ORAL PRESENTATIONS

S1 – A CASE REPORT - UTERINE LEIOMYOSARCOMA

ALEKSANDROVA STANOJEVIĆ ANASTAZIJA [1], Mlinarić Koprivanac Tena [1], Kuharić Josip [1]

[1] *University Hospital Center Zagreb, Zagreb, Croatia*
Department of Oncology and Radiotherapy

Background: Uterine leiomyosarcomas (uLMS) are rare mesenchymal malignant tumors accounting for 1% to 3% of all uterine malignancies and approximately 30% of uterine sarcomas. They are aggressive tumors associated with a high risk of recurrence and death regardless of stage at presentation. Prognosis is based on tumor staging, mitotic count, and tumor size. Patients with FIGO stage I or II have a 5-year disease-free survival (DFS) rate of 75.8% and 60.1%. On the other hand, patients with stages III and IV tend to recur and metastasize very often and have 5-year disease-free survival of 44.9% and 28.7% respectively. If operable, en bloc total hysterectomy is the treatment of choice. Lymphadenectomy is not mandatory because uLMS tend to metastasize through vascular system and lymph node metastases are uncommon. In adjuvant setting, radiotherapy is not recommended and chemotherapy is still a matter of debate. For women who are not amenable to complete surgical resection, treatment is given with palliative intent. Chemotherapeutic regimens showing efficacy against uLMS are doxorubicin, doxorubicin-dacarbazine, gemcitabine-docetaxel, trabectedin, pazopanib, eribulin and vinorelbine. More recently a clinical study phase II found that combination of temozolomide and PARP inhibitor olaparib showed promising results in a group of patients previously treated with chemotherapy. The ORR was 27% and median PFS was 6.9 months. The study design was based on recent molecular discovery of defects in the homologous recombination (HR) DNA repair pathway, including somatic biallelic BRCA2 deletion, in 10% of patients with uLMS.

Case: In March 2021, a 67year old patient was admitted to our Cancer Center. She had uterine tumor spreading to lungs, liver and vertebrae. The histological findings of uterine abrasion performed at her local hospital were negative (no tumor tissue). Clinical examination showed enlargement of uterus with clear cervix and parametria. MRI showed large necrotic tumor inside uterus, many metastatic lesions in liver, vertebrae, pelvic bones, and lungs. CT scan confirmed MRI findings except bone lesions, which according to CT exam were clear, but were later confirmed by the radiologist. Her medical history was: Two previous births, PAP smear in January 2021: normal.She had total thyroidectomy, arterial hypertension, and hypothyroidism and was on anti-hypertensive drugs and levothyroxine supplement. On 9th April 2021. she had surgery at our Cancer Center: Hysterectomy with bilateral adnexectomy, omentectomy and ventral hernia excision. Histological finding was: Leiomyosarcoma of the uterus, the tumor was 9x8x8cm, the infiltration of myometrial wall was 6cm/6cm with the expansion of the tumor beyond the uterine wall to the connective tissue of the right adnexa. Necrosis was up to 50% of the tumor, number of mitoses were 50/10 visual fields. IHC: negative for EMA, CK AE1/AE3, CD10, Cyclin D1, positive for kaldezmon, ER + 70% and PR. +20%. FMI 31.5.: MSS, TMB 2Muts/Mb, PTEN loss. Her clinical presentation before oncological treatment was ECOG 0, with excellent laboratory findings of renal and liver function. Her Calcium level was 2.28. She received initially mono doxorubicin with zoledronate, after which she continued with doxorubicin/dacarbazine chemotherapy protocol. After two administrations of zoledronate she became hypo-calcemic and received calcium supplementation with calcitriol (active form of D vitamin) which was successful in correction of hypocalcemia so patient could continue with reduced dose of zoledronate. After 6 cycles of chemotherapy (1 mono doxorubicin and 5. doxorubicine/dacarbazine) she had CT scan which unfortunately showed progression of the disease in lungs and liver with stabilization of bone metastases.

The second line that she received was mono trabectedine. She received 6 cycles altogether. After first cycle she had dose reduction because of liver toxicity after which her liver function stabilized. Of all other possible adverse effects, she suffered nausea gr II/III. During I and II line of chemotherapy she received primary prevention of neutropenia and did not suffer any substantial delay of the treatment. Unfortunately, her latest CT scan showed further progression of the disease. Patient is still ECOG 0, and is now eligible for III line of treatment, possibly hormonotherapy according to IHC of the tumor.

Conclusion: Uterine leiomyosarcomas represents one of the most difficult gynecological malignancies to treat, especially in the clinical setting of metastatic disease. The ideal regimen for the first-line treatment is yet to be proven. For now, Doxorubicin monotherapy, Doxorubicin-dacarbazine and Gemcitabine-docetaxel are preferred regimens. Translational research with the aim of discovering the vulnerabilities of this tumor type is a matter of high importance and priority. Recent molecular discovery of defects in the homologous recombination DNA repair pathway in some patients with uLMS seems promising.

Keywords: Leiomyosarcoma uteri, chemotherapy, systemic treatment

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S2 – ADJUVANT TREATMENT OF TESTICULAR CANCERS

PERIĆ LUKA [1, 2], Šambić Penc Mirela [1, 2], Canjko Ivana [1], Flam Josipa [1, 2], Kovač Barić Maja [1], Krivdić Dupan Zdravka [2, 3], Pušeljić Nora [2, 4]

[1] *Univesrity Hospital Center Osijek, Osijek, Croatia*
Department Of Oncology
[2] *Faculty of Medicine, Osijek, Croatia*
University of J. J. Strossmayer Osijek
[3] *University Hospital Center Osijek, Osijek, Croatia*
Clinical Department of Diagnostic and Interventional Radiology
[4] *Univesrity Hospital Center Osijek, Osijek, Croatia*
Department of Pediatrics

In the United States, testicular cancer is the most prevalent solid tumor in men aged 15 to 34, with an estimated 8,850 new cases and 410 fatalities in 2017. Seminomas and non-seminomas, which account for half of all cases and differ in treatment techniques and response to therapy, are the two primary types. The five-year overall survival rate is 97% with proper treatment. Testicular cancer is caused by a combination of hereditary and environmental factors, with cryptorchidism being the most prevalent risk factor. The preferred initial imaging test is scrotal sonography. Orchiectomy is both diagnostic and therapeutic if a solid intratesticular mass is found. Treatment is determined by staging, which includes chest CT (computerized tomography), chemical testing, liver function tests, tumor markers alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH). After orchiectomy, treatment options include active surveillance, chemotherapy, retroperitoneal lymph node dissection, and radiation therapy. Sperm banking should be considered early in the treatment process with patients who want to be fertile in the future.

A 37-year-old patient was examined by a urologist in the fifth month of 2021 due to occasional pain in the right testicle that lasted for a month. He denies trauma. An ultrasound of the testis was performed and two nodose zones were observed, one hypoechoic inhomogeneous 2 cm in diameter and the other isoechoic 2.5 cm in diameter. Tumor markers were AFP 2.6, HCG 1, LDH 162. Right radical orchidectomy was performed on 27.05.2021. A pathohistological finding indicates testicular cancer - nonseminoma, T2N0 Ib stage composed of 80% embryonic cells and 20% yolk sac cells, without lymphovascular invasion. The tumor is approximately 4x4.5 cm in size and infiltrates the rete of the testis There are no lung or liver metastases on CT scans of the thorax, abdomen, and pelvis. Ventrally from the right psoas muscle several lymph nodes up to 11 mm are suspiciously altered. A magnetic resonance imaging scan (MRI) of the abdomen and pelvis is also made which does not show pathologically enlarged lymph nodes. In agreement with the patient, the first cycle of BEP chemotherapy (bleomycin, etoposide, and cisplatin) was administrated on 09.07.2021. The patient received only one cycle of chemotherapy and after that, the patient proceeds to normal follow-up examination and active surveillance. Surveillance or adjuvant chemotherapy are viable alternatives for males with low-risk disease. These individuals have a good prognosis, and surveillance prevents chemotherapy-related problems and toxicity. If a sufficiently experienced urologic surgeon is available, adjuvant chemotherapy, active surveillance, and retroperitoneal lymph node dissection (RPLND) are all viable alternatives for men with high-risk disease. There have been several attempts to identify men with clinical stage I non-seminomatous germ cell tumors (NSGCTs) who are at high risk of recurrence and therefore most likely to benefit from adjuvant therapy after orchiectomy. Lymphovascu-

lar invasion (LVI), the majority of an embryonal carcinoma component (EC) in the original tumor, and pathologic tumor stage T3 or T4 are the most commonly used risk factors for recurrence in men monitored for clinical stage I disease after orchiectomy.

These risk variables can help men with testicular NSGCT determine their risk of recurrence. Low-risk tumors that do not have any of these risk markers have recurrence rates of 10 to 14 percent. High-risk tumors are more likely to recur if one or more of these risk factors are present. Active surveillance has been linked to greater recurrence risk in several studies, but overall survival is excellent. One or two cycles of BEP (bleomycin, etoposide, and cisplatin) should be given to all males who choose chemotherapy. Because disease-specific survival is better than 99 percent with either method, and BEP treatment is linked with dose-dependent long-term toxicity, we choose a single cycle over two cycles. There is no one optimum choice for all patients because all three methods are associated with disease-specific survival rates of better than 99 percent. As a result, the choice of modality should be dependent on the patient's preferences.

Testicular cancer is a highly curable disease in which we have several adjuvant treatment options that are largely stage-dependent. Because adjuvant chemotherapy, active surveillance, and RPLND are all acceptable options, the patient's preferences should guide the modality selection.

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S3 – BRACHYTHERAPY IN THE TREATMENT OF GYNAECOLOGICAL TUMORS

JAKŠIĆ BLANKA [1], Prgomet Sečan Angela [1], Fröbe Ana [1, 2]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Oncology and nuclear medicine clinic
[2] *University of Zagreb, Zagreb, Croatia*
School of dental medicine

The beginning of brachytherapy use in the treatment of gynaecological tumors goes way back in 1905. when Dr. Robert Abbe for the first time applied radium in the treatment of cervical cancer. Over the subsequent decades, several medical centers have developed fundamental brachytherapy systems (Paris, Stockholm, Manchester, MD Anderson Cancer Center). By the 1970s, brachytherapy was in wide-spread use for the treatment of cervical cancer. Numerous clinical studies have shown that brachytherapy is an essential component for curative intent radiation and is strongly correlated with improved local control and higer rates of survival (5-year cervix cancer specific survival with and without brachytherapy, 68.5% vs 35.4%). In the past two decades, image guided brachytherapy (IGBT) which uses CT or MRI, was introduced. IGBT using 3D-based volumetric planning enables optimization of the dose in the tumor with the reduction of dose in normal tissues. The clinical evidence supporting IGBT comes from numerous prospective and retrospective studies published in the past decade.

Despite the strong evidence demonstrating the benefit of brachytherapy in the primary and adjuvant treatment of gynaecological tumors, its usage has been declining over the past decades, from 83% in 1988. to 58% in 2009. This decline is a result of the expansion of conformal external beam radiation therapy techniques, most notably intensity modulated radiation therapy (IMRT) and stereotactic body radiotherapy (SBRT), which use has increased from 3.3% in 2004. to 13.9% in 2011. IMRT has been used to escalate the dose to the cervix to give up on brachytherapy. Recent studies have shown that IMRT and SBRT boost results in inferior overall survival as compared to brachytherapy. Survival detriment associated with IMRT or SBRT boost was stronger than that associated with not receveing chemotherapy. Dosimetric analysis have shown that brachytherapy can deliver significantly higher doses of radiation to the primary tumor while sparing normal tissues, compared to IMRT, SBRT or proton therapy. While the value of IMRT, SBRT and other specialized forms of external beam radiation are recognized, none of this systems can compare to the dose escalation or dosimetric properties of a gynaecological implant and evidence has demonstrated a reduction in cervical cancer cure rates if attempts are made to substitute them for brachytherapy.

About 10-30% of patients treated for gynaecological tumors, experience local recurrence. Curative-intent treatment for this patients is salvage surgery which is associated with non-negligible peri-operative morbidity and has substantial impact on long-term quality of life. SBRT was evaluated in pelvic recurrences, however only in retrospective studies. Dosimetric comparisons between brachytherapy and SBRT in this setting, have shown that SBRT delivers higher doses to the organs at risk (OARs), carrying a higher risk of toxicity. The use of modern radiotherapy techniques in pelvic recurrences has failed to give dramatic improvement in local control or toxicity profiles. Interstitial brachytherapy should be the choice for the treatment of central and paracentral pelvic reccurrences because of better conformality than IMRT and SBRT techniques. It is recommended that IMRT and SBRT are to be used only if the pelvic recurrence is not accessible to brachytherapy, like the pelvic wall recurrence or nodal recurrence.

In conclusion, brachytherapy use is independently associated with significantly higher cause-specific and overall survival rates and should be implemented in all feasible cases, despite the fact that it is technically demanding and resource intensive. Althought IMRT and SBRT can spare the adjecent OARs better than conventional external beam radiotherapy (EBRT), brachytherapy remains the only way to deliver very high radiation dose to the center of the tumor with maximum sparing of OARs due to the best conformality. Brachytherapy in the treatment of gynaecological tumors is not optional, it is mandatory.

Key words: image-guided brachytherapy, intensity modulated radiation therapy, stereotactic body radiation therapy

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S4 – CASE REPORT OF LOCALLY ADVANCED NON-SMALL-CELL LUNG CANCER

BUKOVICA PETRC ANA-MARIJA [1, 2], Radojčić Milan [1], Belac-Lovasić Ingrid [1, 2]

[1] *Clinical Hospital Center Rijeka, Rijeka, Croatia*
Department of Radiotherapy and Oncology
[2] *Faculty of Medicine Rijeka, Rijeka, Croatia*
Oncology and Radioteraphy

Lung cancer is among the most commonly diagnosed cancers in Croatia in both genders, as well as the most common cause of cancer-related deaths. There are two major histological subtypes of lung cancer, non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). In the last decade great achievements have been made in the treatment of NSCLC in metastatic setting, with the discovery and identification of druggable oncogenes and compatible targeted therapies, as well as with the utilization of immunotherapy. Until recently, the standard treatment for patients with unresectable locally advanced NSCLC was definitive concurrent chemotherapy and radiation with curative intent, but it was often followed by a rapid progression of the disease. That being said, there was a need for new treatment options that could improve outcomes. The Pacific trial, which evaluated durvalumab consolidation therapy after concurrent chemotherapy and radiotherapy in unresectable NSCLC, demonstrated a statistically significant and clinically meaningful improvement in the terms of progression-free survival and overall survival.

We report a case of locally advanced NSCLC diagnosed in 67–year old male. Computed tomography of the thorax and upper abdomen described the tumor of the upper left lobe with pathologically enlarged

mediastinal lymph nodes. To obtain the diagnose he underwent bronchoscopy and transthoracic needle biopsies. Histopathological examination confirmed the diagnose of adenocarcinoma with no targetable mutations found on further testing, but PD-L1 expression was 50%. As there was no evidence of metastatic disease on fluorodeoxyglucose positron emission tomography/computed tomography scan, he was staged as having T2bN2M0 (Stage IIIA) disease. We recommended radical intent radiation therapy with concurrent chemotherapy and consolidation therapy with durvalumab up to twelve months. Concurrent radiotherapy and chemotherapy was interrupted by the sars-cov-2 virus infection. Follow-up CT scans of the thorax and upper abdomen were made approximately every 3 months. In the end of the treatment, a complete radiological response was achieved.

Keywords: *lung cancer, locally advanced, durvalumab, sars-cov-2 virus*

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S5 – CASE REPORT: THE PATIENT INITIALLY DIAGNOSED WITH HORMONE RECEPTOR POSITIVE, HER 2 NEGATIVE METASTATIC BREAST CANCER (HR+/HER2- MBC) WITH AQUIRED RESISTANCE TO ENDOCRINE THERAPY

JAJAC BRUČIĆ LANA [1], Jović Zlatović Josipa [1]

[1] *Genaral Hospital of Šibenik-Knin County, Šibenik, Croatia*
Department of Internal Medicine

Background: Hormone receptor - positive (HR+) breast cancer is the most common subtype of breast cancer. Only 5-10% are initially presented with metastatic disease. The major goals of treatment for metastatic breast cancer (mBC) are to prolong survival, to improve quality of life with the fewest side effects. The sequential use of endocrine therapy (ET) is the treatment backbone for HR+/HER2- mBC. Despite initially respond to ET most patients will experience disease progression and develop endocrine resistance. However, due to result of numerous studies on the delay or overcoming the endocrine resistance two main treatment options are established: intervenition in the cell cycle progression by targeting cyclin-dependent kinase 4/6 (CDK4/6) or inhibition of the mammalian target of rapamycin/PIK3CA (mTOR/

PIK3CA) pathway. The combination of CDK4/6 inhibitors (CDK4/6 I) with fulvestrant compare to placebo + fulvestrant prolongs survival with favorable toxicity profile in 2nd line treatment.

Case report: A 69-year-old postmenopausal woman with a history of diabetes mellitus and arterial hypertension who was presented in May 2018 with weakness, bone pain and weight loss approximately 10 kg in 3-4 months. At the beginning her performance status was poor (ECOG PS 2). During the physical examination there was palpable 2 cm mass of the left breast between the inner quadrants. MSCT showed multiple secondary lesions of the lung, liver, and bones (mixed osteolytic/osteoblastic changes). Core biopsy provided a pathohistological finding of invasive breast cancer with estrogen receptor positivity of the tumor cells (100%), progesterone receptor positivity up to 5%, HER 2-status negative, Ki67 39.3%, which was classified in the luminal B (Her2 neg) subtype. Bone scan also confirmed diffuse pathological accumulations. An increase in tumor markers (CA15-3: 193, CEA: 10), as well as a moderate increase in liver enzymes were noted in laboratory findings but without criteria for visceral crisis. As treatment with CDK 4/6 I was not available at the time, treatment with letrozole (2,5 mg daily) and zoledronic acid (4 mg IV every 3 month) was started in June 2018. After 3 months patient's clinical condition was improved (ECOG PS 1) and diagnostic work-up described significant regression of lung and liver secondary lesions with a stable disease in bones. The normalization of tumor markers and liver enzymes are also monitored. In further follow-up (after 6 months) the bone scan also described regression. In May 2019 after 11 months of therapy, MSCT showed progression of disease in liver and bones, with increase in pleural effusion as well as an increase in tumor markers (CA15-3: 294). Treatment with the 2nd line of ET was indicated. As therapy with CDK 4/6 I became available, and her PS has improved, she began with fulvestrant (intramuscular injection on days 1 and 15 of cycle 1; then on day 1 of subsequent 28-day cycles) + palbociclib (125 mg daily for 3 weeks followed by a week off over 28-day cycles). The patient received 18 cycles of therapy until October 2020. A significant regression of both visceral and bone metastases was achieved. The therapy was well tolerated. The only serious side effect was grade 3 neutropenia without the need for dose reduction or discontinuation of treatment. The reevaluation in October 2020 described the progression only in bones with a stable lung and liver disease. The PIK3CA mutation testing was done, but unfortunately there was no mutation. Considering patient preferences, we decided to continue treatment with the 3th line of ET-exemestane. After three-month patient's clinical condition became slightly worse, MSCT showed further progression in bones but also progression in the liver and again increase in pleural effusion. As the patient refused intravenous therapy, capecitabin seem to be reasonable option. After six cycles of well tolerated therapy, the stable disease was achieved, unfortunately she no longer reported to control.

