited disease SCLC (T2aN0M0) who after confirmation the diagnosis immediately underwent standard staging evaluation (CT of the chest and upper abdomen, MRI of the brain and *bone scintigraphy*). After complete preoperative evaluation was done, first mediastinoscopy which did not discover occult nodal disease, and then VATS with lobectomy of the middle lobe was performed (pT1cN0M0). After surgery, patient received adjuvant chemotherapy (4 cycles of chemotherapy – PE protocol) and after the control CT scan of thorax and abdomen was normal, PCI was performed. The patient is currently ECOG PS 0. In conclusion, a good selection of patients with limited disease SCLC is crucial, when surgical treatment is considered as therapeutic option. Only small number of these patients who prior to surgery are in stage I-IIA (T1-2, N0, M0) can and will have benefit from this type of treatment.

Key words: limited disease, small-cell lung cancer, surgery

DIAGNOSIS AND TREATMENT EGFR MUT + NSCLC PATIENT - A CASE REPORT

Marina Cekić

Introduction: EGFR TKis represents the standard of care as first-line treatment for advanced EGFR-mutated NSCLC. Patients with localized distant progression and ongoing systemic control, continuation of treatment with EGFR TKI in combination with local treatment of progressing metastatic sites may be considered. About half of the resistance on TKi is explained by the acquired EGFR exon 20 T790M mutations. To date, the only approved medication for patients with T790M mutation is Osimertinib.
Case presentation: We present a 71-year-old never-smoking male with lung adenocarcinoma in the left upper lobe, no enlarged mediastinal lymph nodes, with synchronous adrenal metastasis. Patient underwent a left pneumonectomy with mediastinal lymphadenectomy. Molecular testing showed a mutation in EGFR exon 19 deletion. Patient started treatment with TKi Gefitinib and he underwent a left adrenalectomy. After eighteen months on Gefitinib, the disease progressed. Liquid biopsy showed T790M + and patient started treatment with Osimertinib. After eight months, the disease progressed- local tumor recurrence at the surgical incision.
Discussion: This case demonstrates that surgical intervention can be considered for certain patients with synchronous adrenal metastasis. An aggressive treatment was chosen. This included radical surgical treatment and metastasectomy as well as TKi. The patient had survived 18 months without morphological (CT scan) and metabolic (PET/CT scan) activity of disease until first progression.
Conclusion: Surgical treatment, if the patients can tolerate the surgery, can extend the survival in stage IV NSCLC patients, because surgery remains the only potentially curative treatment. Local Consolidative Therapy (LCT) in oligometastatic NSCLC is a new movement within the oncology field toward being more aggressive in patients who have a better prognosis. Target therapy, directed at mutations in the EGFR gene as the first and second line, provides longer survival with good control of the disease and good quality of life.

CASE REPORT
PEMBROLIZUMAB IMMUNO-RELATED TOXICITY IN TREATMENT NSCLC

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Immunotherapy treatment in a 62 years old female patient with metastatic lung cancer.
After VATS was done, pathohystological finding confirmed Adenocarcinoma pulmonum, with EGFR and ALK negative, PDL1 >50% positivity. Treatment started with Pembrolizumab. After third day of fifth cycle, she was presented to MD with complaint of nausea/vomiting, anorexia and fatigue. In laboratory results, elevated values of liver enzymes, alkaline phosphatase were seen with normal value of bilirubin. Ultrasound was done – no pathologic findings were detected. Viral serology and viral load (HCV, HBC, EBV, CMV) was done – all negative tests. Patient declined alcohol consumption and medication changes. Immuno-hepatitis was diagnosed and treatment started with prednisone 1,5 mg/kg/day and monitoring LFTs every 48 hours. The LFTs abnormalities at 96 hours they rise again and mycophenolic acid is added orally with a pulse of steroids. Infliximab /anti TNFα agents/ was not used due to fear of hepatotoxicity. The patient is placed on prophylaxis with AB therapy/Bactrim/ 30 days into the oral steroids. Best responce was stable disease, but in spite of her request, no further pembrolizumab is given. Six months after the episode of immuno-related hepatitis, the disease remains stable and she is off all anticancer therapy.