Conclusion: The optimal therapy sequencing after progression on ET and CDK4/6 I is not well defined. It should be individualized considering the previous effectiveness of treatment, tolerability, gene mutations and patient preferences. ET alone in the 1st line therapy can be a choice for patient with poor PS. Our case report shows the success of treatment with CDK 4/6 I + fulvestrant in the 2nd line therapy of initially metastatic HR+/HER2- BC with extensive visceral disease. After secondary resistance to ET, she achieved time to second progression of the disease with duration of 17 months with a good treatment tolerance.

Keywords: HR+ breast cancer, endocrine resistence, CDK4/6 inhibitors

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S6 – CHRONIC COMPLICATIONS OF BREAST CANCER TREATMENT – PHYSIATRIST VIEW

BRNIĆ SENIJA [1]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Rheumatology, Physical and Rehabilitation Medicine,
Clinic Unit of Rehabilitation of Cancer Patients

Introduction: The goal of rehabilitation is to help the sick person to achieve maximum physical, mental, social, professional and educational skills in relation to impairment. Oncological rehabilitation is carried out in four phases: preventive, restorative, supportive and palliative. The most important complications of breast cancer treatment that require therapeutic intervention are: postoperative consequences of surgical treatment, lymphedema, peripheral neuropathy, osteoporosis and irradiation plexopathy.

Postoperative complications

The most common postoperative local and regional complications are shoulder dysfunction and pain, axillary web syndrome, unstable scapula, and decreased mobility of the chest wall.

Shoulder dysfunction is manifested by a decreased range of motion and pain, and may be due to a number of reasons: immobilization due to pain, transient acute lymphedema, injuries of n. thoracodorsalis and consequent partial denervation of m. latisimus dorsi, injuries of n. intercostobrachialis and exacerbations of chronic shoulder tendinopathy. Sometimes phantom pain occurs at the site of the operated breast. Axillary web syndrome (AWS) or cording syndrome is characterized by a strip of subcutaneous tissue extending from the axilla down to the elbow, forearm or hand, with consequent pain in the armpit and arm, reduced shoulder movements. The risk of developing AWS is proportional to the number of lymph nodes removed. Unstable scapula occurs as a result of injury of n. thoracicus longus, resulting in partial denervation of the m. seratus anterior, difficulty in raising the arm above the horizontal. Reduced and painful mobility of the chest wall occurs due to the tendency to shorten the pectoral and intercostal muscles. In order to prevent these complications postoperatively and achieve maximum restitution of impaired function, it is necessary to start rehabilitation procedures from the first postoperative day. Commonly used rehabilitation procedures are kinesiotherapy, massage techniques, TENS. The kinesiotherapy program aims to prevent shoulder joint contracture, improve mobility, flexibility, strength and endurance of muscles, and improve posture.

Lymphedema

Lymphedema is an excessive accumulation of fluid rich in protein in the interstitium that can cause chronic inflammation and fibrotic changes in the affected tissue. Lymphedema may be primary or secondary. Secondary lymphedema after breast cancer surgery is caused by a functional overload of the lymphatic system after surgery or radiation. Risk factors for the occurrence of lymphedema are dissection of the axillary lymph nodes, radiotherapy, obesity, old age. There are four types of lymphedema, depending on the time of onset - early, acute, erysipeloid, and delayed. Delayed lymphedema is the most common clinical presentation with insidious onset of painless swelling. The long-term consequences of chronic lymphedema are infections, atropathy, skin hyperpigmentation, elephantiasis, impaired posture and lesions of the brachial plexus. In rare cases, lymphangiosarcoma may occur. Lymphedema therapy is a complex decongestive physical therapy (CDT) that aims to increase lymph transport. CDT includes several treatments: manual lymphatic drainage, compression bandaging, decongestive exercises and skin care.

Peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a disorder and dysfunction of the peripheral nervous system following the administration of neurotoxic chemotherapy.

Neurotoxic chemotherapeutics include taxanes, platinum compounds, vinca alkaloids etc. CIPN is manifested by symmetrical, primarily sensory symptoms, distribution "by type of socks and gloves". Sensory symptoms are most often numbness, paresthesias and painful symptoms and proprioception disorder. Motor and autonomic symptoms may be less common. The intensity of symptoms can vary from mild to severe, and is dose-dependent. Severe motor and sensory impairments, especially gait disorders, significantly affect mobility and overall quality of life. The goals of therapy are to reduce pain and improve function. Different procedures are used in rehabilitation: kinesiotherapy, electrostimulation, proprioceptive training, massage techniques, TENS, orthoses and occupational therapy. Drug therapy includes anticonvulsants, tricyclic antidepressants, and less commonly opioids.

Osteoporosis

Various therapeutic procedures in the treatment of breast cancer reduce estrogen production resulting in increased bone resorption and increased risk of osteoporosis. Evaluation of patients and assessment of fracture risk includes assessment of the following parameters: densitometry (DXA), clinical risk factors and lifestyle factors and laboratory evaluation.

Non-pharmacological prevention for osteopenia: supplementation with calcium (1200 mg per day) and vitamin D (800 IU per day), and by changing lifestyle habits (adequate physical activity). Pharmacological therapy for osteoporosis includes bisphosphonates or denosumab. The decision on therapy is made by a combination of T score and clinical risk factors. Indications for initiation of pharmacological therapy are: osteoporosis (T score ≥-2.5 or history of fractures) or osteopenia (T score between -1.0 and ≤ -2.5) with clinical risk factors present. Bisphosphonates are preferred as initial therapy in women with breast cancer because of their efficacy, long-term safety data, and favorable cost. Denosumab is an alternative choice in patients who have contraindications to the use of bisphosphonates, are poorly tolerated or have a poor therapeutic response. Monitoring of possible complications of therapy is required during therapy.

Irradiation plexopathy

Irradiation plexopathy occurs sporadically, over a wide time span of 6 months to 20 years. It presents with insidious appearance, paresthesias in the arm and hand, and weakness of the muscles, most often the shoulder girdle. The pain is usually absent. Differential diagnosis is important to distinguish it from metastatic tumor plexopathy, with clinical picture, MRI, CT and EMNG. Unlike irradiation plexopathy, tumor plexopathy is often present with rapid progression, muscle weakness is most often present in the hand. The goal of rehabilitation is to achieve optimal function within the existing damage. Commonly used rehabilitation procedures are kinesiotherapy, TENS, electrostimulation, proprioceptive training, occupational therapy and orthotics.

Conclusion: Early detection and multimodal treatment of breast cancer increases the rate and length of survival. Therefore, it is important to timely identify and treat complications of oncology treatment. Rehabilitation therapeutic procedures aimed at preventing and improving the level of functioning of patients can significantly affect treatment outcomes and quality of life.

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S7 – DO WE TREAT PROSTATE CANCER ACCORDING TO GUIDELINES?

MURGIĆ JURE [1], Fröbe Ana [1, 2, 3]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Oncology and Nuclear Medicine
[2] *University of Zagreb, Zagreb, Croatia, Zagreb, Croatia*
School of Dental Medicine
[3] *European Society for Medical Oncology (ESMO), Lugano, Switzerland*
Practising Oncologists Committee

Many international medical entities regularly publish and update guidelines for prostate cancer diagnosis and treatment. The most prominent are guidelines issued by the European Association of Urology/ European Society for Radiotherapy and Oncology/International Society of Geriatric Oncology (EAU/ ESTRO/SIOG), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA).

There are considerable differences and discrepancies between these guidelines in many areas of prostate cancer care that reflect different interpretations of clinical trial data. Moreover, lack of guideline use and guidelines-unconcordant care have been identified in many jurisdictions and highlight challenges to delivering optimal prostate cancer care.

The pace of progress in diagnosis and treatment of prostate cancer is so rapid that regulatory bodies responsible for practice guidelines have issues keeping up with multiple diagnostic and treatment options now available for localized and advanced prostate cancer. Over the last 10 years, the treatment landscape of prostate cancer has been radically transformed, creating new indication areas for novel diagnostic tools and drugs that translate into improved patient outcomes. To complicate matters even further, a combination of recently approved novel treatment options is opening a new chapter in the highly contested field of optimal cancer treatment.

The question 'Do we treat prostate cancer according to guidelines' is a complex one and calls for practice pattern research which is currently lacking in Croatia. REFERENCE from other countries illustrates a wide range of guideline adoption. The most significant obstacles faced are availability and reimbursement status of new drugs and diagnostic tools by national health regulators.

One way of addressing this issue is to focus on areas which bring greatest value and measurable benefit for patients and where multiple guideline bodies overlap in their recommendations.

A specific area of controversy is prostate-specific antigen (PSA)–based prostate cancer screening, where guidelines differ in their recommendations regarding the need for routine screening, appropriate age and life expectancies, and screening intervals. However, all guidelines agree that PSA-based prostate cancer screening requires an informed, shared decision-making process, and that the decision should reflect the patient's understanding of the possible benefits and risks.

The NCCN guidelines recommend germline genetic testing, with or without pretest genetic counseling, for patients with prostate cancer and positive family history of cancer, patients with high-risk or very-high-risk, regional or metastatic prostate cancer, regardless of family history. Germline genetic testing is not endorsed by other guidelines. Somatic genetic tumor testing is recommended in patients with metastatic prostate cancer for homologous recombination gene mutations (i.e., BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2).

The role of multiparametric MRI (mpMRI) is also matter of dispute. The EAU/ESTR/SIOG guidelines recommend mpMRI prior to performing a repeat biopsy when clinical suspicion of prostate cancer persists despite negative biopsies, while NCCN guidelines favor mpMRI before initiation of active surveillance for low-risk patients.

Guidelines are concordant in discouraging use of non evidence-based practices such as abdominal-pelvic CT or routine bone scans in patients with low and intermediate risk prostate cancer. Androgen deprivation therapy (ADT) also should not be used in low-risk prostate cancer.

Active surveillance is strongly endorsed as the preferable care option for most patients with low-risk localized prostate cancer. All guidelines agree that both radical prostatectomy and radiotherapy ±ADT are standard treatment options for patients with intermediate-risk localized prostate cancer.

For high-risk prostate cancer it is obligatory to add a long(er) course of ADT to radiotherapy.

For the first time, new generation imaging is recommended in the setting of biochemically recurrent prostate cancer after radical prostatectomy when salvage radiotherapy is contemplated. Imaging with new radiopharmaceuticals coupled to prostate cancer–specific targets, such as prostate-specific membrane antigen (PSMA), where available; 11C-choline or 18F-fluciclovine PET/CT; or PET/MRI, whole-body MRI and/or 18F-NaF PET/CT all demonstrate superior disease detection performance characteristics and may alter management as evidenced in numerous studies.

Use of novel generation imaging is not supported as a routine staging method in patients with intact prostate and high-risk localized disease or proven metastatic disease. Given the presence of new, life-prolonging androgen axis-targeted agents in hormone-sensitive metastatic setting (enzalutamide, abiraterone, apalutamide) or docetaxel chemotherapy, there is no role for ADT monotherapy in these patients. Guidelines recommend darolutamide, apalutamide and enzalutamide as effective therapeutic options for non-metastatic castration-resistant prostate cancer.

In the setting of metastatic castration-resistant prostate cancer, available novel life-prolonging options on top of maintaining life-long ADT are abiraterone, enzalutamide, cabazitaxel (for docetaxel resistant disease) and apalutamide. Rucaparib and olaparib have been recently approved for BRCA-mutated prostate cancer.

The plethora of therapeutic options presents a challenge for physicians and patients, who must decide on the best sequence and timing for each of them. There are no data supporting one agent over the other. Guidelines unequivocally recommend chemotherapy after proven resistance to androgen axis-targeted therapy, rather than using an alternate drug from the same cluster.

In conclusion, wide diagnostic and therapeutic options are now supported by clinical trials in patients with prostate cancer, however relevant international guidelines variously address these new options in regular patient care. The areas with guidelines consensus and proven highest benefit for patients and clinical value are use of molecular diagnostic imaging in recurrent prostate cancer, adoption of new androgen-axis targeted treatments in non-metastatic castration-resistant and hormone-sensitive metastatic disease, without preference among the available agents. More effort is needed to resolve national reimbursement issues and to address the impact of guideline gaps in routine patient care.

Keywords: prostate cancer, guidelines, chemotherapy, radiotherapy, diagnosis, management

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S8 – HAVE WE MADE ANY PROGRESS IN TREATING METASTATIC UROTHELIAL CANCER?

STRIKIĆ ANTE [1]

[1] *University Hospital Split, Split, Croatia*
Department of Oncology and Radiotherapy

Every tenth One cancer patient worldwide suffers from bladder cancer. Most frequent histopathological type is urothelial cancer.[1] Urothelial cancers are usually localized in the bladder, followed by renal pelvis and ureter. Luckily, ¾ of cases are non-muscle-invasive disease, meaning papillary noninvasive tumor (Ta), lamina propria invasive tumors (T1) or flat high-grade lesions (CIS), and in rest of the patients as a muscle-invasive disease and metastatic cancer.[1]

The last five years brought significant scientific options for cancer patient, however, due to procedura reasons, some of novel therapies are not yet available for clinical use.

Trials such as BLASST -1, ABACUS or PURE-01 investigated the combination of chemotherapy and immune therapy. Nivolumab (BLASST-1) offered patients 49% complete response rate, comparable toxicity and furthermore, 66% of patients achieving non-invasive disease at surgery.[2]

ABACUS (atezolizumab) and PURE-01 (pembrolizumab) investigated the neoadjuvant use of checkpoint inhibitors. When compared, PURE-01 included higher rate of T3 disease (63% vs 23% in ABACUS), and, interestingly, achieved higher rate of PRC, 42% vs 29%. Higher PD-L1 positivity proved to translate into better rate of pathologic complete response.[3], [4]

Updated analysis of POUT trial, a phase 3 trial, after 49 months of follow-up showed no significant overall survival benefit, but significantly increased DFS (disease free surviva; HR 0·45, 95% CI 0·30–0·68; p=0·0001) and MFS (metastasis free survival, (HR 0·48, 95% CI 0·31–0·74; log-rank p=0·0007) with adjuvant chemotherapy in high-risk upper urinary tract versus surveillance. Therefore, platinum-based adjuvant chemotherapy should be considered a new standard. [5]

Adjuvant immune therapy trials - imVIGOR and Checkmate 274 offered conflicting resultsm as atezolizumab (imVIGOr) showed no impact on DFS (0.89 (95% CI 0.74, 1.08); *P* = 0.2446)) or OS (HR 0.85 (95% CI 0.66, 1.09), in high-risk, muscle-invasive urothelial cancer after radical cystectomy.[6] The latter trial, Checkmate 274, showed convincing results in similar patient population. Disease free survival in both ITT (HR 0.70) and, even more in PD-L1 positive population, was significantly prolonged (HR 0.53). [7] While showing weaker effect in upper urinary tract cancers, the impact of nivolumab was consistent

throughout the other subgroups. There was a difference in PD-L1 testing, in the comparator arm, in number of patients with ≤T3 tumors. The striking difference was in toxicity, which was three-fold higher in Checkmate 274 population, than in imVigor 010. Nevertheless, it's uknown why the results were so different. Not having met its primary endpoint, imVigor010 showed valuable insight in exploratory bio-marker: it showed that ctDNA positivity identified patients with high-risk MIUC likely to derive DFS and OS improvement from adjuvant atezolizumab.[8] These findings will be investigated in imVigor 011.

In the JAVELIN Bladder 100 study, avelumab plus best supportive care (BSC) significantly extended OS compared with BSC alone in the two primary populations of all randomized patients and patients whose tumors were PD-L1+, and significantly more patients who received avelumab as first-line maintenance were alive at one year. The clinical benefits of avelumab were seen across a range of patient populations. Median OS was 21.4 months (95% CI, 18.9 to 26.1) vs 14.3 months (95% CI, 12.9 to 17.9), respectively (HR 0.69; 95% CI, 0.56 to 0.86; P<0.001).[9] There was no difference in chemotherapy prior to avelumab treatment as HRs were 0.69 and 0.66 for cisplatin/gemcitabine and carboplatin/gemcitabine respectively.[10]

The biggest outbreak lately is the use of antibody-drug-conjugates or ADC's: enfortumab vedotin and sacituzumab govitecan. Enfortumab vedotin (targeting Nectin-4) should be a new standard of care for patients on +2L of treatment as its OS is impressive 12.9 months vs 8.9 months for chemotherapy (HR HR: 0.70 (95% CI: 0.56, 0.89), maintaining its effect in all subgroups. Prescribing physicians must be aware of its toxicity profile as 51% of patients can develop higher grade toxicity.[11] Sacituzumab govitecan's (targeting Trop-2) safety and efficacy were evaluated in TROPHY (IMMU-132-06; NCT03547973) trial on 112 patients with locally advanced or mUC who received prior treatment with a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor. Main endpoints were objective response rate and duration of response. The confirmed ORR was 27.7% (95% CI:19.6, 36.9) with 5.4% complete responses and 22.3% partial responses. The median DOR was 7.2 months (n=31; 95% CI: 4.7, 8.6; range 1.4+, 13.7).[12]

With so many novel therapies made (or soon will be made) possible, patient selection will be the key to successful treatment. Patient's age, performance status, comorbidities and then treatment options that are available should be carefully considered as it is red-flagged that unfit, trial-ineligible patients may not derive benefit from such treatment.[13]

In conclusion, muscle-invasive bladder cancer is very aggressive disease, with extremely poor prognosis. While, there are new agents and modalities on the horizon, primarily immunotherapy, better understanding of biomarkers and more thorough patient selection will be of significant impact in metastatic urothelial cancer treatment progress.

Keywords: urothelial cancer, enfortumab vedotin, maintenance avelumab, POUT, imVIGOR010, Checkmate 274, Javelin Bladder 100, sacituzumab-govitecan

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S9 – IMMUNOTHERAPY OF LUNG CANCER, WHAT DOES THE FUTURE BRINGS?

JAKOPOVIĆ MARKO [1, 2], Bitar Lela [1], Seiwerth Fran [1], Samaržija Miroslav [3]

[1] *University Hospital Center Zagreb, Zagreb, Croatia*
Department for Respiratory Diseases
[2] *University of Zagreb, Zagreb, Croatia*
Medical School
[3] *University Hospital Centre Zagreb, Zagreb, Croatia*
Clinical Center for Pulmonary Diseases 'Jordanovac'

Lung cancer is one of the most common malignancies and still leading cause of deaths from malignant diseases Worldwide. Situation in Croatia is similar, with 3235 new lung cancer cases diagnosed each year, and around 3000 deaths. Most common histological subtype is adenocarcinoma, and smoking remains majors risk factor for developing lung cancer.

A better understanding of molecular biology of lung cancer has led to the development of many effective targeted therapies such as EGFR, ALK, ROS1, BRAF, KRAS and other tyrosine kinase inhibitors which improved treatment of lung cancer, especially non-small cell subtype. In patients without driver mutations, immunotherapy alone or in combination with chemotherapy is cornerstone of treatment.

Immune checkpoint inhibitors (ICIs) have shown tremendous benefit in the treatment of non-small cell lung cancer (NSCLC) and are now being used as first-line therapies in metastatic disease (pembrolizumab, atezolizumab, nivolumab plus ipilimumab) and consolidation therapy following chemoradiation

in unresectable locally advanced disease (durvalumab). Future approaches of above-mentioned agents include transferring its usage in earlier stages of the disease: neo-adjuvant and/or adjuvant therapy after complete surgical resection with or without chemotherapy in resectable stages I to IIIA.

Future directions remain open. Small cell lung cancer represents around 15% of all lung cancer cases. Its incidence is decreasing due to decreasing number of smokers. Chemotherapy is cornerstone of treatment in metastatic small-cell lung cancer with limited improvement in survival. Adding immunotherapy (durvalumab, atezolizumab) to chemotherapy gain benefit in improving overall survival, and for the first-time improving survival over 12 year. It is important to explore and search for additional targets to get the full benefits of immunotherapy in the treatment of lung cancer. PD-1/PD-L1 and CTLA-4 inhibitors are the most commonly used ICIs in lung cancer, yet development of resistance to these agents remains a challenge.

TIGIT is a promising new immune checkpoint. It is expressed on activated T cells, natural killer (NK) cells, and regulatory T cells (Tregs). In a recently reported randomized phase II trial, combination of anti-TIGIT antibody tiragolumab with atezolizumab led to clinically meaningful improvement in ORR and PFS compared to placebo plus atezolizumab as first-line treatment of patients with advanced, PD-L1 positive NSCLC. Based on these results. FDA has granted breakthrough therapy designation to tiragolumab in NSCLC.

Another potential checkpoint as target is LAG-3 which is expressed on activated CD4+ and CD8+ T cells, Tregs, a subpopulation of NK cells, B cells, and plasmacytoid dendritic cells (pDCs). LAG-3 signaling plays a negative regulatory role in T helper 1 (Th1) cell activation, proliferation and cytokine secretion, a function that is exploited by tumor cells to evade the host immune system. A phase II trial evaluating the efficacy of relatlimab in combination with nivolumab and chemotherapy as first-line treatment of advanced NSCLC is currently ongoing.

TIM-3, a negative regulator of T cell response is expressed on CD4+ and CD8+ T cells, NK cells, DCs, Tregs, monocytes, and macrophages, is another immune checkpoint under investigation. Higher expression of TIM-3 has been associated with poor prognosis in solid malignancies and inhibition of TIM-3 in combination with PD-1/PD-L1 inhibition has been shown to have anti-tumor activity. Different TIM-3 inhibitors together with inhibitors of PD-1 pathway are under development.

The immunomodulatory effects of radiation are well established. Combining ICI with radiation, either concurrently or sequentially, has been studied extensively. A number of clinical trials have been initiated to succeed the success of PACIFIC trial with consolidation durvalumab following chemoradiation in patients with locally advanced, stage III, unresectable NSCLC. Several trials with concurrent use of ICI and chemoradiation are ongoing (durvalumab, pembrolizumab trials).

The list of actionable genomic alterations in NSCLC and corresponding targeted therapeutic approaches have expanded considerably in the recent years. Combination of ICIs with EGFR and ALK tyrosine kinase inhibitors has shown increase in severe treatment related toxicity. KRAS mutation could be perhaps an exception to this limitation. Clinical trials combining ICIs with currently available KRAS G12C inhibitors, sotorasib and adagrasib, are ongoing.

In conclusion, despite extensive use of immunotherapy in treatment of lung cancer, further investigations are needed to improve efficacy of immunotherapy, and to explore potential benefits of combining immunotherapy with other treatment options like chemotherapy, radioanttherapy, new immune checkpoints and targeted agents.

S10 – INDIVIDUALIZATION OF TREATMENT OF OLIGOMETASTATIC COLORECTAL CANCER

OMRČEN TOMISLAV [1]

[1] *University Hospital Center Split, Split, Croatia*
Department of Oncology and Radiotherapy

Oligometastatic disease (OD) represents a transitional state between localized and extended disease in which local control of the metastases might lead to improved outcomes. In most relevant studies, OD is defined by 1-3 or 1-5 metastatic lesions. OD defines patients who might achieve long-term survival if all the metastatic lesions are resected or destructed, using techniques such as surgery, image-guided local ablative methods such as radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CA) or stereotactic radiotherapy (SBRT). Other modalities include: intra-arterial chemotherapy, intra-arterial radiotherapy and even liver transplantation. The clinical scenario in which OD is detected at the time of diagnosis of the primary tumor is called synchronous OD. Metachronous OD means the development of OD after treatment of the primary tumor. Oligometastatic relapse implies recurrence of the disease in the form of OD with control of the primary tumor and oligometastatic progression corresponds to the progression of a limited number of metastases, while other metastases are under the control of systemic treatment. Given the complexity of decision making and numerous therapeutic strategies in OD, treatment decisions require the input from a multi-disciplinary team (MDT) in specialist cancer centers because only with such approach adequate efficiency and safety could be ensured. The surgical approach to metastatic colorectal cancer (mCRC) involves pushing the boundaries of indications for aggressive metastasectomy with the goal of cure even in cases where metastasectomy is technically questionable. Consequently, it is important to expand the indications for non-surgical techniques in definitely unresectable OD. Additionaly, predictive clinical and biological biomarkers need to be evaluated in an attempt to define the "true" OD profile. On the top of that, a significant proportion of patients with resection of an isolated disease rapidly recover, implying the need to improve therapeutic choice and to identify patients who will benefit from local ablative methods. Improving the sensitivity of imaging methods is likely to help define OD. Finally, guidelines for CRC treatment are not entirely clear regarding the OD approach.

In the subset of patients with liver OD the cure is possible and and it should be the goal for substantial number of these patients. Meta-analysis of 60 studies with surgical resection of liver OD published between 1999 and 2010 has shown median 5 and 10-year survival of 38% and 26%, respectively. The summary median OS was 3.6 years. Additionally, retrospective analysis and meta analysis have shown that patients with solitary liver metastases have a 5-year OS rate as high as 71% following resection. About 5% of the patients with CRC will develop isolated pulmonary metastases and, although randomized clinical trials are not available, there is some evidence that highly selected patients (disease free interval >36 months, number of metastases <3, normal CEA and absence of hilar or mediastinal nodes) can benefit from a resection, leading to 5-year OS ranging from 45 to 65%. In the case of synchronous CRC and liver or lung metastases, several treatment scenarios are possible: resection of the primary tumor followed by resection of the metastases; resection of metastases followed by resection of primary tumor then adjuvant chemotherapy; neoadjuvant chemotherapy for 2-3 months followed by resection of the metastases followed by primary tumor resection and then adjuvant chemotherapy; primary tumor resection followed by chemotherapy followed by resection of metastases. Adjuvant systemic chemotherapy (FOLFOX regimen) after complete resection of LM improves recurrence-free survival; however, the OS benefit is not clear.

Image guided thermal ablation (IGTA) has gained wide acceptance in the treatment of metastases in patients with non-resectable disease. It could play adjuvant role after resection or it could be applied concomitant with resection. The question of postablation chemotherapy still remains. Survival after IGTA with adequate margins is comparable to surgical resection in selected patients with liver small volume disease (up to 55% at 5 years). IGTA has some advantages as a treatment for OD: it can be repeated to treat additional progression, it does not impact surgical eligibility for those that can be resected for future progression, it does not require prolonged chemotherapy interruption and it maintains the patients' quality of life. The indications for IGTA are: up to 4 lesions, up to 5 cm in largest diameter of metastases, patient cannot undergo or refuse surgery. The ideal tumor for IGTA is a solitary lesion with largest diameter up to 3 cm with a sufficient surrounding margin (0.5-1-cm). Contraindications of IGTA are: no safe access of the ablation needle to the tumor, anticipated collateral damage to structures nearby the tumor that cannot be protected, uncorrectable coagulopathy, inability of a patient to undergo general anesthesia and diffuse metastatic disease. RFA is the most commonly used IGTA technique. Local recurrence of liver disease after RFA is 2-60%. Local control depends on the size of the lesion, the proximity of the major blood vessels, and the margins. A recent prospective study showed a local tm progression rate of 3% within 12 months and a local tumor PFS of 95% at 30 months with a margin of over 5 mm and a biopsy proven complete tumor necrosis. In a retrospective study comparing MVA with RFA in the treatment of 254 JP significantly lower rate of local disease recurrence to 2-g for MVA vs RFA (6 vs. 20%, p = 0.01) Meta analyzes favor MVA over RFA in local disease control. CA alone or in combination with liver resection leads to results similar to resection with clear margins (5-g survival rate up to 30%). There are currently no studies comparing SBRT with other ablative methods. A review of the REFERENCE shows that SBRT achieves 1-year local control rate of 90-100% and 2-year PFS rate of 16-23% for liver OD and 2-year local control rate of 92% and 2-year OS rate of 70-77% for lung OD which is comparable to surgical resection.

In conclusion, accurate and early confirmation of the existence of OD leads to optimization of the oncological-surgical approach to mCRC. Furthermore, OD may be unresectable which leads to an advantage of local ablative methods over the surgical approach. There is a need for stronger evidence from molecular biology and genomics in defining and understanding of OD and oligometastatic phenotype. Better stratification of OD patients is needed according to treatment outcomes (DFS, OS), functional diagnostic findings, cDNA, IHC, genomics, and disease recurrence pattern. Translational research must separate true OD from non-OD with the aim of an individual approach to treatment taking into account the specifics of treatment modalities and intrinsic biological features of the tumor.

Keywords: oligometastatic, colorectal cancer, individualization, treatment

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S11 – CAN WE GET BETTER AT TREATING HEPATOCELLULAR CANCER?

FLAM JOSIPA [1, 2], Šambić Penc Mirela [1, 2], Canjko Ivana [1], Perić Luka [1, 2]

[1] *Univesrity Hospital Center Osijek, Osijek, Croatia*
Department Of Oncology
[2] *Faculty of Medicine, Osijek, Croatia*
University of J. J. Strossmayer Osijek

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most lethal neoplasm in the world. The treatment approach is determined by the stage of the disease and the degree of liver damage. The objective of treatment in the early stages is to cure the patient completely. Hepatectomy and liver transplantation are recommended for these individuals, which also cures cirrhosis as a cause of HCC. Radiofrequency ablation (RFA) and microwave ablation (MWA) are advised in circumstances where surgical excision is not possible. Chemoembolization, radioembolization, or embolization are indicated in the intermediate stage. Sorafenib, which was approved in 2008 and demonstrated a 2.8-month increase in survival when compared to placebo, was the first drug to show effectiveness. There have been several phase III trials comparing sorafenib to other drugs, however, only the REFLECT study with lenvatinib found it to be non-inferior to sorafenib. As a result, in August 2018, lenvatinib was authorized as the first-line therapy for unresectable HCC.

The IMbrave study, published in May 2020, proved the importance of immunotherapy as a first-line treatment for HCC. Finn et al found that the combination of atezolizumab and bevacizumab improved overall survival by 67.2 % in the atezolizumab and bevacizumab group, compared to 54.6 percent in the sorafenib group, and also showed that survival to disease progression was 6.8 months in the atezolizumab and bevacizumab group, compared to 4.3 months in the sorafenib group. As a result, in the first line of inoperable HCC, the combination of atezolizumab with bevacizumab has become the standard of therapy.

HCC may be separated into two types based on the expression of immune biomarkers: non-inflammatory "cool" tumors, which account for 70% of all HCC, and inflammatory "warm" tumors, which represent about 30% of all HCC.

Regorafenib was added after 9 years to the HCC drug list. A phase III RESORCE trial comparing regorafenib to placebo found a 7.8 to 10.6-month survival improvement. Regorafenib is a tyrosine kinase inhibitor approved in second-line treatment that has been licensed for patients with a Child-Pugh score of A who have progressed on sorafenib.

Cabozantinib, a treatment alternative to regorafenib, is also in the second-line treatment. It improved survival from 8 to 10.2 months in a CELESTIAL phase III trial, while progression-free survival (PFS) climbed to 5.2 months. The REACH study found that ramucirumab increased survival from 7.3 to 8.5 months and survival to disease progression from 1.6 to 2.8 months in individuals with AFP levels more than 400 ng/ml when compared to placebo. Ramucirumab in the second line was particularly effective for patients with ascites, whose overall survival improved from 3.4 to 6.7 months. Checkpoint inhibitors nivolumab and pembrolizumab, which have demonstrated encouraging outcomes in phase II trials, have been approved for second-line therapy of HHC patients.

CheckMate 040 with nivolumab had a 15.6-month survival rate in patients who had previously undergone sorafenib. Unfortunately, no statistically meaningful results were found in phase III investigations. It's worth noting that checkpoint inhibitors have a response rate of less than 25%, and there have been reports of grade 3/4 severe effects. Pembrolizumab was authorized for second-line therapy of HCC after the Keynote-224 trial. The FDA has also approved a combination of nivolumab and ipilimumab in the second line.

Dozens of new discoveries have pushed the frontiers of HCC patient care. The proper use of potential therapy modalities is a significant problem, and what we wish to achieve must include not just overall survival but also patient quality of life.

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S12 – METASTATIC RENAL CELL CARCINOMA: AN INDIVIDUALIZED APPROACH TO FIRST-LINE TREATMENT

GNJIDIĆ MILENA [1]

[1] *Univesrity Hospital Center Zagreb, Zagreb, Croatia*
Department Of Oncology

Renal cell carcinoma (RCC) is a heterogeneous group of malignancies that accounts for 2% of all cancer diagnoses and deaths, and its incidence has been rapidly increasing in the developed world. The most common RCC subtype is clear cell, while papillary, chromophobe, collecting duct and renal medullary carcinoma constitute a group of non-clear cell carcinoma. RCC overall 5-year survival rate is 76%, but drops dramatically to 12% in patients with metastatic disease.

The treatment od metastatic renal carcinoma (mRCC) has changed dramatically over the past 30 years. Initial nonspecific immune approach to targeted monotherapy evolved recently to a combination of either two immune checkpoint inhibitors (ICIs) or an ICI with an antiangiogenesis drug – tyrosine kinase inhibitor (TKI).

A pathway for modern therapeutic regimens is established by emerging evidence that indicate a strong interplay between the immune system and angiogenesis. The new immunotherapy-based combinations that have prolonged survival and created a new standard of care are: nivolumab+ipilimumab, pembrolizumab+axitinib, nivolumab+cabozantinib and pembrolizumab+lenvatinib. As the number of available systemic therapies increase, therapeutic decision-making has become more complex than ever before. Not all patients benefit equally from combination treatments. Whereas these strategies have a highly significant effect in patients with an intermediate or poor prognosis, their advantages are limited in those with favourable risk. It will remain to be seen if these benefits of immune-based combinations persist over time. No head-to-head trials comparing these novel combinations have been conducted so far, so we are left to rely on indirect comparisons.

Moreover, no biomarkers have yet been made available to facilitate treatment choices. Also, the role and timing of cytoreductive nephrectomy in patients with mRCC receiving immunotherapy-based treatment is unclear.

This presentation will try to discuss all the difficulties of choosing the optimal first-line therapy in every-day practice.

Finally, we must be aware that some questions regarding mRCC management still need to be adressed. Those are head-to-head comparisons between the current options in the first-line, higher rate of treatment-related adverse events (TRAEs), treatment sequencing, non-clear cell mRCC treatment and the role of biomarkers to ascertain the best treatment choice.

Keywords: metastatic renal cell carcinoma, thyrosine kinase inhibitors, immune checkpoint inhibitors, combination therapy

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S13 – MULTIDISCIPLINARY APPROACH TO NEOADJUVANT TREATMENT OF UROTHELIAL CANCER - ONCOLOGIST'S PERSPECTIVE

JAZVIĆ MARIJANA [1], Murgić Jure [1], Miletić Marija [1], Tomašković Igor [3, 2], Bokarica Pero [4], Fröbe Ana [1, 5]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Oncology and Nuclear medicine
[2] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Urology
[3] *Faculty of Medicine, J.J. Strossmayer University of Osijek, Osijek, Croatia*
Department of Urology
[4] *University Hospital Sveti Duh, Zagreb, Croatia*
Department of Urology
[5] *University of Zagreb, Zagreb, Croatia*
School of Dental Medicine

The treatment of muscle-invasive bladder cancer (MIBC) is complex and requires a multi-disciplinary approach among urology, radiology, pathology and oncology. A multidisciplinary team can decrease the time to both diagnosis and treatment, as well as increase accuracy of diagnosis. Another reason for multidisciplinary care is that many cancers involve complex treatment plans that require extensive discussions between specialists in real time. Radical cystectomy (RC) with bilateral pelvic lymphadenectomy remains the standard of care for patients with MIBC. Neoadjuvant cisplatin-based chemotherapy is standard treatment for MIBC before RC. Despite an overall survival benefit for patients undergoing RC after neoadjuvant chemotherapy (NAC), acceptance rates are still low. Immunotherapy has also been used with success in locally advanced and metastatic urothelial cancer and is moving into the MIBC space. Neoadjuvant radiation should not be used in patients with MIBC prior to RC.

Neoadjuvant chemotherapy

The standard treatment for patients with urothelial MIBC is RC. However, RC provides 5-year survival in about 50% of patients. The use of NAC improves survival in this population. This was demonstrated in a meta-analysis of 11 randomized trials that compared cisplatin-based NAC plus local therapy with local therapy alone. The most recent meta-analysis included four additional randomised trials. The results of this analysis confirmed the previously published data and showed an 8% absolute improvement in 5-year survival. Despite the survival benefit obtained by NAC, common clinical practice is confronted with unmet needs that must be addressed. About 40–60% of patients present residual disease despite NAC, which is associated with a higher risk of recurrence. Unfortunately, many patients are not candidates to receive cisplatin due to renal impairment or low performance status. For patients with kidney function impairment, studies have evaluated replacing cisplatin with carboplatin. However, there is no randomized data supporting the use of carboplatin for the treatment of bladder cancer in the neoadjuvant setting.

There are limited prospective comparisons of NAC approach and no predictive biomarkers exist to identify which patients benefit from NAC and thus allow treatment individualization. Clinical staging using bimanual palpation, CT or MRI may result in over- and understaging and have a staging accuracy of only 70%.

It is unclear if patients with non-urothelial histology will also benefit from NAC. A retrospective analysis demonstrated that patients with neuroendocrine tumours had improved overall survival and lower rates of non-organ-confined disease when receiving NAC.

For select patients with MIBC who are not candidates for RC or who desire preservation of their native bladder, radiation therapy (RT) plus concurrent chemotherapy is indicated rather than chemotherapy or RT as a single-modality treatment.

Neoadjuvant immunotherapy

The use of immune mediated treatment in non-muscle invasive bladder cancer (NMIBC) has been well documented with the widespread use of Bacillus Calmette–Guérin (BCG) instillation. Recently, checkpoint inhibitors have been investigated as a neoadjuvant treatment after the reported efficacy of checkpoint inhibitors in metastatic urothelial carcinoma. Pembrolizumab, a programmed death−1 (PD−1) inhibitor, was recently licensed for high-risk BCG-unresponsive NMIBC employing immunotherapy at an early stage of the illness. Nivolumab was approved as an adjuvant treatment for high-risk muscle invasive urothelial carcinoma, after showing a better disease-free survival rate compared to the placebo.

Whereas numerous trials in the perioperative setting are currently continuing, the role of immune checkpoint inhibition in the neoadjuvant setting is still not clear. Most studies have been mainly performed in patients who are ineligible for cisplatin-based chemotherapy. Results from early phase I/II studies using neoadjuvant atezolizumab (ABACUS), pembrolizumab (PURE-01), combination of durvalumab plus tremelimumab, and nivolumab plus ipilimumab have reported complete pathologic response rates between approximately 30-40%. Similar pathologic complete response rates have been seen in patients receiving immunotherapy in combination with cisplatin-based chemotherapy prior to RC. However prospective trials with longer follow-up is required to report on the survival benefits. Identification of selection criteria for patients who can maximally benefit from this treatment modality ought to be aimed for in future trials.

Neoadjuvant radiotherapy

Neoadjuvant radiation should not be used in patients with MIBC prior to RC. As a single modality, preoperative RT can eradicate disease in a small proportion of patients undergoing cystectomy. However, subsequent randomized trials demonstrated that while preoperative RT can improve local control, it has no impact on survival when compared with cystectomy alone.