IMMUNE-RELATED HEPATOTOXICITY
Case report

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Introduction: Immune checkpoint inhibitors (ICIs) are increasingly used to treat a variety of cancers. Despite the promising results, adverse events, as a result of immune-related toxicities, affecting a variety of organs, remain a concern. Immune-mediated hepatitis is defined as an elevation in the patient's liver function tests that has no alternate etiology**.** Hepatitis is usually mild but may be severe, requiring modification or cessation of treatment. Median time to onset is highly variable: 4 weeks to 25 weeks.
Case presentation: We present a case of 59 years old male patient, with no history of chronic diseases, heavy smoker. CT scan of the chest and FNA biopsy were performed and lung adenocarcinoma was diagnosed, cIIIb. EGFRwt, ALK rearrangement-negative. PD-L1 expression 80%. The treatment has been carried out with Pembrolisumab in Clinic for pulmonology, Clinical Center of Serbia during two months period (april/may 2018.). Ten days after completing the third cycle, patient complained of intensive weakness, dark urine, pain in joints. Physical examination showed icterus of the sclera and the skin. Laboratory findings showed elevated liver enzymes and hyper-bilirubinemia grade IV /AST 5179 (0-37); ALT 6414 (0-41); GGT 176 (0-55); Bilirubine T 237,1 (0-20,5); bilirubine D 149,1/. Serologic analysis HIV, HbsAg, Anti HCV were negative. He was immediately hospitalised in Metabolic unit of Emergency Centre, CCS. The treatment was continued in Clinic for gastroenterology and hepatology, and the rehabilitation resumed in the hospital of the regional medical centre. Immunotherapy was permanently discontinuated. Patient was treated with supportive therapy including corticosteroids, albumine iv, 8% Hepasol and other infusions, FFP 10 ml/kg. Liver enzymes and the other laboratory findings (coagulation status, proteins, albumine) were normalized within a month, and his general condition got better. Control CT scan of the chest showed partial response. Treatment was continued with chemotherapy, Paclitaxel, Platina. After first cycle radiography of the chest showed futrher regression. Patient is asimptomatic, PS 1.
Conclusions: Hepatic adverse event related to immunotherapy in our study was manageable. All patients undergoing ICPi therapy should be assessed for signs and symptoms of hepatitis with serum transaminases and bilirubin measured before every cycle of treatment. Further studies are needed to develop biomarkers to identify patients at risk to develop such toxicities.
Keywords: Hepatotoxicity; immune checkpoint inhibitors

TARGETED THERAPY AND IMMUNOTHERAPY IN ADVANCED LUNG ADENOCARCINOMA – CASE REPORT

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BACKGROUND: Non small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 85% of all cases. NSCLC does not represent a single disease entity, but rather a group of distinct molecularly-driven neoplasms that shifted therapeutic approach to a personalized setting. Most common mutations in lung adenocarcinoma, with defined therapeutic approach, are EGFR mutation (10% of all lung adenocarcinomas in Caucasian race), followed by ALK translocation (4% of all lung adenocarcinomas). Nowadays, there are well defined targeted therapeutic options, which includes several generations of TKI and ALK inhibitors, which represent first line therapy in EGFR and ALK positive lung adenocarcinomas. Immunotherapy entered the field of lung cancer recently. In contrast to cytotoxic chemotherapy, immunotherapeutic agents produce their antitumor effect by modifying the innate immune process or by inducing a cancer-specific immune response. The main immunotherapy approach in lung cancer is based on checkpoint inhibition, which includes the monoclonal antibody blockade of the cytotoxic T-lymphocyte antigen-4 (CTLA-4) and antibody blockade of the programmed cell death -1 (PD-1) receptor and PD-1 ligand (PDL-1).

CASE: First case we are presenting is 69 years old male who was diagnosed with ALK positive lung adenocarcinoma in stage IIIB, with significant comorbidities, who was receiving first generation of ALK inhibitors during 26 months. Second case is 61 years old female, who was diagnosed with IIIB stage lung adenocarcinoma, EGFR and PD-L1 negative, who was receiving anti PD-L1 and anti CTLA-4 therapy in third line setting, which was followed with maintenance monotherapy with anti PD-L1 antibody, during 16 months. Both patients had good radiological response, which was verified as partial regression, measured by RECIST criteria, and significant clinical improvement.

Keywords: lung adenocarcinoma, targeted therapy, immunotherapy

POSTER PRESENTATIONS

PP 1
APPLICATION OF THE 8TH REVISION OF TNM CLASSIFICATION OF LUNG CARCINOMA

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Introduction. In preparation for the 8th edition of the TNM classification for lung cancer the International Association for the Study of Lung Cancer (IASLC) analyzed 70,967 cases of non-small cell lung cancer (NSCLC). Analysis of the cases of NSCLC has allowed proposals for revisions to the T, N and M descriptors and TNM Stage groupings.
Goal. To present result of pTNM classification at Institute for pulmonary diseases of Vojvodina in one-year period.
Material and methods. All patients diagnosed and operated with NSCLC in one year period were included in this study. Exclusion criteria were incomplete resection and primary tumor resection without lymph node resection.
Results. From 185 patients, 57 (31%) were females and 128 (69%) were males, aged from 26 to 82 years (average 62 yrs (±7,7)). Pathohistological diagnosis revealed adenocarcinoma in 46%, squamous cell carcinoma in 42%, large cell neuroendocrine carcinoma (LCNEC) in 6%, while other types of carcinoma were diagnosed in 6% of patients. Size of the tumor ranged from 1 cm to 10,5 cm. In 64 patients we found lymph node metastasis, of which 47 (73,4%) had N1, and 17 (26,6%) N2 stage of the disease. Invasion of visceral pleura was found in 28 (15%) patients, type PL1 in 71,4% and PL type 2 in 28,6%. After applying 8th revision of TNM, in 48,65% (90) of patients TNM stage has changed.
Conclusion. Multi-disciplinary approach and the close cooperation among medical and radiation oncologists, pulmonologists, surgeons, radiologists and pathologists is important in properly staging of lung cancer as well as, in treatment plans.
Key words: lung carcinoma, TNM classification, diagnosis