Conclusions: The most important reason for multidisciplinary approach is that many people working together may reach more intelligent solutions than an individual working alone. The coordination of care in urothelial cancer remains a challenge for patients and physicians alike. We believe by utilizing a multidisciplinary approach, efficiency and quality of care increases.

Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin-combination chemotherapy. Checkpoint inhibitors are increasingly tested also in the neoadjuvant setting, either as monotherapy or in combination with chemotherapy or CTLA-4 checkpoint inhibition. Data from two phase II trials have been presented with encouraging results.

Keywords: neoadjuvant treatment, multidisciplinary approach, urothelial carcinoma.

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S14 – MULTIDISCIPLINARY APPROACH TO NEOADJUVANT TREATMENT OF UROTHELIAL CANCER - UROLOGIST'S PERSPECTIVE

TOMAŠKOVIĆ IGOR [1, 2], Jazvić Marijana [3], Murgić Jure [3], Miletić Marija [3], Bokarica Pero [4], Nikles Sven [1], Pezelj Ivan [1], Tomić Miroslav [1]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Urology
[2] *Faculty of Medicine, Osijek, Croatia*
University of J. J. Strossmayer Osijek
[3] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Oncology and Nuclear medicine
[4] *University Hospital Sveti Duh, Zagreb, Croatia*
Department of Urology

Bladder cancer incidence shows more than half a million cases in the world annuallly (1). Approximately 200,000 patients die from it, mostly atributable to muscle invasive disease (3). Muscle-invasive bladder cancer (MIBC) has a poor prognosis with recurrence rate in more than half of patients even after radical surgery, mostly due to occult metastatic disease at the time of diagnosis (4,5). Treatment of muscle invasive bladder cancer (MIBC) became more complex in the recent years. Previously, the standard of care for MIBC assumed radical surgical treatment only- cystectomy with some kind of supravesical urinary diversion. Recent advances in oncological tretatment brought changes and neoadjuvant chemotherapy (NAC) followed by radical surgery became standard of care (6). It comprises platinum based chemotherapy in eligible, fit patients followed by radical cystectomy and extensive lymphadenectomy with urinary diversion. Treating micrometastatic disease at the time of diagnosis, when the disease burden is lowest, justifies NAC (7). The results of recent metaanalysis showed that use of NAC endowed an 8% absolute 5-year survival benefit. Preliminary data from Vesper trial showed dose-dense NAC MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) has good pathological response but shows low tolerability (8). Even in the light of growing number of studies justifying NAC, there is meta-analysis showing that NAC + RC had no benefit to cystectomy or radiotherapy alone (4).

Although this NAC concept is stated in the Guidelines, the utility of NAC remains low. NAC before RC was administered in lessthan 21% of patients with MIBC (9). There are concerns that urologists contemplate when deciding about NAC, such as comorbidities like renal impairment, poor performance status, and symptomatic disease. Cisplatin-based regimen may be contraindicated in as much as 40% of patients due to its' nephrotoxicity (9). It is of note that suboptimal regimens have no benefit compared to RC alone. Bladder cancer treatment is further complicated by its histological heterogeneity.

Further concerns when administering NAC are:

- delays beyond 12 wk (from time of diagnosis or end of NAC) are considered oncologically unsafe
- the risk of immunosuppression with NAC must be weighed against the average 5–9% benefit for most patients.
- clinical trials are characterized by having strict in- and exclusion criteria. ABC Collaboration analysis had only 3% of patients with a renal function (GFR) < 60 mL/min3. In contrast to the clinical trial population, it is estimated that only 36% of patients presenting with advanced UC are treated with cisplatin, and it is estimated that 40–59% of UCC patients are not eligible for standard cisplatin-based chemotherapy (10,11).
- chemosensitive disease that responds to cisplatin-based regimens, varies from 50 to 70% in the metastatic setting. If this translates to premetastatic setting, a significant number of patients are non responders and this approach represents overtreatment (12)
- Patients may tolerate chemotherapy better before surgery compared to postoperative chemotherapy but some will delay surgery due to chemotherapy adverse effects and some will even progress during NAC treatment
- Chempotherapy protocols, timing and delivery of treatment vary throughout the world. It makes treatment efficacy evaluation difficult and comparison between treatments chalenging

Conclusion: NAC represents modern approach to eligeble MIBC patients, but it must be acknowledged that not all patients will benefit from this approach. Identification of the nonresponders could avoid side effects and delay in surgery. Selection criteria for patients who can maximally benefit from this treatment modality should be elucidated in future trials (13). NAC ineligible patients need different approach prompting furtehr investigation of immunotherapy in this setting. Therefore, molecular and other biomarkers that would better stratify patients responsive to NAC or to alternative therapies are urgently needed for better patients selection (14).

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S15 – NASOPHARYNGEAL CANCER – CASE PRESENTATION

PURGAR LEVARDA NEVA [1], Prpić Marin [1, 2], Kust Davor [1], Fröbe Ana [1, 2]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Oncology and Nuclear Medicine
[2] *University of Zagreb, Zagreb, Croatia*
School of Dental Medicine

Nasopharyngeal cancer has unique epidemiological characteristics with clear regional, racial, and gender prevalence. While more than 85% total cases are reported in Asia, in Europe it is considered a rare type of tumor and only about 5,000 patients were diagnosed in 2020. According to the Croatian Cancer Registry from 2019, there were a total of 937 cases of head and neck cancer in the Republic of Croatia, of which a total of 29 newly diagnosed cases of nasopharyngeal cancer (22 males and 7 females) and as in the world statistics the prevalent number of cases was in men, almost 75%.

We report the case of a male patient who was 63 years old at the time of the diagnosis. The patient reported for an ENT examination due to conductive hearing loss, which gradually worsened over four months. Endoscopic exam showed bulging tumor mass on the right lateral wall of the nasopharynx near the opening of the Eustachian tube and an oropharyngoscopic exam showed another mass protruding on the right lateral wall. Biopsy specimen indicated it was a non - keratinizing squamous cell carcinoma. Computed tomography of head and neck described tumor on the right lateral wall of nasopharynx about 2x3 cm in size and at the level of the oropharynx an infiltrate of 2x2,6x6 cm, narrowing the oropharyngeal lumen. The scan showed no distant metastases, so the patient was staged as T2N2M0, stage III (AJCC-TNM 8th). The patient was presented on the Multidisciplinary tumor board (MDT) for head and neck cancer where it was decided to perform definitive concurrent chemoradiotherapy and adjuvant chemotherapy. He received tumor dose of 5000 cGy to the to the elective areas of the lymph nodes on the neck bilaterally and 7000 cGy to the primary tumor and pathological lymph node, concurrently with cisplatin chemotherapy every three weeks. After concomitant treatment, the patient was examined by an ENT specialist who described a significant regression of the primary process, so he has received 3 adjuvant cycles of cisplatin-based chemotherapy with continuous infusion of 5- fluorouracil. According to a study by Baracos et al., patients with head and neck tumors are extremely prone to tumor cachexia and weight loss,

right behind pancreatic cancer and gastroesophageal cancer. Therefore, it is essential to provide adequate supportive care during treatment since tumor cachexia is associated with multitude of morbidities which affect the quality of life and overall well-being of the patient. The patient was closely monitored and NRS 2002 nutritional screening was regularly preformed. As the risk increased from the beginning to the end of treatment an adequate nutritional support based on addition of EPA at a dose of 2g / day was recommended. The side effects of the treatment the patient had were mostly grade 1 (loss of appetite and taste, difficulty swallowing, xerostomia and nausea), except for oral mucositis and radiation-induced skin reaction (grade 2), according to the CTCAE. Three months after the end of treatment, CT described at the site of the primary tumor a focal zone of enhanced contrast imbibition, suspicious of the residue of the infiltrative process. There was a complete regression of the pathological lymph node. Due to a thorough suspicion of residual disease, a biopsy was performed, but no tumor tissue was found. Almost 4 years after completion of treatment, the patient comes for regular check-ups and is still without any signs of disease.

Recurrence of the disease may be influenced by the characteristics of the patient and the disease itself (age, sex, T stage of the relapsed tumor and overall disease volume, time elapsed since the end of initial treatment and plasma EBV DNA levels) and those related to the treatment (total dose given during radiotherapy and surgical treatment options). Although high levels of Epstein-Barr virus antibodies have been detected in nasopharyngeal cancer patients since the 1960s, plasma EBV DNA values do not yet have a defined role in the treatment strategy. Its determination before and after treatment may further assist in subgroup distribution within TNM stage of the disease and has a prognostic role - elevated plasma EBV DNA after treatment is a negative prognostic factor. For now, the standard first line for recurrent or metastatic nasopharyngeal carcinoma is the platinum-based chemotherapy, the response time is on average less than six months. Novelties in treatment come from the RATIONALE 309 study for local disease recurrence and JUPITER 02 for metastatic disease. Both studies combined checkpoint inhibitors with platinum-based doublet chemotherapy and showed higher progression-free survival compared to the control group. The results of the overall survival have yet to be awaited.

In conclusion, nasopharyngeal cancer should not be overlooked in everyday practice, despite its rarity and specific endemic distribution in the world. Decision on further treatment should be made on MDT and discussed with the patient. Because of the increased nutritional risk due to treatment, patients with head and neck cancer should be intensively monitored for weight loss and tumor cachexia. In the case of inoperable relapse or metastatic disease the results of clinical studies with checkpoint inhibitors represent a promising new strategy, but the course of treatment has yet to be defined.

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S16 – NEW DEVELOPMENTS IN NEOADJUVANT AND ADJUVANT TREATMENT OF NON-SMALL CELL LUNG CANCER

RADIĆ JASNA [1, 2], Marić Brozić Jasmina [1, 2], Fröbe Ana [1, 3]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Oncology and Nuclear medicine
[2] *University of Zagreb, Zagreb, Croatia*
School of Medicine
[3] *University of Zagreb, Zagreb, Croatia*
School of Dental Medicine

Implementation of biomarker testing and enabling access to novel therapies have significantly prolonged overall survival (OS) in stage IV non- small cell lung cancer (NSCLC). However, the standard of care for the past two decades for patients with stage IB-IIIA surgically resected tumors has remained four cycles of cisplatin-based adjuvant chemotherapy, with a survival benefit of 5% at 5 years. Neoadjuvant chemotherapy confers OS benefit over surgery alone, although there has been no robust head-to-head comparison with adjuvant chemotherapy. Encouraged by the success of a biomarker-driven approach in advanced NSCLC and recognising the need to improve survival outcomes in early-stage NSCLC, the interest in revisiting perioperative strategies is rising.

Adjuvant treatment

There are pros and cons to adjuvant therapies. There is no delay of surgery, no risk of disease progression resulting in missing opportunities to use curative surgery, and therapeutic decisions are guided by biomarkers. However, patients require longer treatment, there are no intermediate end points, biomarkers are less predictive, and long-term follow-up is needed to detect disease-free survival (DFS) and OS.

Results from the multicenter IMpower010 trial established PD-L1 inhibitor atezolizumab as a potential new standard of care in adjuvant treatment. Updated findings published in 2021 showed that, compared with best supportive care, atezolizumab given for 1 year reduced the risk for disease recurrence or death by 34% in patients with stage II/IIIA NSCLC with PD-L1 expression ≥ 1% and by 21% in all patients in the stage II/IIIA following surgery and chemotherapy.

Preliminary results from the phase 3 KEYNOTE-091 trial show that adjuvant pembrolizumab given for 1 year led to a statistically significant and clinically meaningful improvement in DFS vs placebo in patients with stage IB/IIIA NSCLC following resection regardless of PD-L1 expression. At the interim analysis, there was also an improvement in DFS for patients with PD-L1≥50% in favor of pembrolizumab. KEYNOTE-091 appears to provide a second trial supporting the use of adjuvant PD-L1 inhibition in early-stage disease. The ANVIL trial (adjuvant nivolumab) has been completed but the data are still not available.

Many phase 3 trials investigating adjuvant immunotherapy (BR31, CANOPY-A) and chemoimmunotherapy (ALCHEMIST, MERMAID-1) are ongoing.

In the field of targeted adjuvant treatment, updated data of the pivotal phase 3 ADAURA trial that established neoadjuvant osimertinib in patients with resected, *EGFR*-mutated, stage IB-IIIA NSCLC showed that osimertinib reduced the risk for CNS death or progression by 82% in this patient population. ADAURA has many limitations, for example, in the adjuvant setting, it is not known whether the 2-year DFS superiority with EGFR directed therapy will translate into an OS benefit with osimertinib, so the

ALCHEMIST trial is currently testing adjuvant EGFR- and ALK-directed therapy using OS as the primary endpoint.

Neoadjuvant treatment

Neoadjuvant systemic therapy can lead to early eradication of micrometastatic disease, guide the choice of or need for adjuvant therapy; early treatment is better tolerated and induces fewer toxicities. There's somewhat earlier trial endpoints, not in terms of OS or DFS but in terms of potential predictive and prognostic biomarkers. However, neoadjuvant therapy delays surgery, which could increase the risk for surgical complications. Further, there is an increased risk for disease progression, which could result in missing the opportunity for curative surgery.

The immune checkpoint inhibitors (ICIs) are the interesting treatment option in neoadjuvant therapy of NSCLC due to the fact that early-stage tumors have a greater host immunity fitness and lower clonal heterogeneity, which is the basis for achieving better major pathologic response (MPR) rates with ICIs than neoadjuvant chemotherapy alone. Most initial studies with neoadjuvant immunotherapy selected MPR, pathologic complete response (pCR) and event- free survival (EFS) as primary or secondary endpoints, leading to a significant reduction in the time and cost of research and development compared with the use of OS and median survival time as endpoints. Other benefits of neoadjuvant immunotherapy are chronic effects on survival and potential synergetic effects with chemotherapy.

Early, but promising results from the phase 3 CheckMate 816 trial which investigated neoadjuvant nivolumab plus chemotherapy for 3 cycles compared to chemotherapy alone for patients with resectable stage IB to IIIA NSCLC were presented in 2021. Nivolumab plus chemotherapy yielded significant improvement in pCR in the intent-to-treat population (24.0% vs 2.2% with chemotherapy alone) and at all disease stages. Surgical outcomes and EFS favoured the chemoimmunotherapy combination as well.

To confirm these benefits, many phase III clinical trials are being conducted, and there is a growing demand for research on related issues, including the patient selection, optimization of chemoimmunotherapy regimens, influence of treatment on the safety of surgery, standardization of radiological response and pathologic evaluation and ways to identify pseudoprogression and avoid resultant misjudgment in surgery and adjuvant therapy

Since 2019, studies have introduced stereotactic body radiotherapy (SBRT) before surgery in early-stage disease as safe and feasible approach. Coupled with encouraging data from neoadjuvant immunotherapy and the success of radioimmunotherapy approaches, ongoing studies are combining SBRT and immunotherapy in early-stage disease. Early results are promising, showing high rates of MPR, but highlighting the need for careful patient selection and further studies in larger cohorts.

There have been a number of targeted agents explored so far in the neoadjuvant setting, and have demonstrated trends toward improvements in pathologic response rates, mostly in the EGFR-mutated population. Updated findings from a phase 2 trial that evaluated osimertinib given for 1-2 cycles prior to surgery showed an induced pCR rate of 69% in patients with resectable EGFRmt NSCLC. The phase 3 NeoADAURA study is currently evaluating 9 weeks of neoadjuvant osimertinib, chemotherapy and their combination in patients with EGFRmt NSCLC. There are ongoing studies in other molecular subsets (eg, the ALINA trial in ALK rearranged NSCLC, NAUTIKA1 in multiple genomic alterations).

Conclusion: The most effective treatment strategy for early stages of NSCLC remains unclear. With further standardisation of trial endpoints across studies, coupled with the implementation of novel tech-

nologies including radiomics and digital pathology, individual risk-stratified neoadjuvant and adjuvant treatment approaches are poised to make a striking impact on the outcomes of early-stage NSCLC.

Keywords: non- small cell lung cancer, neoadjuvant treatment, adjuvant treatment

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S17 – NEWS IN LUMINAL BREAST CANCER TRAETMENT

PETRIĆ MIŠE BRANKA [1, 2]

[1] *University Hospital Center Split, Split, Croatia*
Department of Oncology and Radiotherapy
[2] *University of Split, Split, Croatia*
School of Medicine

Endocrine-based therapies (ET) for hormone receptor positive (HR+) breast cancer (BC) are the preferred initial treatment strategy owing to durable responses in the majority of patients, favorable toxicity profiles, and relatively convenient administration. Endocrine resistance develops through multiple potential mechanisms, and translational studies looking at cyclin-dependent kinase (CDK4/6)-resistant breast cancers suggest that ET could still be effective if a druggable genomic alteration were identified. Despite the current challenges in the field, the success of CDK4/6 and PI3K inhibitors in combination with either an aromatase inhibitors (AI) or a selective estrogen receptor downregulators (SERD) illustrates the targeted therapies in advanced HR+ BC.

Mutations in estrogen receptor alpha (*ESR1*) gene are one of the more common treatment-acquired alterations. *ESR1* mutations are present in only 3% of untreated HR+ BC, but in 25% of AI-treated HR+ BC. SERD, ie fulvestrant were subsequently developed to address *ESR1* mutations**.** PADA-1 is the first phase 3 trial to demonstrate that, in most patients, resistance-associated mutations in the *ESR1* can be detected and targeted before tumor progression. Women with HR+/HER2- metastatic breast cancer (mBC) benefit from switching from an aromatase inhibitor to fulvestrant in palbociclib combination therapy when an *ESR1* mutation is detected without disease progression. Risk for disease progression or death was a significant 37% lower for the women who switched to fulvestrant to those who stayed on standard therapy. Median progression-free survival (PFS) was 11.9 months in the fulvestrant arm and 5.7 months in the standard therapy arm. This clinical benefit with early fulvestrant use might justify the implementation of the PADA-1 treatment strategy as a valid option in routine care**.**

Novel agents targeting the estrogen receptor (ER) are oral SERDs (elacestrant, giredestant, camizestrant, amcenestrant, rintodestrant). Multiple ongoing trials are looking to combine novel SERDs with CDK4/6i and PIK3CAi. The complete estrogen receptor antagonist (CERAN), OP-1250, has demonstrated activity in preclinical models of HR+ mBC. It has no activity as agonist binding to uterine ER and therefore no increased risk for endometrial cancer. Whereas SERDs and CERANs bind reversibly to the ER, the selective estrogen receptor covalent antagonist (SERCA) H3B-6545 binds covalently to the Cys530 residue of the ER. It demonstrated activity in wild type or *ESR1m* HR+ BC.

The most important group of epigenome-modulating drugs for treating HR+ BC are histone deacetylase (HDAC) inhibitors. A randomized phase 2 study (ENCORE 301) that looked at the combination of entinostat, an HDAC inhibitor, with exemestane in postmenopausal women with HR+ mBC suggested that the addition of entinostat to exemestane significantly prolonged PFS. However, the subsequent phase 3 study did not show a PFS or overall survival (OS) benefit.

Samuraciclib is an oral selective inhibitor of CDK7 with synergistic activity with ET (SERM, SERD) in HR+BC. The phase 2 modular study showed clinical activity for patients with HR+ mBC who were treated with the CDK7 inhibitor samuraciclib plus fulvestrant, and who were previously heavily pretreated with CDK4/6i. Preclinical data indicate that CDK7 inhibition activates the p53 pathway in TP53 wild-type, HR+ BC cells, inducing apoptosis. Patients with TP53 wild-type tumors represent ≈70% of patients in this setting, meaning that samuraciclib has the potential to benefit the majority of patients. Samuraciclib has been granted fast-track status by the US Food and Drug Administration (FDA).

Despite outcome improvements in adjuvant therapy over the years, up to 20% of patients with HR+/HER2- early breast cancer (eBC) will experience recurrences in the first 10 years after surgery, with either locoregional disease or distant metastases, becoming, in the latter scenario, incurable.

Given the success of CDK4/6i and ET for HR+/HER2- mBC, there is great interest in determining whether the survival benefit translates into an adjuvant breast cancer setting. Final analysis of the PALLAS trial, with 5,796 recruited patients and a 31-month median follow-up, did not show significant improvements in survival end points for the addition of 2 years palbociclib to adjuvant ET. A smaller trial of 1 year of adjuvant palbociclib in the specific situation of high-risk disease after limited response to neoadjuvant chemotherapy, PENELOPE-B, also showed no significant invasive disease free survival (iDFS) benefit. By contrast, the monarchE trial investigating 2 years of adjuvant abemaciclib in high-risk patients (nodus positive disease) reported an interim result, suggesting a significant iDFS benefit for CDK4/6i and an updated analysis confirmed a relative 30% hazard rate reduction at a median follow-up of 27 months (HR 0.70, P <0.0001). Ribociclib is currently being studied in the adjuvant setting in the NATALEE study. On October 2021, FDA approved abemaciclib with ET (SERM or AI) for adjuvant treatment of adults HR+/HER2-, node positive eBC et high risk of recurrence and Ki 67 score ≥ 20%.

OlympiAD and EMBRACA trials demonstrated the efficacy of PARP inhibitors, compared to chemotherapy, in patients with HER2 negative mBC carrying a germline BRCA mutation. Patients with ER+/HER2-BRCA-mutated mBC seemed to have a higher risk of early disease progression while on CDK4/6 inhibitors and benefit from PARPi, especially when prescribed before chemotherapy. Importantly, 50% of all BRCA1/2 mutated breast cancers are actually of ER+/HER2- subtype. Recently, the large phase III OlympiA trial investigated the benefit associated with olaparib given for a year as an adjuvant treatment in HER2- eBC patients with germline BRCA1/2m. Patients with ER+/HER2- eBC had unfavorable features (more than four positive lymph nodes for those with initial surgery, or non-pCR and a CPS+EG score ≥ 3 in those treated with neoadjuvant therapy). Olaparib as adjuvant therapy after neoadjuvant or adjuvant

chemotherapy and local therapy resulted in significantly longer survival free of invasive or distant disease than placebo in such patients (iDFS HR 0.58, P<0.001; DDFS HR 0.57, P<0.001). In June 2021, the American society of clinical oncology (ASCO) updated their guidelines to recommend 1 year of adjuvant olaparib in ER+/HER2- eBC with at least four involved axillary lymph nodes.

SWOG S1007 RxPONDER trial found that postmenopausal women with HR+/HER2+ eBC with 1-3 positive lymph nodes and 21-gene recurrence score of ≤ 25 (Oncotype DX) derived no further benefit from chemotherapy added to ET and can safely avoid adjuvant treatment with it. On the other hand, premenopausal women with the same characteristics experienced a 45% relative risk reduction in invasive DFS events with the addition of chemotherapy.

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S18 – NEWS IN THE TREATMENT OF HEAD AND NECK CANCERS

RAKUSIC ZORAN [1]

[1] *University Hospital Centre Zagreb, Zagreb, Croatia*
Department of Oncology

The use of PD-1 inhibitor of pembrolizumab with or without chemotherapy in the first-line treatment of recurrent/metastatic (R/M) head and neck cancers, as well as the use of nivolumab and pemrolizumab in platinum refractory R/M patients has long been the standard of care for these patients. The progress made in survival has stimulated additional enthusiasm for the treatment of R/M disease, but also for the treatment of locally advanced head and neck cancers. However, subsequent clinical trials did not demonstrate the superiority of the investigational drugs over the already mentioned combinations. It is related to R/M disease (combination of durvalumab and tremelimumab in the EAGLE study, and nivolumab and ipilimumab in the CheckMate 651 study) as well as in locally advanced disease - concomitant chemoradiotherapy with the addition of avelumab (Javelin H&N 100) or immunoradiotherapy with pembrolizumab (GORTEC 2015-01 PemroRad study).

A large number of patients ultimately do not benefit from immunotherapy due to primary resistance or relapse after a period of response due to acquired resistance. While nivolumab and pembrolizumab provided improved OS in R/M head and neck cancers, only a subset of these patients had a response. Key reason for primary resistance to checkpoint inhibitots is the lack of recognition of tumor cells by T cells due to the absence of tumor antigens, as cancer cells may develop mechanisms to avoid antigen presentation and detection. A recent study showed that primary resistance to immunotherapy based on PD-1 inhibitors may be abnormal intestinal microbiome composition, and the use of broad-spectrum antibiotics while receiving immunotherapy can significantly compromise the survival of treated patients.

The de-escalation approach in the treatment of HPV+ head and cancer has not been successful, confirmed in phase III studies TROG 12.01 and De-ESCALaTE HPV. Unlike other de-escalation studies, OPTIMA-II treated a group of HPV+ oropharyngeal cancers including T4, N3 disease with a significant smoking history, groups of patients who were excluded from other studies. In this study, high-risk disease was defined by any of the following factors: T4 disease, N2c or N3 disease, >20 pack-year smoking history, or non p16 subtype of HPV, while none of these features was defined as low-risk (based on 7th edition of the AJCC). Patients with low-risk disease and tumor reduction ≥50% were treated with TORS or RT (50 Gy) alone. Patients with low-risk disease and tumor reduction of 30-50% or high-risk disease with tumor reduction of ≥50% received CRT at a reduced dose (45-50 Gy). All others received standard dose of CRT (70–75 Gy). This study showed that the deep response rate (defined as the percentage of patients with ≥50% tumor reduction according to RECIST 1.1) was 70.8%, with 2-year PFS and OS of 90.4% and 93.3%, respectively. In addition, of the nine patients eligible for TORS, six (67%) were found to have a pathologically complete response of the primary tumor and lymph nodes, and all nine (100%) did not require adjuvant RT. Dynamic blood biomarkers, such as HPV DNA during induction therapy in HPV+ oropharyngeal cancer, may be prognostic in the context of a response-adaptive de-intensification paradigm.

There is a growing interest in the use of neoadjuvant immunotherapy in locally advanced head and neck tumors. Preliminary results of several early-stage studies have shown that this is a possible treatment option, but with modest results. Phase Ib study with neoadjuvant immunoradiotherapy (NIRT) included patients with previously treated locally advanced p16-positive (stages I-III, AJCC, 8th edition) and p16-negative head and neck cancers (stages III-IVA) Initially, two groups of patients were treated with

neoadjuvant SBRT, with GTV-only radiation for 1 week at a total dose of 40 Gy in 5 fractions, (Group 1), or 24 Gy in 3 fractions (group 2), in combination with nivolumab 240 mg every 2 weeks × 3. After reviewing the safety profile, two groups were added that were treated with a lower radiation dose (24 Gy, 8 GyX3) with and without immunotherapy: group 3 who were treated only with SBRT as a control group, and group 4, p16-negative, who were treated as group 2. Surgery was planned in all patients 5 weeks after SBRT, followed by adjuvant nivolumab 480 mg every 4 weeks, 3 doses, starting 4 weeks after the operation. Among 10 HPV-positive patients treated with nivolumab and SBRT, the pCR rate was 90% (group 1: 5/5; group 2: 4/5) and the mPR rate was 100%. Among HPV-positive patients treated with neoadjuvant SBRT alone (cohort 3), the pCR rate was 50% (n = 3). Among HPV-negative patients (group 4), pCR and mPR rates were 20% (n = 1) and 60% (n = 3), respectively.

In a phase 2 study, 40 patients with R/M head and neck tumors were treated in the first line with a triplet combination of monalizumab (NK cell checkpoint inhibitor), cetuximab, and durvalumab. The median age was 65 years (48-91), 12 (30%) patients had HPV+ oropharyngeal cancer, and 25 (63%) were current or former smokers. The median follow-up was 16.3 months, 13 patients had a confirmed response, ORR 32.5%, including 3 complete responses. The median time to response was 1.8 months, 6/13 patients were still on treatment, with a median duration of response not yet achieved [7,1-NR], a median PFS- was 6.9 months and OS after 12 months was 59%. Grade 3-4 treatment-related adverse reactions (TRAEs) occurred in 19 patients (48%); the most common events were elevated lipase or amylase levels and acneiform dermatitis. Preliminary data suggest a promising antitumor activity of the triplet of monalizumab, cetuximab and durvalumab in the first-line treatment of R/M SCCHN with an acceptable safety profile.

We are witnessing great news and advances in the treatment of head and neck tumors, upwards due to the application of immunotherapy and sophisticated radiotherapy techniques. However, challenges with further advances in the treatment of this disease require additional knowledge of the biology, molecular characteristics, biomarkers and gene mutations of these tumors.

Keywords: head and neck cancers, locally advanced disease, recurrent/metastatic disease, de-escalation therapy, immunotherapy.

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S19 – NOVELTIES IN TARGETED THERAPY OF THE NON-SMALL CELL LUNG CANCER

BOBAN MARIJO [1, 2]

[1] *University Hospital of Split, Split, Croatia*
Department of Oncology
[2] *University of Split, Split, Croatia*
School of Medicine

The targeted therapies have dramatically improved the treatment outcomes in advanced non-small cell lung cancer (NSCLC). The fast development of targeted therapies results in a constantly growing list of approved drugs. Consequently, the therapeutic landscape is becoming increasingly complex and demanding.

EGFR Exon 20 Insertions account for 12% of EGFR mutations and exhibit inherent resistance to approved tyrosine kinase inhibitors. As a result, the standard of care remains platinum-based chemotherapy, with an associated reduced median overall survival (OS) of 16 months.

Amivantamab is a fully human EGFR-MET bispecific antibody. In a phase I CHRYSALIS study, amivantanab in platinum pretreated EGFR exon20ins NSCLC population achieved overall response rate (ORR) of 40%, with a median duration of response (DOR) of 11.1 months. The median progression-free survival (PFS) was 8.3 months.

Mobocertinib is an oral tyrosine kinase inhibitor designed to selectively target EGFR exon 20ins mutations. In a phase I/II study in platinum-pretreated patients cohort, with confirmed ORR of 28%, median DOR assessment was 17.5 months. Median PFS assessment was 7.3 months. Median OS was 24.0 months.

Based on these results, the FDA approved both amivantanab and mobocertinib for treatment of adult patients with EGFR exon 20ins locally advanced or metastatic NSCLC whose disease progressed on or after platinum-based chemotherapy.

The optimal treatment of patients who progressed on EGFR TKIs (especially osimertinib) represents a great challenge.

Treatment with the combination of amivantamab and lazertinib (third generation EGFR TKI) in phase I CHRYSTALIS study yielded responses in 36% of chemotherapy-naive patients who progressed on osimertinib. Among these patients, a subgroup of patients with genetic EGFR and MET-based biomarkers of resistance were more likely to respond (ORR 47%, median PFS 6,7 months).

In phase I study, in patients with EGFR mutation who progressed on EGFR TKI and chemotherapy, patritumab deruxtecan, a novel HER 3 - targeted antibody-drug conjugate, obtained an ORR of 39%, median PFS was 8,2 months.

KRAS mutations are found in 25 to 30% of non–squamous NSCLC. Among all KRAS mutations, the most common is KRAS G12C which can be found in approximately 13% of all lung adenocarcinomas.

Sotorasib is a small molecule that specifically and irreversibly inhibits KRAS G12C. In phase 2 portion of the CodeBreaK100 trial, the ordination of sotorasib in pretreated patients with the KRAS G12C mutation NSCLC, an ORR was observed in 37.1% of the patients, with a median DOR of 11.1 months. The median PFS was 6.8 months and the OS was 12.5 months. FDA and EMA approved sotorasib for the treatment of adults with advanced NSCLC with *KRAS* G12C mutation who progressed after at least one prior line of systemic therapy. Adagrasib, also a specific and irreversible inhibitor of KRAS G12C, received FDA breakthrough therapy designation on the basis of the KRYSTAL-1 phase I/II study as it showed an ORR of 45% in NSCLC pretreated patients with KRAS G12C mutation.

RET fusions are present in 1-2% of NSCLC patients. Previous studies of multikinase RET TKIs showed disappointing results. Implementation of specific RET TKIs significantly improved treatment outcomes. Updates of pivotal studies with pralsetinib and selpercatinib confirmed excellent efficacy of these drugs.

Pralsetinib was investigated in the phase I/II ARROW study in two cohorts of patients: previously treated and untreated. In patients who had received prior platinum-based chemotherapy, the ORR was 61% and DOR was not reached. In treatment-naıve patients, the ORR was 70% and the median DOR was 9.0 months.

Selpercatinib was similarly evaluated in phase I/II LIBRETTO-001 study, again with separate cohorts. The ORR in previously treated and untreated patients was respectively 64% and 85%, with a median PFS of 19,3 months in previously treated patients, while it was not reached in untreated patients.

DESTINY-Lung01 phase II study evaluated trastuzumab deruxtecan in HER 2 mutation NSCLC refractory to standard treatment. Trastuzumab deruxtecan showed robust and durable activity, ORR occurred in 55% of the patients. The median DOR was 9.3 months. Median PFS was 8.2 months, and median OS was 17.8 months.

Keywords: non-small cell lung cancer, targeted therapy, treatment outcomes

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S20 – NOVELTIES IN TREATMENT OF HER2-POSITIVE BREAST CANCER

BAŠIĆ KORETIĆ MARTINA [1], Podolski Paula [1], Šarić Nera [1], Soče Majana [1], Baučić Maja [1], Vušković Sanja [1]

[1] *University Hospital Center Zagreb, Zagreb, Croatia*
Department of Oncology and Radiotherapy

Breast cancer (BC) is heterogenous disease. HER2 positive BC makes about one fifth of all breast cancers, with unique nature and very aggresive behavior. In recent decades HER2 targeted therapy exibited revolutionary advances in treating breast cancer, significantly decreasing risk of relaps in early disease and improving survival in metastatic disease. In early BC, all tumors bigger than 2 cm in diameter and/or positive lymph nodes should receive neoadjuvant chemotherapy with dual HER2 blocade with pertuzumab and trastuzumab. Neoadjuvant therapy enables insight into clinical or radiological response and allows to change and improve therapy depending on response. Moreover, if achieves complete pathological response (CPR), is connected with improved prognosis. In early BC more individual approach is prefered, allowing avoidance of anthracyclins when possible, as results of APT and TRAIN-2 studies confirmed in selected populations. After neoadjuvant therapy, adjuvant approach depends on pathological response. In Afinity trial, N+ patients that achieved CPR after neoadjuvant treatment, derived IDFS benefit with pert/trast combination adjuvantly. Patients that do not achieve CPR, should receive trastuzumab-emtasine, as KATHERINE trial confirmed with recurrence risk reduction od 51%. In metastatic disease, first line prefered combination includes pertuzumab and trastuzumab with taxane as shown in pivotal CLEOPATRA study. After 8 years of follow-up improved median OS (57.1 vs 40.8 months), with survival of 37 vs 23% was shown.After progression, considered second-line therapy was TDM-1, based on EMILIA study that demonstrated improved PFS and OS compared with lapatinib/capecitabine. In the last year, results of DESTINYBreast-03 trial were presented: in patients that were previously treated with a taxane and trastuzumab (60% pertuzumab), received in second line T-DM1 or trastuzumab- deruxtecan (T-DXd). In this study, treatment with T-DXd resulted in a significant improvement in PFS: 75.8% vs 34.1% with T-DM1 after 1 year. Tucatinib is a small oral HER2 selective inhibitor, which showed superior efficacy in combination with capecitabine and trastuzumab in highly pretreated patients (receiving previously trastu-

zumab, pertuzumab and TDM-1). In HER2CLIMB study combination with tucatinib significantly improved PFS: 7.8 vs 5.6 months. At 24 months median OS was 21.9 vs 17.4 months. Neratinib is small ireversible pan TKI-inhibitor, that showed efficacy in combination with capecitabine, in patients that received two or more prior HER2 regimens. In NALA trial combination of neratinib and capecitabine compared to lapatinib with capecitabine, was associated with an improvement in PFS, with no significant OS benefit. Margetuximab is monoclonal antibody designed to increase antibody dependent cellular toxicity. In SOPHIA trial, patients with metastatic BC were included after at least two lines of HER2 therapy. Margetuximab improved PFS -5.8 vs 4.9 months with no effect on OS. In TULIP trial, trastuzumab duocarmazine efficacy was compared to treatment by physician's choice, in patients who had received at least two prior lines of treatment, with PFS 7.0 vs 4.9 months. In PHOEBE trial patients that previously received trastuzumab and chemotherapy, were included to recieve pyrotinib (pan-HER inhibitor) or lapatinib with capecitabin. Combination with pyrotinib presented with improved median PFS: 12.5 vs 6.8 months. Many other treatment combination are being investigated in HER2 positive BC. In PANACEA trial with pembrolizumab and trastuzumab, 15% responsewas seen in PDL1+ patients. KATE2 trial that combined atezolizumab and TDM1 showed numeric trend to better PFS and OS in PD-L1+ patients. Moreover, CDK4/6 and HER2 signaling association has been proved, with singergism in antitumor activity. In MonarcHER trial, patients received trastuzumab and fulvestrant with abemaciklib,abemaciclib or chemotherapy with a trastuzumab. Improved PFS was observed in triplet combination with PFS 8.3 vs 5 months.

Treatment of HER2-positive BC is improving with many new treatment options in metastatic and early setting. In metastatic disease, after progression to two standard lines, there is no evidence supporting preferred approach. So decisions has to be made depending of different factors like comorbidities, prior therapies, drug availability, treatment toxicity and site of metastates.

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S21 – NSCLC WITH KRAS G12C MUTATION TREATMENT – A CASE REPORT

BITAR LELA [1], Srdić Dražena [1], Seiwerth Fran [1], Jakopović Marko [1, 2]

[1] *University Hospital Center Zagreb, Zagreb, Croatia*
Department for Respiratory Diseases
[2] *University of Zagreb, Zagreb, Croatia*
School of Medicine

Introduction: New therapeutic options for advanced non-small-cell lung cancer (NSCLC) substantially increased patients quality of life and reduced mortality. Check-point inhibitors for patients without driver mutations and new targeted therapies for patients with oncogenic driver mutations have substantial clinical benefit. Treatment for KRAS mutation has been unmet need until sotorasib availability.

Case report: The female patient was diagnosed with non-small-cell lung cancer, adenocarcinoma, in October 2020 at the age of 60. She was non-smoker and there were no significant co-morbidities except arterial hypertension. She was in very good performance status, ECOG PS 0. Initial stage of the disease was T4N2M1b-IV. We did predictive biomarkers, EGFR, ALK and ROS1 were negative and PD-L1 was 0%. The patient received 4 cycles of chemotherapy with pemetrexed and cisplatin and continued with pemetrexed maintainance for 4 cyles. Eventually the maintainance therapy was discontinued because of peripheral neuropathy. In April 2021 clinical and radiological disease progression was verified and the patient started with immune check-point inhibitor atezlizumab. Unfortunately after 2 months of therapy further disease progression was verified and the patinet developed bilateral pulmonary infiltrations requiring domestic oxygenotherapy. In the meantime initial tissue sample at the time of dijagnosis was sent to FMI next generation sequencing and the result was positive KRAS G12C mutation. In July 2021 she started with sotorasib (Amgen EAP) in the standard dose of 960mg orally once daily. In September 2021 radiological partial response was verified and the patients performance status improved significantly. There was no need for oxygenotherapy. She did not experience any treatment related side-effects nad is currnetly terated with full dose sotorasib with very good peformance status and quality of life.