PP 2
SCLEROSING PNEUMOCYTOMA: OUR TEN-YEAR EXPERIENCE

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Introduction: Sclerosing pneumocytoma represents a rare, benign tumor of the lung with uncertain histogenesis and challenging diagnosis.
Goal: The goal of this study is to analyze demographic, clinical, morphological, histological and immunohistochemical features of sclerosing pneumocytoma.
Methods: This is a retrospective study of six patients diagnosed with sclerosing pneumocytoma in the ten-year period at the Insitute for Pulmonary Diseases of Vojvodina. The study analyzed various parameters that are: sex, age, symptoms, size and location of the tumor and its gross and histological features.
Results: Sclerosing pneumocytoma was more frequently diagnosed in females (83%). The patients ranged in age from 38 to 61. Most of the patients (66%) were asymptomatic. Two patients underwent a video assisted thoracoscopic surgery, 2 patients had a video assisted minithoracotomy, and 2 patients underwent a thoracotomy in order to remove the tumor. In 50% of the patients the tumor was localized in the lower left lobe, in 33% it was localized in the upper right lobe, and in the 16.6% the location was in the lower right lobe. The tumor size ranged from 1 cm to 2.5 cm. Pathological examination of all 6 cases reported that all 4 major histological patterns were found in tissue sections: solid, papillary, sclerosing and hemorrhagic. In all 6 cases, immunohistochemical analysis showed positive expression of TTF-1 and panCK in surface epithelial cells, and TTF-1 positivity and panCK negativity in round stromal cells.
Conclusion: Due to similarity with lung adenocarcinoma, adequate diagnosis of sclerosing pneumocytoma requires histopathological analysis with applying of immunohistochemical methods.
Keywords: sclerosing pneumocytoma; histopathology; immunohistochemistry.

PP 3

PLASMA ctDNA ANALYSIS FOR THE DETECTION OF EGFR T790M SECONDARY MUTATION IN LUNG ADENOCARCINOMA PATIENT– CASE REPORT

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Introduction: Acquired resistance and progression of epidermal growth factor receptor (EGFR)-driven non-small-cell lung cancer after the first or second generation tyrosine kinase inhibitors (TKIs) therapy present a challenge for clinicians. Analysis of plasma circulating tumor DNA (ctDNA) is a potential diagnostic tool to determine the presence of EGFR T790M secondary mutation which causes about 40-50% of these resistant cases.

Case report: We present a case of a 71 year-old Caucasian man, former smoker with a positive family history for lung cancer, who visited our hospital because of cough and fatigue. In November 2017 computed tomography demonstrated nodules in the left lung and left-sided pleural effusion. Video-assisted thoracoscopic surgery (VATS) was performed and biopsy of parietal pleura yielded the diagnosis of lung adenocarcinoma (stage IV, ECOG 1) harbouring EGFR exon 19 deletion. In January 2018 gefitinib was selected for the treatment. Despite the initial response, this patient acquired resistance to gefitinib with metastatic changes in bones, liver and lungs - progression-free period of about 10 months. Liquid biopsy, which required only 5 mililitres of peripheral blood, allowed EGFR mutation testing by analysis of ctDNA. The result identified the presence of deletion in exon 19+exon 20 T790M point mutation. Cobas® Mutation test v2 was used to detect EGFR mutations in tissue and plasma. This patient was initiated on osimertinib treatment, the third generation TKI, in November 2018.

Conclusions: Molecular characteristics of a tumor can be determined from plasma-derived ctDNA which presents convenient and minimal invasive liquid biopsy.

Keywords: EGFR, ctDNA, T790M, osimertinib

PP 4

THE ADEQUACY OF BRONCHOSCOPIC BIOPSY IN THE DETECTION OF EPIDERMAL GROWTH FACTOR RECEPTOR IN LUNG ADENOCARCINOMA

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INTRODUCTION: Adenocarcinoma (ADC) of the lung is the most common type of lung cancer. The most reliable method in detecting EGFR mutations is real-time RT-PCR. It is recommended to sample three to five biopsy samples with a minimum of 200-400 preserved tumor cells (TC).
The aim of this research is to determine are they bronchoscopic samples adequate for the determination of EGFR mutations in ADC.

MATERIAL AND METHODS: This retrospective analysis included of 60 patients with ADC diagnosed in the Institute for Pulmonary Diseases in Sremska Kamenica during the period 2010. to 2015. All cases included the identification of morphometric parameters, concentration of isolated DNA and EGFR mutation type.

RESULTS: Biopsy samples of an average size of 1.32 mm were most commonly obtained by transbronchial biopsy (63%). In 35% of cases there were one and two samples, ≥ 10% of preserved tumors was found in 68% of cases. Considering the number of TC, the majority of cases (33%) were classified into Group V (>200≤500 TC) and only 8% of cases in Group II (>20≤50 TC). There was no statistically significant difference between the concentration of isolated DNA in wilde type and mutated EGFR ADC (p=0.641). Invalid results were found in 10% of cases. Only two mutations were detected (insertions in exon 20 and exon 21).

CONCLUSION: Bronchoscopic samples were adequate for the determination of EGFR mutations since the majority of bronchoscopic samples had more than 100 TC.