We treated 4 patients with sotorasib since May 2021 until December 2021. There were 2 females and 2 males, with median age 61 years (47-74). All of the patients were treated with immune check-point inhibitors previously. The best response on sotorasib therapy was partial response in 2 patients and stable disease in 2 patients. Only one of the patients progressed at the data cut-off date and that patient had duration of response of 5 months. Only one patient did not experience any side-effects. months. 3 of our patients experinenced hepatic side effects, alanine aminotranferase increased and aspartate aminotrasferase increased, CTCAE grade 2-3. Onset of side effects was 4 weeks, 8 weeks and 12 weeks respectively. The treament was stopped for median of 14 days after which was resumed in one level lower dose of 480 mg

once daily. 2 patients remained without further increase and had stable disease, but one patients progressed after second dose reduction.

Conclusion: Sotorasib showed clinical efficacy with very good tolerability in patients with KRAS G12C mutation. Drug efficacy remained stable regardless of dose reduction.

E-mail: lleellaa@gmail.com

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S22 – PAN-TUMOR BIOMARKERS IN ERA OF AGNOSTIC ONCOLOGY

TOMIĆ SNJEŽANA [1]

[1] *University Hospital of Split, Split, Croatia*
Department of Pathology

Precision medicine has provided new perspectives in oncology, yielding research on the use of targeted therapies across different tumor types, regardless of their site of origin, a concept known as tissue-agnostic indication. Since 2017, the Food and Drug Administration (FDA) has approved the use of three different agents for tumor-agnostic treatment: pembrolizumab (for patients with microsatellite instability or high tumor mutational burden) and larotrectinib and entrectinib (for patients with NTRK fusions).

Tumor MSI/MMR status can be tested using immunohistochemistry (IHC), polymerase chain reaction (PCR) and, more recently, NGS techniques. IHC for the MMR proteins MLH1, MSH2, MSH6, and PMS2 is a practical and widely available methodology among pathology laboratories. dMMR by IHC is defined by the absence of nuclear staining of some of the above mentioned MMR proteins in the tumor with preserved internal positive cell controls. If IHC expression of at least one of those proteins is lost, the diagnosis of dMMR is established. In cases of indeterminate IHC results, a molecular test preferentially based on PCR is indicated. This can be done using two panels: The National Cancer Institute (NCI) panel, which evaluates two single nucleotide repeat loci, and three dinucleotide repeat loci, and pentaplex PCR, using five polyA mononucleotide repeats Tumors with instability at 2 or more of these markers are defined as MSI-H. Pentaplex PCR is the preferred panel given its higher sensitivity and specificity. More recently, the use of NGS panels has been validated for MSI-H diagnosis, and the reported concordance rates between NGS testing and IHC or PCR are high.

The NTRK1, NTRK2, and NTRK3 genes encode the neurotrophin receptors TRKA, TRKB, and TRBC, which are predominantly transcribed in the nervous system in adult tissues. The TRK family plays an

important role in nervous system development through regulation of cell proliferation, differentiation, apoptosis, and survival of neurons in both central and peripheral nervous systems.

Fusions involving these genes are the most common mechanisms of oncogenic TRK activation and are found in both adult and pediatric tumors. NTRK fusions are enriched in rare cancer types, including infantile fibrosarcoma, congenital mesoblastic nephroma, secretory breast carcinoma, and mammary analog secretory carcinoma. Common tumors, such as lung, melanoma, and colorectal cancers, have low frequencies of these genomic alterations.

There are different methods for identifying NTRK fusions. The use of FISH or RT-PCR is not recommended as a screening tool and should be reserved for cases where NTRK fusions are highly recurrent (ETV6-NTRK3 fusion) as in the case of infantile fibrosarcoma or secretory breast carcinoma. FISH is not able to identify the gene fusion partner, requires expertise, and is more expensive when a multiplex assay is used. RT-PCR provides direct evidence of a NTRK fusion and detects only known fusion partners and breakpoints. RNA or DNA based NGS methods are able to assess NTRK fusions with the advantage of providing other important molecular information, including the presence of other oncogenic drivers, tumor mutation burden, and monitoring of patients for the development of resistance mutations. RNA based NGS has some advantages over DNA, since it is an approach that allows de novo detection of gene fusion transcripts that have not been previously described and increases the sensitivity of detection in low tumor purity samples. For tumors that rarely harbor NTRK fusions, front-line NGS-based approaches or a two-step approach with IHC followed by sequencing tests are indicated. Tumors are considered positive if ≥ 1% of tumor cells exhibit positivity at any intensity above the background. The staining pattern is variable in intensity and localization (nucleus, cytoplasm, or membrane). IHC shows lower sensitivity for NTRK3 fusions and lower specificity for tumors with neuronal and muscular differentiation.

TMB can be defined as the total number of somatic mutations per megabase (mut/Mb) of the examined genome. Tumors with high TMB have a high neoantigen burden, which might increase T-cell reactivity. Thus, it was hypothesized that tumors with high TMB are more responsive to immune checkpoint inhibitors (ICIs). In fact, several retrospective and prospective studies have suggested that high TMB is associated with improved response to immunotherapy in several tumor types. But, the predictive role of TMB in the benefit of immunotherapy has been surrounded by controversy. This can be partially explained by the fact that TMB has been calculated using different platforms. In addition, TMB is influenced by tumor purity, ploidy, sequencing depth of coverage, and analytic methodologies. Furthermore, the threshold definition of high TMB is still not optimized across cancer types. Additionally, while the use of large panels (covering > 1.1 megabase of the sequenced coding region) has been validated in the context of clinical trials, it is important to highlight that their use tends to overestimate the mutational burden compared with whole exome sequencing. Multiple ongoing initiatives are attempting to standardize TMB assessment, and further work is necessary to establish the best cut-off for using TMB as a predictive biomarker of response to immunotherapy

In addition, other molecular alterations have potential for histology-agnostic designation, including RET alterations, BRAF mutations, fibroblast growth factor receptor (FGRF) aberrations, KRAS 12 G, ROS1, ALK, NRG1, HER2, and POLE/POLD17.

Keywords: pan-tumor biomarkers, MSI/MMR, NTRK fusions, tumor mutational burden

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S23 – PANCREATIC CANCER: CURRENT STANDARDS AND FUTURE PERSPECTIVES

BAN MARIJA [1]

[1] *University Hospital of Split, Split, Croatia*
Department of Oncology and Radiotherapy

Pancreatic cancer is one of the deadliest cancers in the world, and one of the most difficult to treat. In 2020, an estimated 495,000 individuals worldwide were diagnosed. According to Croatian Institute for public health 743 patients were diagnosed in Croatia in 2019. Most patients with advanced disease die within a year of treatment, and most with localized early-stage disease do not survive beyond five years.

Pancreatic cancer incidence has doubled in the past 25 years, due in part to global population aging and the increasing percentage of people who have diabetes or are obese. These three factors all increase risk of developing pancreatic cancer, and help explain locations of highest risk and disease incidence. Additional risk factors include consistent heavy alcohol consumption, and familial history. Some of the mutations have been identified that contribute to genetic risk, and which can help determine the most effective treatment. Most common are pathogenic variants in BRCA2, associated with hereditary breast and ovarian cancer, and the ATM gene which are associated with about a 406-fold increased risk. Mutations in the mismatch repair gene most associated with hereditary non-polyposis colorectal cancer have about an eight-fold risk, as well as mutations in genes most notably associated with hereditary pancreatitis. If it is available, germline genetic testing for all pancreatic cancer patients, regardless of family history should be considered.

Clinical challenges of pancreatic cancer include late/advanced presentation (vague symptoms, limitations if current imaging modalities, no adequate screening modality); rapid tumor growth and metastasis; high recurrence rate following surgery; relative resistance to conventional therapy and few predictive biomarkers to guide treatment.

Fewer than 20% of newly diagnosed patients are candidates for surgery. Adjuvant chemotherapy recommendation depends of pathohystologic findings. Combination of gemcitabine/capecitabine or m FOLFIRINOX are preferred regimens.

In 30%–40% of patients, while the tumour is confined to the pancreatic region, resection is not feasible, mainly due to vascular invasion. This subgroup of patients might be assigned into two different categories: borderline resectable and locally advanced disease.

Borderline resectable disease should be treated with neoadjuvant chemotherapy. Options include the following FOLFIRINOX/modified FOLFIRINOX, with or without subsequent chemoradiation; gemcitabine+ albumin-bound paclitaxel, with or without subsequent chemoradiation; gemcitabine + cisplatin (≥2–6 cycles) followed by chemoradiation (only for known BRCA1/2 mutations).

In patients with unresectable locally advanced pancreatic cancer chemotherapy is the mainstay of treatment in combination of local ablation whenever is possible. Radiofrequency ablation (RFA), stereotactic body radiation therapy (SBRT) and microwave ablation appear to be feasible. Several of these ablative techniques have been shown to provide pain relief and improved survival.

Metastatic disease treatment depends upon disease burden and especially performance status. For patients with good performance status FOLFIRINOX and mFOLFIRINOX as well as nab-paklitaxel/gemcitabine combination is preferred, and for those with poor performance status gemcitabine monotherapy should be offered. Patients with germline BRCA mutations cisplatin/gemcitabine protocol might be an option. Olaparib is approved for maintenance treatment of adults with deleterious or suspected deleterious germline *BRCA*-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

Second and other treatment lines depends on patient performance status, previous treatment, drug availability and patient preferences. New drug formulations such as encapsulated form of irinotecan, according to NAPOLI I trial shown benefit in terms of progression free survival and overall survival for patients previously treated with gemcitabine based chemotherapy.

Personalized and precision medical treatments have not been as effective for pancreatic cancers as they have with other types of cancer. Some precision medicine treatment options have been developed that are showing partial and complete responses. But they tend to be for rare mutations, such as germline BRCA1 and BRCA2 (5%-7% of patients), K-ras mutations (less than 1%), and MMR deficiencies (less than 5%). New chemotherapy drugs being developed, such as those targeting the stroma. Immunotherapy and predicts that it will be used in conjunction with chemotherapy in the future.

Palliative therapy should be administered early in the course of the disease ie. for the pain relief, obstructive jaundice and duodenal obstruction secondary to tumor infiltration.

Keywords: pancreatic cancer, standard treatment, future perspective

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S24 – PERIOPERATIVE CHEMOTHERAPY IN LOCALLY ADVANCED GASTRIC CANCER-CASE REPORT

ŠUNJIĆ MARIN [1], Soldić Željko [1], Fröbe Ana [1, 2]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Clinic for Oncology and Nuclear Medicine
[2] *School of Dental Medicine, University of Zagreb, Zagreb, Croatia*

60-year-old man suffering from abdominal pain, nausea, loss of appetite (weight loss of 10 kg in the last 3 months) was referred to our hospital. Upper gastrointestinal endoscopy revealed exulcerated tumor formation in the angular and antral part of stomach. Pathological examination of biopsy specimen revealed well differentiated adenocarcinoma. Computed tomography (CT) showed a tumor process of the stomach with suspected infiltration of the pancreas, spreading to regional lymph nodes, without distant dissemination.

These findings confirmed the diagnosis of this patient as locally advanced gastric cancer. We diagnosed this patient as cT4bN1. The tumor markers were within normal levels. Then, the patient underwent perioperative chemotherapy according to FLOT treatment regimen (four preoperative and four postoperative 2-week cycles).

The FLOT4 study has established FLOT as the new standard of care for perioperative chemotherapy in patients with resectable gastric cancer who can tolerate a triplet chemotherapy regimen. After four courses of chemotherapy, CT revealed a partial reduction in gastric wall thickening and shrinkage of lymphadenopathy. Spleen-preserving total gastrectomy with lymph node dissection was scheduled 7 weeks after completion of the last cycle of preoperative chemotherapy. Histological examination of the resected specimen and the harvested lymph nodes revealed a well differentiated intestinal adenocarcinoma pT4aN2. Postoperative four-cycle adjuvant chemotherapy using FLOT was administered shortly after surgery. The patient tolerated the therapy well. The patient has been regularly attending our clinic for follow-up examination with CT and tumor markers every 3- 6 months. The patient is still alive without any evidence of local recurrence or metastatic disease 18 months since surgery.

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S25 – PERSONALIZATION OF THE APPROACH TO THE METASTATIC UTERINE CANCER: A CASE REPORT

ČERINA DORA [1], Tica Sedlar Ivana [1]

[1] *University Hospital Center Split, Split, Croatia*
Department of Oncology and Radiotherapy

Case report: In the time of modern oncology, individualization is accentuated in a paradigm shift that is happening when approaching the patient. Personalized approach comprises of a timely indicated treatment-orientated workup and timely administration of the available conservative or targeted treatment[1]. Uterine cancer is the most common gynecological cancer in developed countries and despite its general good prognosis, 15-20% of women are being diagnosed with metastatic disease[2,3]. In such cases, chemotherapy or hormonal therapy are still the mainstay of the treatment with rather unsatisfactory outcomes, less than 12 months median time of overall survival[3,4]. According to the recent findings uterine cancer harbors a high level of genomic alterations but is somewhat insufficiently explored[5,6]. Here we present a case of a 63 year old female patient diagnosed in October 2020 with stage IV metastatic uterine cancer, according to the Federation of Gynecology and Obstetrics (FIGO) classification. Patient had patohistological confirmation of mixed tumor (endometriod and clear cell carcinoma) via curettage and confirmed metastatic disease via PET/CT scan. After presentation to the multidisciplinary team (MDT), patient was administered with first line systemic treatment and comprehensive genomic profiling (CGP) was performed on her tumor specimen. The CGP analysis showed that our patient had highly microsatellite-instable tumor with 28 mutations per megabase indicating the potential use of opted immunotherapy with checkpoint inhibitors (nivolumab, atezolizumab, pembrolizumab, avelumab, cemiplimab, durvalumab). Also, analysis reported several genomic alterations, activating such as PIK3CA mutation with everolimus, temsirolimus and alpelisib as opted targeted therapy. Furthermore, inactivating mutations were PTEN with temsirolimus and everolimus, and BRCA2 mutation with PARP inhibitors (niraparib, olaparib, rucaparib, talazoparib) as opted targeted therapy. All targeted therapies opted were approved in the EU for other tumor types. Our patient has received 6 cycles of the TC (carboplatin with paclitaxel) chemotherapy (last cycle in February 2021) with partial regression of the disease as best response, after which she developed profuse vaginal bleeding and had to go several times to the Emergency gynecology. Hence, the MDT recommended palliative symptomatic operative procedure. In March 2021, she underwent surgical procedure of hysterectomy, bilateral adnexectomy, extirpation of the right iliac lymph nodes and omental resection where her diagnosis was once again confirmed with pT1b stage tumor and 2 lymph nodes both without tumor tissue. Consequently, and because of the slow postoperative recovery, the MDT suggested intensive follow up. In May 2021, on her first follow up visit, she had disease progression in para-aortic lymph nodes. Considering the fact that at that time, National Committee for the CGP-driven treatment was in the establishment, MDT suggested to send documentation to the Committee and also to do the PET/

CT scan to assess the actual disease dissemination. Since the PET/CT scan has shown oligometastatic disease progression, our patient received radiotherapy to the para-aortic lymph nodes in the dose of 30 Gy in July 2021. While waiting for the Committee, we have continued with the follow up and in October 2021, one year after the initial diagnosis, diagnostic MSCT of the abdomen and pelvis has shown enlargement of the lymph nodes. Since then, our patient is receiving hormonal therapy with megestrol-acetate and currently she is stable and diagnostic workup has shown disease regression. Our patient is in excellent general health throughout the whole treatment and our main treatment strategy is to obtain maximal control of the disease with hormonal therapy, while waiting for response and continuing to explore different ways of providing her with the optimal, personalized therapy.

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S26 – POSITIONING OF INTRAOPERATIVE RADIOTHERAPY IN BREAST CANCER TREATMENT

ANTUNAC KATARINA [1]

[1] *University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Division of Oncology and Radiotherapy

Intraoperative radiotherapy (IORT) of breast cancer is not proven equivalent to external beam whole breast radiotherapy (WBRT). In the majority of cases IORT cannot replace WBRT in patients with breast cancer in whom adjuvant radiotherapy is indicated.

Intraoperative radiotherapy can be delivered using electrons or photons.

In ELIOT trial 1305 patients older than 48 years with early breast cancer size up to 25 mm undergoing breast conserving treatment were randomised to receive either one dose of 21 Gy delivered with 3- 10 MeV energy electrons through ELIOT system or external beam whole breast radiotherapy, prescribed dose being 50 Gy in 25 fractions followed by a boost of 10 Gy in five fractions. After a median follow up of 5.8 months, local relapse rate was 4.4% in patients who received IORT and 0.4% in patients receiving WBRT ($p < 0.0001$). No difference in overall survival has been observed.

In TARGIT A trial patients with early breast cancer age 45 years or more were randomised to receive either IORT with TARGIT system using 50 keV photons (Intrabeam), prescribed dose being 20 Gy or WBRT, prescribed dose 45-50 Gy in 25 fraction, with or without boost dose on tumor bed. After a median follow up of 2 years and 5 months, 5-year risk for local recurrence was 3.3% for TARGIT group versus 1.3% for WBRT group (p=0.042). No difference in local relapse rate has been observed between IORT and WBRT if patients received IORT concurrently with lumpectomy (prepathology sub-group). Overall survival rates did not differ between the groups.

According to some authors, evidence remains insufficient for use of IORT in women with early stage breast cancer outside of a clinical trial, due to several reasons. First of all, breast cancer local relapse rates nowadays are considerably lower than 30 years ago. At that time, women undergoing breast conserving surgery (BCS) only, had 10 year local recurrence rate of 25%, compared to 7% in case of adjuvant WBRT after BCS. In the control arm of TARGIT A trial, local recurrence rate was just 1.3%, due to progress in the overall treatment of early breast cancer. It is to expect that in patient not receiving adjuvant WBRT, local relapse rate nowadays would have been around 3%- as observed in patients undergoing IORT in TARGIT A trial. Therefore, IORT is not only inferior to WBRT, but is also probably equivalent to no irradiation at all in terms of reduction of the risk of local relapse.

Also, in the meantime, robust data corroborating omission of adjuvant radiotherapy in low risk breast cancer patients has become available.

NICE (The National Institute for Health and Care Excellence) guidelines clearly state that low-energy x-ray IORT (Intrabeam radiotherapy system) is not recommended for routine commissioning for adjuvant treatment of early invasive breast cancer during breast-conserving surgical removal of the tumour. NCCN does not recommend IORT as a modality to deliver partial breast irradiation, when indicated. According to ASTRO (American Society for Radiation Oncology) guidelines, electron beam IORT can be used in women with invasive cancer that otherwise can be considered "suitable" for partial breast irradiation. Nevertheless, low-energy x-ray IORT should be used just within the context of a prospective registry or clinical trial, similar to NICE guidelines.

However, clinical trial data support low-energy x-ray IORT (Intrabeam) to be used to deliver boost dose on the tumor bed, when indicated. That would be in premenopausal patients, or in patients with grade 3 tumors, Her2 positive tumors, triple negative tumors or tumors with positive resection margin.

All of the above, except margins, is usually known prior to breast conserving surgery and those patients can be offered IORT on tumor bed. IORT must always be followed by whole breast radiotherapy.

5 years after IORT as a tumor bed boost delivered with low kilovoltage x-rays, prescribed dose being 20 Gy and followed by whole-breast radiotherapy, low local recurrence and chronic toxicity rates were observed.