PP 5
MALIGNANT PLEURAL MESOTHELIOMA - OUR FIVE-YEAR EXPERIENCE

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INTRODUCTION: Malignant pleural mesothelioma (MPM) is a rare malignant neoplasm of the pleura and can be divided into three subtypes: epithelial, sarcomatoid and biphasic. MPM presents with different respiratory symptoms and several chest CT features similar to more common pleural diseases.
The aim of this study is to describe the clinical data and histopathological features in all cases of MPM.
MATERIAL AND METHODS: This retrospective analysis included clinical data of 44 patients with MPM diagnosed in the Institute for Pulmonary Diseases in Sremska Kamenica during the period 31. jun 2013. to 31 jun 2018.
RESULTS: There were 44 patients (37 male and 7 women) with a median age of 67.4 (range, 39 to 83) years. Twenty of the patients with MPM (45%) presented with a pleural effusion and about half patients had chest pain and cough. Other symptoms of MPM includeed fatigue, weight loss and sweats. The ipsilateral pleural tickening presented in 52% patients with MPM. Video-Assisted-Thoracic Surgery (95%) and Thoracotomy (5%) confirmed the histologic and immunohistochemical analysis. An extensive immunohistochemical panel was done. All the cases (100%) were positive for D2-40 and negative for MOC3, CEA, TTF-1 and napsin A.
CONCLUSION: The diagnosis of MPM based on immunohistochemistry. There is no single specific marker for mesothelioma. Different combinations of markers were used depending on the differential diagnosis MPM of other malignant pleura diseases.
Key words: malignant pleural mesothelioma, CT chest, immunohistochemistry.

PP 6
SURGICAL TREATMENT OF PRIMARY LUNG CANCER AND SOLITARY CONTRALATERAL METASTASIS - CASE REPORT

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Introduction: Thoracic surgery should be considered as a therapeutic option for patients with stage IV NSCLC with a solitary contralateral metastasis since it improves survival.
Case report: A 60-year-old lung cancer patient, a smoker suffering from paranoid schizophrenia, depression, COPD and angina pectoris, presented with cough, dyspnea and chest pains. The chest X-ray showed bilateral infiltrations. The chest CT scan revealed one lesion in the right upper lobe and the other in the left lower lobe. Cytology of the CT guided transthoracic needle biopsy from the left lower lobe established stage **T1N0M1a** adenocarcinoma**,** confirmed by PET-CT scan as well. EGFR mutation analyses were negative and four cycles of Cisplatin/Gemcitabin chemotherapy were applied. The control chest CT scan showed a reduction of the left lower lobe infiltration, but the lesion in the right upper lobe persisted unchanged. Histopathology of the right upper lobe bronchoscopy sample confirmed a metastatic adenocarcinoma. The control PET CT registered no progression. The primary tumor was surgically treated by the left lower lobe S9/S10 bisegmentectomy and the solitary metastasis was surgically treated by the right upper lobe S3 segmentectomy. The patient received four cycles of Gemcitabin/ Cisplatin based adjuvant chemotherapy. Both the control chest CT and abdominal US findings were free of metastases.
Conclusion: The surgical treatment is reasonable as we expect a better survival of our patient.
Key words: lung cancer, solitary pulmonary metastasis, surgical treatment.

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PP 7
MANAGING TOXICITY OF AFATINIB – A CASE REPORT

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Background: Afatinib is an irreversible second-generation EGFR tyrosine-kinase inhibitor (TKI) which is one of the recommended first line treatment options for EGFR mutated lung adenocarcinoma. Its side-effects are common and well-known but could potentially be serious. We present a case of a patient with severe side effects and their management.

Case presentation

A 76-year-old non-smoker female with ECOG PS1, was diagnosed with stage IV lung adenocarcinoma, EGFR mutation positive (L858R) in December 2016. Tumor board indicated treatment with Afatinib.

Upon initial presentation at our institute she complained of fatigue and dry cough. Echocardiography done in August 2016. showed an ejection fraction (EF) of 45%. A new echocardiogram reported EF of 53%. Due to her age and cardiologic comorbidities, treatment with Afatinib was started in initially reduced dose of 30mg per day.

On her first monthly check-up the patient complained of persistent fatigue and cough, and reported diarrhea for the past 7 days, with 7-8 loose stools per day and loss of 4 kilograms. She had not reported the diarrhea and had not stopped Afatinib. On admission she was PS2 with rash grade 2 and diarrhea grade 3. Echocardiogram was without changes, EF 53%. CBC was in normal range, but urea and creatinin were significantly increased, with creatinin clearance 18ml/min. Chest X-ray showed no signs of progression. Stool cultures were negative for clostridium difficile toxins or other pathogens. Afatinib was stopped immediately and intensive symptom management initiated. After 7 days of treatment the patient was feeling better and renal function was normalized. We restarted Afatinib with a further dose reduction to 20mg.

After 3 months of treatment CT scan showed stable disease which was the best response throughout treatment. The patient was well, with infrequent diarrhea up to grade 2 which she managed with loperamide and occasional short breaks in therapy. Rash was up to gr.1. She complained of minimal symptoms of dry cough. During further course of therapy, no major side effects which required treatment breaks occurred. After 17 months of therapy with Afatinib the patient presented with shortness of breath, dyspnea and cough. Her ECOG PS was 3. CT scan showed progression of the disease. Palliative radiotherapy of the primary tumor was indicated. She was last seen in October 2018, in PS3, palliative care was recommended.

Conclusion: Side effects of EGFR TKIs are well known and common but can lead to severe problems during treatment. Recognising and managing them in a timely manner is of utmost importance to the patients' well being and the continuation of treatment. Dose reductions during afatinib use do not lead to its lower efficacy and this should be used when treating older or frail patients.

Keywords: Lung cancer, EGFR mutation, Afatinib, toxicity

PP8

THE LATE RELAPSE OF EWING SARCOMA/PNET PRESENTING AS PULMONARY METASTASES –A CASE REPORT

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Introduction: Ewing sarcoma is a poorly differentiated, highly malignant, round cell tumour without cellular or structural differentiation. It is characterised by an aggressive clinical course with a high rate of local recurrence and distant metastases. Approximately 75% of cases are localised at diagnosis, and 25% are initially metastatic.

Case Report: The patient was hospitalised for dry cough, hoarseness, headache and the body weight loss of about 4 kg in two months. In February 1987 he had radiation therapy (60Gy) for neuroblastoma of the right nasal cavity proliferating into the lumbar spine, epipharynx, the right ocular cavity, and the frontal sinus, which was diagnosed with transnasal biopsy. In October 2014, the invasive pulmonological diagnostics (bronchoscopy and TTP) was performed and the cytopathological examination of the material obtained from the right lower lobe resulted in malignant cells originating from a Sarcoma Ewing/PNET. The patient underwent a video-assisted thoracoscopy and right anterolateral thoracotomy. A tumour in the upper lobe was seen, as well as a tumor in the lower lobe that invaded the entire lower lobe. The atypical resection of the upper lobe, lobectomy of the right lung lower lobe and mediastinal lymphadenectomy were performed. The definitive histopathological finding corresponds to Sarcoma Ewing/PNET.

Conclusion: Ewing sarcoma/PNET represents a diagnostic and therapeutic challenge. Due to the rarity of this neoplasm and a low number of cases reported in the literature, our findings may be useful for pathologists and surgeons and alert clinicians to the diagnosis, prognosis and recurrence of these tumors.

Key words: Ewing’s sarcoma, metastases, relapse

PP 9
EGFR T790M RESISTANCE MUTATION IN NON-SMALL-CELL LUNG CANCER: OUR EXPERIENCE IN LIQUID BIOPSY AND MOLECULAR TESTING

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Introduction: Patients with non-small-cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR) activating mutations will inevitably become resistant to the first- or second-generation tyrosine kinase inhibitors (TKIs). Approximately 40-55% of resistant cases are due to the acquired EGFR T790M mutation. Circulating DNA found in blood (liquid biopsy) has been proposed as an alternative source of tumor DNA. The aim of this study was the determination of EGFR T790M mutation frequency in investigated population.
Methods: This study included 33 NSCLC patients with EGFR mutations who had experienced progressive disease to TKIs at the Institute for Pulmonary Diseases of Vojvodina and the Special Hospital for Lung Diseases "Dr Jovan Bulajić ". The EGFR mutations were detected by the cobas® EGFR Mutation Test v2.
Results: All tested patients were of Caucasian descent and had the adenocarcinoma subtype of advanced NSCLC. There were 19 (57.6%) female and 14 (42.4%) male patients, the median age was 64.4 (range 43-78 years). The median progression-free survival was 13.6 months (range 2-36 months). All of 33 patients underwent liquid biopsy and T790M mutation was detected in plasma samples of 11 patients. Among the 22 T790M liquid biopsy-negative patients, 7 patients underwent re-biopsy procedures. Of the 7 patients in the rebiopsy group, T790M mutation was identified in 4 samples. Overall, T790M mutation rate established by liquid biopsy and re-biopsy was 45.5% (15/33). T790M always coexisted with a primary EGFR mutation.
Conclusions: Liquid biopsy and tissue biopsy should have complementary roles in identifying T790M-positive patients suitable for the treatment with the third generation TKI.
Key words: Lung cancer, EGFR, T790M, liquid biopsy

PP 10
ERLOTINIB AS SUBSEQUENT THERAPY IN ADVANCED LUNG ADENOCARCINOMA – CASE REPORT

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According to GLOBOCAN data in 2018, lung cancer is the most common cause of cancer-related mortality worldwide, responsible for nearly 1,8 milion deaths a year. Adenocarcinoma as subtype of Non Small Cell Lung Carcinoma (NSCLC) accounts for 40% of all of lung cancers. Expected median survival for patients with locally advanced and metastatic lung cancer is approximately one year. For patients with detected Epidermal Growth Factor Receptor (EGFR) mutations, treatment with targeted tyrosine kinase inhibitor (TKI) can significantly improve their survival rate. This targeted therapy have shown positive efficacy, tolerable toxicity and less side effects compared to widely applied conventional chemotherapy. First-line treatment with erlotinib in patients with detected EGFR mutations (egzone 19 and L858R deletions) results in positive response rate in about 60% of cases. Here we present a patient with metastatic lung adenocarcinoma who has had a complete lung tumor regression since using erlotinib as a subsequent treatment.
Key words: adenocarcinoma, erlotinib, EGFR.

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PP 11
SMALL BOWEL METASTASIS FROM LUNG CANCER

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INTRODUCTION: Lung cancer represents the leading cause of tumor death in the world with 50% of patients presenting metastatic disease at the time of diagnosis. Gastrointestinal (GI) lung cancer metastasis were thought to be extremely rare, but a much higher incidence has been noted in several autoptic reports. Clinical relevance of GI metastasis is low, but can increase with the higher number of newly diagnosed patients and with the efficacy of systemic chemotherapy in advanced stages. Prognosis of complicated GI lung cancer metastasis seems to be worse than the natural course of the disease and acute bleeding or perforation of metastatic site can be accelerated by chemotherapy.