At University Hospital for Tumors IORT with Intrabeam system has been in use since October 2021 as a method to deliver boost dose on tumor bed in patients with right breast cancer that would otherwise be given external beam boost dose.

In conclusion, IORT with low-energy x-ray cannot replace whole breast radiotherapy but can be used to deliver boost dose on tumor bed. IORT with electrons can be used in subset of patients with low risk disease who are suitable for partial breast irradiation. It is to notice that those patients have such a low risk of tumor relapse that, most probably, do not need adjuvant radiotherapy at all.

Keywords: breast cancer radiotherapy, intraoperative radiotherapy (IORT), external beam radiotherapy (EBRT), whole breast radiotherapy (WBRT), boost dose on tumor bed

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S27 – PROSTATE CANCER - SURGERY OR RADIOTHERAPY?

SOLARIC MLADEN [1]

[1] *University Hospital Center Zagreb, Zagreb, Croatia*
Department of Oncology and Radiotherapy

Radiotherapy is a widely accepted therapeutic procedure for the local radical treatment of prostate cancer. Radiotherapy has been shown to provide excellent long-term disease control with a risk of local recurrence of less than 10% (Zumsteg ZS, 2015). Radiotherapy significantly reduces the risk of death from prostate cancer and improves overall survival. However, radiotherapy is only one of the therapeutic options for radical local treatment and is used in about 1/3 of patients (Scherzer ND, 2019). The second, dominant therapeutic option is radical prostatectomy. A comprehensive comparison of these treatment modalities is necessary for optimal access to patients with localized prostate cancer.

The ProtecT study is the only published high quality prospective, randomized, comparative study of radiotherapy, prostatectomy, and active monitoring (Hamdy FC, 2016). The study included 1,643 mostly low-risk patients who were randomized to active surveillance, radiotherapy, or prostatectomy. With a median follow-up of 10 years, no difference in overall survival was found between the groups. No difference was found between prostatectomy and radiotherapy in progression-free survival. There are a number of other studies comparing the effectiveness of radiotherapy and prostatectomy. They are mostly retrospective, of lower quality and reliability. Several meta-analyzes were performed that included most of these studies. A meta-analysis of 12 studies involving 17,137 patients showed a significant advantage of

prostatectomy in overall and disease-specific survival, but better biochemical control of the disease in irradiated patients (Chen L, 2017). A recent meta-analysis, which included 25 mostly retrospective studies, also shows the advantage of prostatectomy in overall and disease-specific survival, but better biochemical disease control and better survival without distant metastases in irradiated patients (Wang Z, 2020). Large cohort comparisons based on epidemiological registries confirm the advantage of prostatectomy in survival (Zhou X, 2020; Wang F, 2021). An additional subgroup analyzes defined groups of patients in whom prostatectomy and radiotherapy were equally effective in preventing death from prostate cancer. This applies to patients in the age group > 70 years, patients with low disease stages, and to those patients with a very high Gleason score (9 or 10) (Wang F, 2021; Knipper S, 2020). Some of the studies suggest an equal effect of radiotherapy and prostatectomy in low- and moderate-risk patients on disease-specific survival, but other studies still favor prostatectomy (Guo X-X, 2021; Chen L, 2017; Wallis CJD, 2016).

The results of retrospective studies may be partly the result of other, unrecognized factors. This mainly refers to the suboptimal dose of radiation, avoiding performing hormone therapy with radiation and the lack of curative salvage therapy due to local treatment failure (Dell'Oglio P, 2016; Aas K, 2021; Agarwal PK, 2008). Irradiated patients typically have more extensive comorbidities which has a direct impact on the difference in overall survival. However, no direct impact of comorbidity on disease-specific survival has been demonstrated (Rajan P, 2017).

Radiotherapy and prostatectomy have different side effects and different early and late complications. The ProtecT study showed a significant adverse effect of prostatectomy on erectile function and urinary control, while in irradiated patients, significant bowel problems were reported (Donovan JL, 2016). This difference is particularly pronounced during the first few years of treatment, and the differences are reduced by further monitoring (Hoffman KE, 2020). Although patients treated with prostatectomy are more often dissatisfied with the treatment performed, no significant difference was shown in the long-term quality of patients treated with one of these two modalities (Wallis JD, 2022; Donovan JL, 2016).

Based on published research, it is not possible to give an undoubted advantage to radiotherapy or prostatectomy. The choice of local treatment should be based on the patient's age, comorbidities, prognostic indicators and patient expectations. Then it represents the optimal choice of local treatment.

S28 – RADIOTHERAPY NETWORK IN CROATIA

BELAC LOVASIĆ INGRID [1], Pavlović-Ružić Ira [1], Zahirović Dag [1]

[1] *Clinical Hospital Center Rijeka, Rijeka, Croatia*
Department of Radiotherapy and Oncology

The predictions from Worl health organizations say that there will be an increase in incidence of malignant diseases worldwide. As a result of increased incidence, an increase in mortality is also expected. Cancer is, and will be, a top priority issue for health authorities.

Radiotherapy as very effective modality of cnacer treatment plays a major role in fight against cancer. In Croatia it is estimated that approximately 170.000 people is currently treated or have been treated for carcinoma. Estimations are that approximately 60% of people having a malignant disease will have the need for radiotherapeutic treatment during the course of disease. Radiotherapy is used as a mean of def-

finitive curative treatment and also very often as a palliative measure. The need for adequate radiotherapeutic approach in Croatia is currently unmet.

In Croatia, in public health system, there are five radiotherapeutic centers localized in major clinical centers. Locations are geographically idealy distributed thus covering the entire country population. There is no need for development and constitution of new radiotherapeutic centers.

Problem in Croatia is the number of linear accelerators and even more their age. Currently there are 15 linear accelerators in above mentioned institutions. This means that in Croatia there are approximately 2.5 linear accelerators per million inhabitanats while in Europe this number is 5.3 accelerators per million inhabitants. This numbers are showing the urgent need for action in improvement of radiotherapy service.

Apart from the needed strategic planning and strong financial investments in radiotherapeutic infrastructure, In Croatia, we have to think about long term sustainability of those systems. Sustainability means not only having hardware but above all investmment in young people in all radiotherapy segments in the sence of giving them opportunity for continous education and improvement.

There is an absolute need for developing radiotherapy network which should include all the existing centers. Networking is needed for distribution of data between centers bringing them to possible interoperability and gaining possibility of delivering different advanced radiotherapy techniques in different centers.

Networking of radiotherapy centers will enable also the objective outcome measurement in institutions, it should bring standadization of procedures between institutions and finally gain better outcome for our patients.

According to national strategic plan for fight against cancer, the above mentioned goals, which, if implemented, should by the year 2030. significantly improve availability and quality of radiotherapy treatment meaning better cancer treatmet outcomes for our country.

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S29 – METASTATIC SPINAL CORD COMPRESSION – RADIOTHERAPY

RENDIĆ-MIOČEVIĆ ZRINKA [1], Beketić-Orešković Lidija [2, 1]

[1] *University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department for Radiotherapy and Oncology
[2] *School of Medicine, University of Zagreb, Zagreb, Croatia*
Department of Clinical Oncology

Spinal cord is one of the most common sites of bone metastases, with most common sites of primary tumors in breast (29%) and lungs (17%), which is partly a reflection of general incidence of those tumors. Around 20% of patients with spinal metastases will experience MSCC (metastatic spinal cord compression) syndrome. Most often, the metastatic lesion is located within the thoracic spine, most commonly in the verterbral body which results in anterior epidural spinal compression. Ttreatment options for MSCC include: decompressive surgery with postoperative radiotherapy, radiotherapy only, corticosteroids as early as possible (on mere suspicion on MSCC or the latest at the time of MSCC diagnosis), specific oncological therapies according to the tumor type and symptomatic therapy, (analgetic therapy, mainly opiates).

Radiation therapy is for decades one of the most important and widely used treatment modality for patients with MSCC. In fact, MSCC is still considered one of the rare urgent indications for radiation therapy. Urgency, ie.the need to initiate radiotherapy as soon as possible (optimally within 24-48 h from the onset of neurological symptoms) depends on the presence and duration of neurological impairment as well as on severity of neurologic symptoms. If a patient is ambulatory with initial/mild neurological impairment (imminent or initial compression), general consideration is that radiotherapy should be delivered urgently, at the latest within 48 h from MSCC diagnosis. Paralysis that lasts longer than 48-72 h is in most patients considered irreversible, so in that patients urgency to initiate radiotherapy is not of such importance.

In the last 2 decades 3D conformal radiotherapy (3D-CRT) has become standard technique in radiotherapy of MSCC. In the last decade, many studies and clinical trials compared radiosurgery (SBRT using IMRT or VMAT techniques) to 3D-CRT in terms of analgetic effect and recovery of neurological deficit. While many of the results were in favour of SBRT, there is a consensus that SBRT should not be used in urgent patients with imminent paresis or paralysis, as the treatment planning process in SBRT usually takes few days, up to one week. Such period in patients with urgent indication for radiotherapy is not acceptable, as one week of delay in delivery of radiotherapy can be detrimental in terms of neurological recovery. So in urgent patients, 3D-CRT remains the gold standard for irradiation of MSCC.

There are several dosing regimens in MSCC radiotherapy. The choice of dosing regimen depends on patients general condition, performance status and life expectancy, as well as whether radiotherapy is applied for the first time or there is a need for re-irradiation of the same vertebral segment. In conventional 3D-CRT, the RT fractionation schedules are used, ranging from a single fraction of 8 Gy to fractionated courses (20 Gy in 5 fractions or 30–40 Gy in 10–20 fractions). In SBRT, relatively high radiation doses must be used to achieve optimal outcomes by overcoming tumor resistance. Typically, SBRT is delivered as 18–24 Gy in a single or in two fractions or as 27–40 Gy in 3–5 fractions. Allthough there are studies that found single fraction of 8 Gy non-inferior to fractionated schedules (20 Gy in 5 fractions; 30 Gy in 10 fractions), most authors suggest that single fraction radiotherapy should be applied in non-ambulatory patients or ambulatory patients with poor prognosis, while fractionated regimens are recommended in ambulatory patients with good prognosis or post-spinal surgery.

In patients with no response on radiotherapy or relapsed pain and/or neurological deficit after shorter symptom improvement, re-irradiation of previously irradiated vertebral segment(s) should be considered. The aims of re-irradiation are to achieve pain relief and prevent local complications due to tumor progression without radiation myelopathy. However, because of the low radiation tolerance dose of the spinal cord, re-irradiation of in-field recurrence is debated. Depending on the radiation dose previously delivered, ususlly re-irradiation is applied with 8 Gy in single fraction or 20 Gy in 5 daily fractions. Cumulative (initial radiotherapy + re-irradiation) total biological effective dose (BEDtotal) <120 Gy2 to the spinal cord is suggested as a safe dose limit to avoid radiation myelopathy.

Long-term outcome in patients with MSCC depends on degree of neurological symptoms and overall prognosis considering extension of primary tumor to other organs. Poorer prognosis is associated with non-ambulatory status of the patient, poor performance status, >3 involved vertebrae, presence of other metastases (visceral or bone), shorter time to motor deficit development and histological type of primary tumor (breast and prostate cancer and haematological malignancies have better prognosis compared to other histologic types of cancer). Median survival of patients with MSCC is around 6 months, although 1/3 of patients lives longer than one year after MSCC diagnosis.

Keywords: metastatic spinal cord compression, 3D-conformal radiotherapy, radiosurgery, dosing regimens, re-irradiation

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S30 – ONCOLOGICAL TREATMENT OF SARCOMAS

ZAHIROVIĆ DAG [1]

[1] *Clinical Hospital Center Rijeka, Croatia, Rijeka, Croatia*
Department of Radiotherapy and Oncology

Sarcomas are heterogeneous group of "solid" tumors arising from mesenchymal tissue. Because of wide variety of sarcoma originating tissues there can be recognized more then 50 different subtypes. Regarding the pathohystological diferentiation sarcomas can be divided in two large basic groups: Soft tissue sarcomas (STS) and Bone sarcomas (OS).

In the diagnostic approach for initial diagnosis tumor biopsy is adviced and should be performed along the future resection axis, with minimal dissection and very carefull attention, because of possibility of disease dissemination during procedure.

Pathological exam should be done by pathologist experienced with sarcomas. Morphologic assesment includes immunohistochemical analysis and cytogenetic analysis necessary for having a propper pathohistological diagnosis.

Tumors are classified by their TNM stage and histological grade according to AJCC (American Joint Comitee on Cancer)/FNCLCC (French Federation of Cancer Centers Sarcoma group).

Surgical approach is still the standard primary treatment with intention to obtain clear surgical margins. In some cases positive or close surgical margins may be acceptable if more radical surgery would provide inadequate anatomical and functional outcome. Radiotherapy and chemotherapy combined or solitary can be used in neoadjuvant setting with intention of downstaging of primary tumor prior to surgery.

Surgical resection shuold be extensive, performed „en bloc" together with biopsy site, but radical resection of entire anatomic compartment is usually not needed. Also, lymph nodes in resected area should be examined.

Postoperative radiotherapy must be considered in case of positive surgical margins (margin lower then 1cm from soft tissue, bone involvement, major blood vessels or nerve infiltrated).

In several clinical studies, the role of adjuvant chemotherapy has been evaluated. No clear evidence regarding improved overall survival has been seen in patients with R0 resection when doxorubicine and ifosfamide chemotherapy have been applied in adjuvant setting. On the other hand if R1 resection has been performed, adjuvant chemotherapy has shown benefit in recurrence free survival and overall survival.

In occurence of unresectable or diseminated metastatic disease systemic treatment is indicated. For such a treatment chemohterapy combinations of anthracyclines and ifosfamid or dacarbazine have been routinely used. Other combinations may include gemcitabine with docetaxel, vinorelbine, pegylated lyposomal doxorubicine and temozolomide.

Novel agents like trabectedine when used in treatment of advanced lyposarcoma and leiomyosarcoma in second line after anthracycline based therapy have shown some activity in progression free survival (PFS) time prolongation.

Targeted therapy (TKI, mTOR etc.) also may play a role in treatment of advanced soft tissue sarcomas.

Principles for treatment of bone sarcomas are simillar to those of soft tissue sarcomas. Surgical excision should be wide enough thus obtaining clear resection margins. Limb sparing surgery is preffered if

possible. Radiotherapy can be added as neoadjuvant or adjuvant to surgery. Option of preoperative chemotherapy can be feasible in some sarcoma subtypes.

Advanced disease is commonly treated with chemotherapy conatining antracyclines, ifosfamide, platinum based compounds. Metastatic disease, if localised, can and must be treated surgicaly or with radiotherapy or both.

Patients should be treated in clinical centers with experience of treating patients with sarcomas based on multidisciplinar team decisions. All diagnostic and therapeutic steps in specialized centers are coordinated and patients are given the needed multimodal approach and treatment. Still there is a lot of research still to be done to try to identify the most appropriate way of systemic treatment of sarcomas.

Keywords: sarcoma, chemotherapy, radiotherapy

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S31 – SYSTEMIC ONCOLOGIC TREATMENT OF THYROID CANCER

DABELIĆ NINA [1], Jukić Tomislav [1, 2], Fröbe Ana [1, 3]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Oncology and Nuclear Medicine
[2] *University of Zagreb, Zagreb, Croatia*
School of Medicine
[3] *University of Zagreb, Zagreb, Croatia*
School of Dental Medicine

Thyroid cancer (TC) is rare, accounts for approximately 1% of all malignant tumors, but still represents over 90% of endocrine malignancies. Various histotypes of TC have different pathohistologic features and biologic behavior and are treated differently.

Differentiated thyroid carcinoma (DTC) is a term that comprises papillary and follicular thyroid carcinomas. It represents around 95% of all TC patients. Hematologic metastases in DTC occur in 10%. In 30%-50% of distant metastatic patients, resistance to radioiodine develops. Definition of radioiodine refractory/resistant disease comprises the presence of at least one tumor focus that does not accumulate radioiodine or disease progression within one year upon radioiodine therapy. Biologic targeted therapies, in particular tyrosine-kinase inhibitors (TKI), have a role in the treatment of locally/locoregionally advanced unresectable or metastatic radioiodine-refractory DTC.

Systemic treatment of DTC is currently based on multiple kinase inhibitors (MKI); cytotoxic chemotherapy has almost been abandoned for the treatment of DTC metastases owing to toxicity and lack of efficacy. Two phase III trials in patients with progressive advanced radioiodine-refractory DTC treated with anti-angiogenic MKI, one trial with sorafenib and the other with lenvatinib, showed statistically significant improvement in median progression-free survival (PFS) over placebo. **Sorafenib**, with a response rate (RR) of 12%, showed improvement in PFS of 10.8 months versus 5.8 months with placebo (HR 0.59, P<0.0001). **Lenvatinib**, with RR of 65%, showed improvement in PFS of 18.3 months versus 3.6 months with placebo (HR 0.21, P<0.001). This led to their approval for the treatment of progressive advanced radioiodine-refractory DTC by the FDA and EMA.

When considering MKI therapies, one should keep in mind that they are associated with better PFS but are not curative. TKIs can cause side effects that can have a significant negative impact on patients' quality of life, even lethal outcomes. Patients with rapidly progressive (within one year per RECIST-criteria) and/or symptomatic disease are candidates for therapy, while asymptomatic patients with indolent disease should be closely monitored.

In the past few years, kinase inhibitors directed against an abnormally active oncoprotein have become available. Their use is restricted to tumors with either a point mutation such as *RAS* or *BRAF* or a fusion such as *RET*, *TRK*, or *ALK*. Therefore, screening for any of these abnormalities in thyroid cancer tissue is performed in patients with the extended disease. Whenever an abnormality is present, a specific inhibitor can be used as a first-line treatment. The use of specific inhibitors directed against a *RET*, *TRK*, or *ALK* gene fusion has produced extremely large tumor responses in a large proportion of treated patients. In patients with a *BRAF*V600E mutation, a BRAF-inhibitor (**dabrafenib**) alone or in association with a MEK-inhibitor (**trametinib**) induced a tumor response in up to 54% of patients when administered on a long-term basis. Moreover, the inhibition of the MAPK pathway with this combination on a short term

basis (4–6 weeks) might induce a **redifferentiation of refractory thyroid tumor cells**, and in case of reappearance of tumor radioiodine uptake, 131-I treatment is administered following rhTSH stimulation, and this modality might be an alternative to long-term treatment.

Experience with immunotherapy in the treatment of DTC distant metastases using anti-checkpoint inhibitor antibodies is still limited.

Larotrectinib and **entrectinib** are tumor-agnostic tropomyosin receptor kinase (TRK) inhibitors that are indicated for the treatment of advanced or metastatic solid tumor cancers with neurotrophic tyrosine receptor kinase (NTRK) gene fusions.

NTRK fusion can be present in either DTC (usually papillary TC) or in ATC. NTRK-inhibitors are achieving impressive tumor responses in this subgroup of patients.

Medullary thyroid carcinoma (MTC) is a rare malignancy that arises from thyroid parafollicular (C cells) and represents 2–4% of all thyroid malignancies. MTC may be sporadic or inherited, the latter as part of the MEN 2 syndromes.

Metastatic MTC can have an indolent clinical course, therefore, it is necessary to assess which patient to cure and when to initiate the treatment. Multidisciplinary tumor boards of various specialists involved in the diagnostics and therapy of the patients with MTC in highly specialized centers with a high volume of patients provide optimal patient management.

The multikinase inhibitors (MKI) **vandetanib** and **cabozantinib** are approved for the treatment of progressive or symptomatic metastatic/unresectable MTC. Although these treatments have been shown to improve PFS, with higher ORR compared to placebo, no MKI has been shown to increase the overall survival (OS) yet, except in the subgroup of patients with *RETM918T*-mutations on cabozantinib therapy.