CASE REPORT: We present a clinical case of 59-year old male, former smoker, who was hospitalized in the beging 2017.g. , throuhg our emergency department due to hemoptysis. Diagnostic approach revealed IV stage squamous cell lung carcinoma with multiple pulmonary and hepatic metastases. In that time we didn`t have immunotherapy and molecular testing for PD-L1, so patient underwent chemotherapy. After third cycle of chemotherapy, acc 20 days, patient presenting with acute abdomen due to small bowel perforation confirmed by CT scan. He undergo explorative laparotomy, finding difuse peritonitis and stenosis of small intestine 70 cm far from Treitz, with perforation. After resection, latero-lateral anastomosis was made by stapler. Pathohistology diagnosis of resected small intestine long 16.5 cm, was GI lung cancer metastasis. Patient died several months after.

CONCLUSIONS: Complications of GI metastases, although rare, must be considered as possible cause of acute abdomen in patients with lung cancer. Identification of clinical indicators of GI metastasis may help in the therapeutic strategy. But lung cancer metastases to the small bowel often indicate a poor prognosis; surgery is indicated for palliation.

PP 12
ALECTINIB IN THE TREATMENT OF ADVANCED LUNG ADENOCARCINOMA - CASE REPORT

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Numerous prognostic parameters are used today in the treatment of lung cancer in addition to surgical treatment, radiotherapy and chemotherapy. By detecting gene mutations (EGFR testing), immunohistochemical analysis of ALK rearrangement and PD-L1 testing, a quality therapeutic choice tailored to each patient is provided.

In this paper we present the case of a 34-year-old female patient with advanced lung adenocarcinoma (EGFR negative) where ALK translocation was detected during treatment with the first line of chemotherapy with a positive therapeutic response.

KEY WORDS: lung cancer, adenocarcinoma, anaplastic lymphoma kinase, alectinib

PP 13
RECURRENT MALIGNANT MELANOMA PRESENTING AS ISOLATED PLEURAL METASTASES: A CASE REPORT

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Introduction: Metastatic melanoma is a rare form of skin cancer, but one that comes with a high mortality rate. Pulmonary involvement is frequently seen in metastatic melanoma with only 2% of malignant melanoma patients with thorax metastasis presenting with pleural effusions. Independent of site, metastatic melanoma carries a very poor prognosis with a 10-year survival of less than 10%.
Case report: We report a case of a 56-year-old male patient with unilateral pleural effusion as an unusual metastatic manifestation of malignant melanoma. The patient's medical history included hypertension and completely resected stage IA malignant melanoma on the neck 17 years before this presentation. He was admitedat Institute for Pulmonary Diseases of Vojvodina in May 2018 with progressive cough, occasional dyspnea and fever, which lasted six weaks. Computed tomography (CT) of the chest revealed massive right pleural effusion with few parietal pleural masses along. Diagnostic thoracentesis after removal of 850 milliliters of yellow fluid, showed lymphocytic cytology. Bronchoscopy was performed, endoscopic finding was extramural compression on intermediate, middle and basal. Materials showed usual hystologic elements. A video-assisted thoracoscopic surgery and biopsy of the affected nodular parietal layer of the pleura were performed. Direct pleural visualization revealedclusters of pink and white tissue arising from the parietal pleura. Immunohistochemical staining was positive for Vimentin, WT-1, S100, Melan-A and HMB-45, which confirmed diagnosis of metastatic melanoma.
Conclusion: Althoughit is a rare form of skin cancer, our findings may draw attention of clinicians to prompt diagnosis and prognosis of such tumors.
Key words: malignant melanoma; metastasis; pleural effusion.

PP 14
LUNG CANCER ASSOCIATED WITH BULLOUS EMPHYSEMA– CASE REPORT

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Introduction: Previous studies have indicated that there is a correlation between lung cancer and chronic obstructive pulmonary disease (COPD). Some authors address pulmonary emphysema as a risk factor for the development of lung cancer.
Case report: A 41-year-old previously healthy male, smoker, was diagnosed with bullous disease. The disease started with dyspnea. Based on a chest X-ray pneumothorax was suspected but a CT scan revealed giant bullae in the right apex. Lung volume reduction surgery (LVRS) was performed and pathohistology confirmed bullous emphysema. 27 months later hemoptysis and chest pain appeared. The CT showed a tumor mass at the level of surgical staplers. Fine needle aspiration (FNA) was done and cytology confirmed adenocarcinoma. Further surgical treatment was not possible because PET/CT showed that the disease had spread to the liver and bones. The patient received four cycles of Gemcitabine/Cisplatine and two cycles of Cisplatina /Etoposid chemotherapy and a Gamma knife procedure was performed due to brain metastases.
Conclusion: Patients with COPD should be considered for a lung cancer low-dose screening programme.
Key words: lung cancer, emphysema bullous disease, COPD, screening CT.

PP 15
LONG-TERM SURVIVOR SCLC – CASE REPORT

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INTRODUCTION: Small cell lung carcinoma is a very aggressive form of cancer, accounts for 10-15% of all lung cancers. Diagnosis at an early stage improve the prognosis of the disease.
CASE REPORT*:* We are presenting case of 71 years old female, smoker, diagnosed with stage III A (T2bN2M0) small cell lung carcinoma, with a good performance status. The patient had a chronic obstrucitve pulmonary disease as an associated disease. Initial CT scan of thorax showed infiltrative lesion of 57mm in right lung hilum with ateletasis of upper and middle lobes and mediastinal lymphadenopathy 4R- 21mm. CT scan of head pointed to old ischemic lesiones. Chemotherapy fourth cycle with Etoposid+Cisplatina combined with competitive chest radiotherapy in dose 40Gy/20fr was perfomed. Conformal chest radiotherapy started after second cycle of chemotherapy. When combined tretman chemiotherapy with radiotherapy finished, in the contuination of treatman prophylactic whole brain radiotherapy in dose 20Gy was performed. During treatment patient's performans status was good and without significant side effects.
After above mentioned therapy procedures the patient was radiologic followed for 6-year (CT scan, PET CT, chest X ray, abdominal US) wich showed SD. The last CT scan of thorax in May 2017 pointed to the postradiation state with the sequences, both sides more extensively to the right, with no signs of the cancer dissemination of the underlying disease, with infiltrative nodus in the right lung. Patient was alive 7 years after diagnosis, with no evidence of relaps. In October 2017 the patient died due the worsening of a chronic obstructive pulmonary disease.
CONCLUSION: Early diagnosis and multimodal therapy of patients with SCLC is important for long-term survival.
KEYWORDS: Small cell lung cancer, chemotherapy, radiotherapy, long-term survival

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PP 16
IS ANEMIA DURING CHEMOTHERAPY PROGNOSTIC FACTOR FOR PATIENTS WITH NON-SMALL CELL LUNG CANCER?

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Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, and it accounts about 85% to 90% of all lung cancer cases.
The aim of this study was to determine the influence of anemia during chemotherapy as a prognostic factor in patients with non-small cell lung cancer (NSCLC).
This was a retrosceptive-prospective study in which we analyzed 200 patients with NSCLC, stages III and IV, who were treated with chemotherapy (HT) protocols gemcitabin/ cisplatin, and cisplatin/etoposide, (100 patients each protocol). In retrospective period we analyzed hematologic toxicity, and in prospective period which lasted for two years we evaluated survival. In both groups of patients, the experimental group consisted of patients with hematologic toxicity, and the control group was created of patients without hematologic toxicity.
There were no differences in all grades of anemia during chemotherapy between the groups ($p>0.05$). There was no statistically significant difference between the reduced initial values of hemoglobin and the development of anemia all grades, (2, 3 and 4), during treatment with chemotherapy in both groups ($p=0.155$, $p=0.123$, $p<0.05$ for group A and $p=0.103$, $p=0.308$, $p<0.05$ for the group B). Anemia is identified as a prognostic factor in both group of patientes using univariate statistical analysis (group A $p<0.025$, goup B $p<0.000$), but none of the analyzed parameters did not show statistical significance in the multivariate analysis (in group A $p>0.857$, $p>0.808$, $p>0.683$, and in group B $p>0.233$, $p>0.068$ and $p>0.149$). There was a statistically significant difference in survival of patients in both groups – in group A (Long rank test, $\chi2=7.708$; $p<0.01$), and in group B (Long rank test, $\chi2=16.434$; $p<0.01$) (gradus 0, 1 i 2). There was a statistically significant difference in survival of patients in both groups – in group A (Long rank test, $\chi2=16.434$; $p<0.01$) and in group B (Long rank test, $\chi2=20.897$; $p<0.01$). (gradus 0, 3 i 4).
In conclusion we can say that statistical analysis confirmed that anemia during chemotherapy is prognostic factor in both groups, but it is not independent prognostic factor.
Key words: anemia, chemotherapy, NSCLC, prognostic factor

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PP 17
VIDEO-ASSISTED THORACOSCOPIC THYMECTOMY FOR MASAOKA STAGE I THYMOMA: RIGHT-SIDED THREE-PORTAL APPROACH

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Introduction: Median sternotomy was the traditional approach for treatment of all resectable Masaoka stages of thymomas. In recent years minimally, invasive video-assisted thoracoscopic thymectomy has gained acceptance as an alternative approach in cases where all oncologic goals can be met.
Case series: During 5-year period, we performed a total of six right-sided video-assisted thymectomy for Masaoka stage I. All patients were females, ages 35-74 years old, with median age of 49 years. Half of the patients had a sero-positive myasthenia gravis, while the other halfhad had anterior mediastinal masses. Video-assisted thoracoscopic right-sided three-portal technique was our approach of choice. Median operative time from the induction of general anesthesia to extubation was 81 minutes. All patients received one-right sided pleural drain which was removed after secernation decreased bellow 100ml/24h. The median length of hospital stay was 3.8 days, ranging from 2-6 days. By reviewing the literature median length of hospital stay in the median sternotomy group was 9 days. The size of the resected thymic and adjective mediastinal tissues determined the length of hospital stay. Patohistological results showed: three B1, one of A, AB and B1thymomas, all in Masaoka stage I. In all cases R0 resections were achieved.
Conclusion: The benefits of minimally invasive thymectomy in comparison with transsternal approach can be found in shortening the length of hospital stay and pain reduction. R0 resection must be the main oncologic goal. If it can be achieved, minimally invasive thymectomy can be recommended.
Key words: Thymectomy, Thymoma, Video-Assisted-Thoracic-Surgery

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PP 18
NEW RADIOTHERAPY TECHNIQUES IS FEASIBLE IN GERIATRIC LUNG CANCER PATIENTS - CASE REPORT

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INTRODUCTION: More than one third of lung cancer patients are diagnosed in age above 75 years. Some of them don't recive standard of care therapy- chemotherapy and radiotherapy becouse of age, concerns about fragility and the usefulness of therapy for patients with comorbidities.

CASE REPORT: We present a case of a 79 years old women, ECOG PS 1. In april 2017. CT scan of the thorax showed tumor mass in the right hilus, infiltrating right main bronchus, lymph nodes at the 10R position in the conglomerate with described mass. Bronchoscopy was performed, and the pathological examination confirmed adenocarcinoma in the right main bronchus and metastatic spread to the lymph nodes position 4R. TNM stage was T2bN2M0.The patient was treated with 50 Gyexternal beam RT in 25 fractions using intensity modulated radiation technique (IMRT). There was no elective mediastinal irradiation. Radiation treatment was performed on linear accelerator ELECTA Versa HD, using IGRT softverSymmetry counting respiratory motionfor precise treatment delivery on moving target. After radiotherapy patient recived four cycles chemotherapy Cisplatin/Gemcitabin until October 2017.Control chest RTG showed partial regression of tumor mass. In the follow up period, until now there were no toxicities and nodeterioration of performans status.

COCLUSION: Geriatric population are complex group with increasing co-morbidity and shrinking physiological reserve. Fit elderly person with adequate organ function should be offered similar treatment as younger patients.

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METASTATIC RECURRENCE OF TYPICAL PULMONARY CARCINOID TREATED WITHCOMBINED TREATMENT MODALITIES

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Introduction: Bronchial carcionidtumours(BCT) are rare and uncommon group of lung tumors. They represent about 1% of all primary lung tumors. About 80% are centrally located, within the lobar and segmental bronchi. Recurrence of typical pulmonary carcinoid after complete resection is very rare (3–5%).
Case report: In 2012 a 61-year-old malepresented at the Oncology Department of Institute for pulmonary diseases of Vojvodina with a history of cough and fever. Chest CT scan revealed oval mass(4x6cm) in the right lower lobe.Bronchobiopsy from tumor reported adenocarcinoma. Right lower lobectomy was performedand patohistological finding wastypical lung carcinoid(pT2bN0Mx). At the beginning of 2016.radiologically and bronchoscopic progression of the disease has been reported. Patient received endoluminal brachytherapy. Subsequently the first line chemotherapy according to PE protocol was applied. In September 2017electrocauterisation of tumor in the right main bronchus and APC was performed. Pathohistological finding of resection fragment was typical carcinoid of lung with low proliferative Ki index.Magnetic resonance imagingrevealed an enhanced nodular lesions compatible with a liver metastases. Somatostaticreceptor scintigraphyshown secondary deposits with expression SSNR in the liver and lungs (cT4N3M1c). Patient started using SomatulinAutogel. After five treatments progression of the disease has been verified. Oncology Board introduced the third line therapy with afinitor.
Conclusion: Only a small number of patients with typical carcinoid experience recurrences, with a median time to recurrence of 4 years (range, 0.8–12 years), longer than that for atypical carcinoid. Evidence supporting optimal treatment strategies for BCT is lacking but the recent publications indicate that multimodal treatment is associated with prolonged survival.
Key words: lung; typical carcinoid; brachitherapy; afinitor

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LONG-TERM SURVIVOR NSCLC – CASE REPORT

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Introducion: Lung cancer is the most often diagnosed cancer type worldwide, and at the same time it is the most common cause of deaths among all cancer types.
Case report: In this paper we are presenting the case of a long-term patient in the initially fourth stage of the disease, who has been treated with four lines of chemotherapy. It is about male patient, 61 years old, current smoker, with bronchoscopically confirmed stage IV (cT3N2M1a) squamous cell lung carcinoma of the right lung. First line chemotherapy (HT) with Cisplatin/Gemcitabine was completed, with accomplished partial response. Ten months later radiological disease progression in the lung was observed as an increase of size of the primary tumor (T3N2M1a). Patient had a good performance status, ECOG 1, and the treatment was carried out with 4 cycles second line HT, Cisplatin/Vinorelbine. After second line HT completiton, stable disease was confirmed. New progression of the disease in terms of tumor size enlargement (T3N2M1a) was noted 6 months after second line HT completition. The patients still had good performance status, so we continued treatment with third line HT, Carboplatin/ Etoposide in 4 cycles. After 10 months of radiological stable disease, further radiological disease progression was detected as a new metastatic lesion located in right kidney and increasing the size of primary lung tumor (T4N2M1c). Since the patinet was still in good condtition, treatment was continiued with the fourth line HT with Gemcitabin/Carboplatin in 4 cycles, and the treatment is still ongoing. After almost 4 years of diagnosis, the patient is still alive, the treatment is ongoing and has a good quality of life.
Conclusion: We can say that the chemotherapy prolong survival in patients with NSCLC and should be used as standard therapy in patients who have good performance status.

KEYWORDS*:* chemotherapy, lung cancer, survival

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