As these drugs are nonselective, significant off-target toxicities may occur. Recently, next-generation small-molecule tyrosin-kinase inhibitors (TKIs) have been developed. These highly selective RET-inhibitors are specifically designed for highly potent and selective targeting of oncogenic RET alterations, making them promising drugs for the treatment of advanced MTC.

Two specific *RET*-kinase inhibitors, **selpercatinib** and **pralsetinib**, were FDA-approved for the treatment of *RET*-mutant MTC in 2020. While there have been no trials directly comparing the MKIs to these *RET*-kinase inhibitors, these agents seem to be better tolerated than MKIs, possibly due to the lack of VEGF inhibition.

Anaplastic thyroid carcinoma (ATC) is undoubtedly the TC histotype with the poorest prognosis. The conventional treatment includes surgery, radiotherapy, and conventional chemotherapy. Chemotherapy includes the use of doxorubicin or taxanes (paclitaxel or docetaxel), generally with platin compounds. However, frequently, these treatments are not sufficient and systemic treatment with kinase inhibitors is necessary. These include multitarget tyrosine kinase inhibitors (lenvatinib, sorafenib, sunitinib, vandetanib, etc.), single target tyrosine kinase inhibitors (dabrafenib plus trametinib vemurafenib against BRAF), everolimus against mTOR, vascular disruptors (e.g. fosbretabulin), and immunotherapy (e.g. spartalizumab and pembrolizumab). Therapy should be tailored to the patients and to the tumor genetic profile. A BRAF mutation analysis is mandatory, but a wider evaluation of tumor mutational status (e.g. by next-generation sequencing) is desirable. When a BRAFV600E mutation is detected, treatment with dabrafenib and trametinib should be preferred: this combination has been approved by the FDA. Alternatively, lenvatinib, regardless of mutational status, reported good results and was approved in Japan for treating unresectable tumors. Other single target mutation agents with fair results are everolimus when a mutation

involving the PI3K/mTOR pathway is detected, imatinib in case of PDGF-receptors overexpression, and spartalizumab in case of PD-L1 positive tumors.

Key words: differentiated thyroid cancer; medullary thyroid cancer; *RET*-proto-oncogene, molecular targeted therapy; anaplastic thyroid cancer; treatment

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S32 – SYSTEMIC TREATMENT OF CERVICAL CANCER

MARUŠIĆ JASNA [1]

[1] *Clinical Hospital Center Rijeka, Croatia, Rijeka, Croatia*
Department of Radiotherapy and Oncology

According to GLOBOCAN for 2020, cervical cancer is still in the high fourth place in terms of incidence (6.5% of all cancer cases) and mortality (7.7% of all cancer deaths) in women worldwide.

The highest share of new cases (70%) and deaths (85%) was recorded in low- or middle-income countries. The cause of cervical cancer in most cases is infection with high-risk types of human papillomavirus (HPV), and as primary prevention is recommended vaccination against HPV, and as a secondary screening program.

According to the latest available data from the Croatian Cancer Registry, in 2018, 274 new cases of cervical cancer were recorded in Croatia (rate 13/100 000). The mean age at diagnosis was 55.6 years.

Mortality data show that in 2018, 125 women died from cervical cancer (rate 5.9 / 100,000). In the last 10 years in Croatia, we have recorded a declining trend in the standardized incidence rate of cervical cancer, while mortality is stable.

Data from the latest international cancer survival study (CONCORD-3) show that Croatia, with a five-year survival rate of 63.2% for women diagnosed with cervical cancer between 2010 and 2014, ranks 20th out of 28 European countries.

Until very recently, surgery plus chemoradiotherapy and platinum-based chemotherapy (CT) with or without bevacizumab remained the standard first-line treatment for women with locally advanced or metastatic cervical cancer.

KEYNOTE -158 phase II study of pembrolizumab in 77 pt demonstrated an objective response rate of 14.3% and a median overall survival (OS) of 11 months. FDA granted pembrolizumab as a second-line agent and it was first immunotherapy drug approved for treatment of recurrent/metastatic cervical cancer whit positive expression of PD-L1 based

In October 2021, new FDA approvals expanded treatment options for women with advanced cervical cancer. According to results from the KEYNOTE-826 study addition of immunotherapy to standard first-line treatment extends survival by eight months for patients with recurrent, persistent or metastatic cervical cancer.

One of the most important studies presented at IGCS 2021 was the phase III EMPOWER-CERVICAL 1 trial of the PD-1 inhibitor cemiplimab 350 mg every 3 weeks vs investigator's choice of chemotherapy in patients with recurrent metastatic cervical cancer resistant to platinum-based chemotherapy and at least 1 prior line (N = 608). The median OS in this subset of patients was 11.1 months for cemiplimab vs 8.8 months for chemotherapy (HR: 0.73; range: 0.36-0.85; *P* <.00306). These results represent a clinical breakthrough.

Recent approvals have also expanded nonimmunotherapy options in the second line. In September 2021, tisotumab vedotin received the FDA's accelerated approval as a second-line treatment for patients with recurrent or metastatic cervical cancer and disease progression on or after CT regardless of a biomarker. Thus, tisotumab vedotin has become the second-line therapy of choice for patients with progression on pembrolizumab plus platinum-based CT in frontline treatment or if their tumor lacks an actionable biomarker. In the phase II innovaTV 204 study of tisotumab vedotin, the overall response rate (ORR) was 24%, median duration of response was approximately 8 months (95% CI: 4.2-not reached), and overall survival was 12 months., the phase III innovaTV 301 trial was initiated. The innovaTV 301 trial is comparing tisotumab vedotin vs chemotherapy as second-line or third-line treatment for relapsed or metastatic cervical cancer (N = 482).

There are several trials for which we hope to see positive data. Some trials are exploring the role of immunotherapy in patients with locally advanced disease; like the phase III CALLA trial of chemoradiotherapy with or without durvalumab and the phase III KEYNOTE-A18 trial of chemoradiotherapy with or without pembrolizumab.

For patients who are not good candidates for tisotumab vedotin as a second-line therapy, there are several trials. The 2-arm, noncomparative phase II study of balstilimab (anti–PD-1) plus zalifrelimab (anti–CTLA-4) exhibited a promising ORR (~15% to 20%) in patients with recurrent or metastatic cervical cancer who relapsed after previous platinum-based therapy

Another ongoing trial is the phase I/II trial of bintrafusp alfa, a bifunctional fusion protein that comprises TGF-βRII (TGF-β trap) fused to a human monoclonal antibody blocking PD-L1. In patients with heavily pretreated recurrent cervical cancer, bintrafusp alfa achieved an ORR of 28.2%. Finally, the phase II SKYSCRAPER-04 trial is evaluating the safety and efficacy of combining tiragolumab, a TIGIT inhibitor, and atezolizumab rather than atezolizumab alone as a second-line therapy in patients with metastatic and/or recurrent PD-L1–positive cervical cancer.

Cellular therapy shows great promise for the treatment of recurrent, metastatic, or persistent cervical cancer. Lifileucel - autologous tumor-infiltrating lymphocyte (LN-145), has been in development for a few years, and so far showed a ORR of 44%.

Immunotherapy has shown promising activity in cervical cancer.

Keywords: cervical cancer, immunotherapy, checkpoint inhibitors

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S33 – THE IMPORTANCE OF MULTIGENE TESTING IN THE SELECTION OF ADJUVANT BREAST CANCER TREATMENT

NALBANI MARIO [1], Curic Zvonimir [1]

[1] *General Hospital Dubrovnik, Dubrovnik, Croatia*
Department of Oncology

Hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER 2 -) breast cancer is the most common subtype of breast cancer. Although usually associated with a good prognosis, depending on clinical and histopathologic characteristics of the tumor, between 10 to 50 % of HR +, HER 2 - early breast cancer patients relapse despite locoregional treatments and adjuvant endocrine therapy. Chemotherapy, therefore, represents a possible opportunity to reduce the risk of relapse and cure patients. Unfortunately, an overview of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 2012 showed that only about 10% of patients benefit from chemotherapy. Also, chemotherapy has known short and long-term toxicities, and withholds patients from work, declining quality of life. Therefore it is imperative to correctly identify patients who would benefit from chemotherapy.

While all HR-positive tumors are driven by ER signaling, substantial heterogeneity within this subgroup exists. This is seen through the variability of histologic tumor grade, quantitative levels of ER, and PgR expression or expression of proliferative genes such as Ki-67. Although these classical clinicopathological parameters showed clear prognostic information according to EBCCG 2012 analysis none of them showed enough predictive value. Because of that prognostic tools such as predict or adjuvant online calculators, which combine multiple prognostic factors, were developed and are widely used to calculate the prognosis of patients and indirectly possible chemotherapy benefits. These calculators are only retrospectively validated.

Multigene testing emerged as a new prognostic but also predictive tool for decision-making regarding chemotherapy use in early breast cancer. Four multigene tests for early breast cancer are usually used in practice: Oncotype DX®, EndoPredict®, MammaPrint®, and Prosigna®.

First-generation tests Oncotype DX® and MammaPrint® measure levels of mRNA expression of genes deemed important for the aggressive behavior of cancer, and through complex validated algorithms calculate an individual score on a scale from 0 to 100, which correlates with a 10-year risk of relapse. Oncotype distinguishes itself with its predictive value for chemotherapy use. Both tests are prospectively validated through randomized trials.

Second generation test EndoPredict® and Prosigna® combine the expression of genes with clinicopathological characteristics and try to upgrade on first-generation tests. Unfortunately, they lack predictive value and are only retrospectively validated. Altogether the main purpose of these tests is to identify patients at such a low risk of relapse that the possibility that chemotherapy would lower the risk of relapse is negligible.

At our institution, general hospital Dubrovnik, Oncotype DX®, which uses recurrence score (RS), is the most commonly used test as it is the only test that showed predictive value for chemotherapy use. Through earlier research HR +, HER 2- patients who are node-negative with RS less than 11 were found to be at such a low risk of relapse that chemotherapy benefit would be unlikely. Patients with RS more than 31 were found likely to benefit from the use of chemotherapy. TAILORx is a randomized phase 3 trial of HR +, HER 2-, axillary node-negative breast cancer. In trial, 6711 patients, (69%) of initially tested patients who had midrang

RS of 11 to 25, were randomized to receive either chemoendocrine therapy or endocrine therapy alone. At 9 years, the two treatment groups had similar rates of invasive disease-free survival and overall survival. Some benefit from chemotherapy could not be excluded in women 50 years of age or younger with a recurrence score of 16 to 25, although it is not clear if this is the effect of chemotherapy itself or of ovarian suppression achieved by chemotherapy. Post hoc analysis incorporated histopathological criteria to RS, making RSclin score which further refines the benefit of chemotherapy in premenopausal women. RxSPONDER is a second phase 3 randomized trial targeting HR+, HER 2- breast cancer, but with one to three positive axillary lymph nodes. Patients with RS of 25 or lower were randomized to receive endocrine therapy only or chemoendocrine therapy. Among postmenopausal women, invasive disease-free survival did not differ between the treatment arms. Among premenopausal women, invasive disease-free survival at 5 years was 89.0% with endocrine-only therapy and 93.9% with chemoendocrine therapy. The relative chemotherapy benefit did not increase as the recurrence score increased.

In conclusion, Oncotype DX® has a negative predictive value, both in node-negative and up to three node-positive patients, showing that postmenopausal women with RS less than 25, regardless of axillary node staus, have no benefit from chemotherapy. In premenopausal women, the situation is more complex.

In node-positive premenopausal women, there is still no evidence to withhold chemotherapy, wherein node-negative patients individualized approach is needed.

We will present our experience with multigene testing at general hospital Dubrovnik during 2021. We tested six patients, all with Oncotype DX®. Among six patients, five were postmenopausal, out of which three node-positive, and one node-negative premenopausal women. In four out of six cases, our initial decision regarding chemotherapy use was changed based on RS score. We also tested how are we as clinicians concordant regarding indications for multigene testing, and regarding chemotherapy use based on classical clinicopathological parameters. Besides ours, we asked for the opinion six of our colleagues from different clinical centers and general hospitals. There is a low level of concordance. Complete agreement on indications for multigene testing was achieved in only one case, with high concordance (six out of seven) in two more cases. More surprisingly there was a higher level of concordance for chemotherapy use based on classical parameters. In two cases there was a complete agreement wherein in two more there was high concordance. If we would take a majority of opinions, Oncotype DX® would show different results in 5 out of six cases regarding the benefit of chemotherapy use.

To conclude, multigene testing is a new powerful weapon in decision making regarding chemotherapy use in the adjuvant setting with main problem being reimbursement issues which are preventing its wider implementation in every day practice.

Keywords: multigene testing, adjuvant chemotheraphy, OncotypeDX

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S34 – THE IMPORTANCE OF MULTIMODALITY TREATMENT FOR METASTATIC COLORECTAL CANCER: A CASE REPORT

JERKOVIĆ IVONA [1], Golčić Marin [1], Redžović Arnela [1], Belac-Lovasić Ingrid [1, 2]

[1] *Clinical Hospital Center Rijeka, Croatia, Rijeka, Croatia*
Department of Radiotherapy and Oncology
[2] *Faculty of Medicine Rijeka, Rijeka, Croatia*
Oncology and Radioteraphy

According to the GLOBOCAN study, colorectal cancer (CRC) is the second leading cause of cancer death globally. In patients with CRC who develop liver metastases, surgery, with or without perioperative chemotherapy, remains the cornerstone of the treatment. However, up to 90% of the patients will present with unresectable metastases in the liver, requiring systemic treatment. Nonetheless, a growing body of research suggests that combining chemotherapy with local therapies such as radiofrequency ablation or stereotactic ablative radiotherapy (SABR) has the potential to result in long-term survival, even in the inoperable metastatic setting.

We report a case of a 47-year-old woman who was diagnosed with a rectosigmoid adenocarcinoma in March 2014. After the initial staging, an anterior resection of the rectosigmoid colon was performed, resulting in a final diagnosis of a stage II adenocarcinoma (pT3N0M0) with lymphovascular invasion. Following the surgery, the patient completed six months of fluoropyrimidine-based adjuvant treatment. In February 2017, a regular follow-up assessment showed metastases in II and VIII liver segments. After a multidisciplinary team evaluation (MDT), a complete metastasectomy was performed, followed by five months of fluoropyrimidine-based adjuvant treatment. In November 2018, a local recurrence was revealed in the place of the surgical clip. Although the MDT recommended the surgery, the patient refused and was instead referred to SABR in December 2018, resulting in a good control of the disease. The procedure was repeated in March 2020 due to another local recurrence in the liver. However, four months after the repeated SABR, imaging confirmed newly developed multiple liver lesions, which were deemed inoperable by the MDT. As the tumor molecular analysis showed that the patient had a KRAS, NRAS, and BRAF wild type adenocarcinoma, XELOX combined with cetuximab was started as a first-line treatment for the metastatic disease. After six cycles of biochemotherapy, a good radiological response enabled a local therapy attempt with microwave ablation in March 2021 and was followed by capecitabine as maintenance therapy. Due to further disease progression in the liver and lungs, a decision was made to reintroduce XELOX and cetuximab. However, following 4 cycles of treatment, the disease progressed again, and FOLFOX and bevacizumab were started as a second-line treatment. The latest radiological evaluation took place in February 2022 and showed further disease progression. The patient is clinically well and is currently preparing to start a third line of treatment.

Although metastatic CRC patients have a poor prognosis, our case emphasizes that long-term survival is possible primarily when systemic treatment is combined with surgery and radiotherapy.

S35 – TOXICITIES ASSOCIATED WITH MELANOMA TREATMENT - A CASE REPORT

VRLJIČAK ANTONELA [1], Urch Kristina [1], Dabelić Nina [1], Marić Brozić Jasmina [1, 3], Fröbe Ana [1, 2]

[1] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Department of Oncology and Nuclear Medicine
[2] *University of Zagreb, Zagreb, Croatia*
School of Dental Medicine
[3] *University of Zagreb, Zagreb, Croatia*
School of Medicine

Introduction: The incidence of melanoma has been rising over the last 40 years. Although it represents less than 5% of all cutaneous malignancies, melanoma accounts for the majority of skin cancer deaths. The outcome of melanoma depends on the clinical stage at the time of diagnosis. The prognosis is very good for patients with thin melanomas who present with localized disease, with a 5-year survival rate of more than 90 %. For patients who present with thicker melanomas (more than 1 mm), the 5-year survival rate varies from 50 to 90 %, depending on tumor ulceration, tumor thickness, and mitotic rate. In patients with regional lymph node involvement, survival rates are 30-40%. Long-term survival has been less than 10%. Until very recently, many doctors in the melanoma field may have felt despair at having little to offer patients with the widespread metastatic disease. The introduction of targeted therapy and immunotherapy has drastically changed the management and the outcomes of patients with metastatic melanoma.

Case report: Herein we present a case report, of a 63-year old male who presented in March 2017 with two suspicious tumors on the back. One was located on the central thoracolumbar area, and the other was located on the right subscapular area. They were both surgically removed. Pathohistological exam (AJCC 7th edition) showed that thoracolumbar tumor was a melanoma, SSM, T1bNxMx, Cl III, Br II, its thickness was 0.86 mm, with 1 mitosis/mm^2, without ulceration. Pathohistological exam (AJCC 7th edition) showed that the subscapular tumor was also a melanoma, SSM, T1aNxMx, CL II, Br I, its thickness was 0.54 mm, without mitosis/mm^2 or ulceration. A month after the first surgery, re-excisions of the scars, bilateral axillary SLNB, and left axillary dissection were performed. The pathohistological exam showed nodal involvement in the left axillary region, and from July to August 2017 adjuvant radiotherapy was conducted on the left axillary region. Three months after completion of radiotherapy, axillary ultrasonography showed suspicious lymph nodes and a cytological examination confirmed melanoma lymph node metastasis. A redissection of the left axilla was done in December 2017. Pathohistological finding reaffirmed the diagnosis of a BRAF mutated metastatic melanoma. In March 2018, an MSCT scan revealed melanoma recurrence in the retrocrural lymph nodes. The patient was presented at the Multidisciplinary tumor board (MTB) for skin malignancies. Due to the location of the disease, local treatment was not feasible and the MTB proposed immunotherapy with pembrolizumab as first-line treatment for metastatic melanoma. Therapy commenced in April 2018 and after 15 cycles, disease progression occurred. The patient was presented at MTB and the combination of BRAF/MEK inhibitors vemurafenib and cobimetinib was initiated. The treatment started in March of 2019. However, as early as two weeks after the beginning of targeted therapy the patient developed side effects including rash (grade 3), diarrhea (grade 1), and ocular side-effects (retinopathy, grade 2). Therapy was briefly discontinued. The patient was examined by an ophthalmologist and ophthalmic treatment was started. All side-effects improved after ten days, only rash (grade 1) remained. Treatment with vemurafenib and cobimetinib was continued, at a reduced dose. However, retinopathy (grade 2)

reappeared even after dose reduction and therapy was permanently discontinued after 4 cycles. Given the radiologically confirmed excellent response to treatment with BRAF/MEK inhibitors, the MTB indicated a switch to a different available combination of BRAF/MEK inhibitors, dabrafenib and trametinib. The treatment started in May 2019 and briefly after the patient developed first-degree pyrexia. After complete resolvement of pyrexia symptoms, treatment was continued at the same dose. After treatment continuation, first-degree pyrexia reappeared. Treatment was again discontinued, and after complete resolvement treatment was continued with a reduced dose of dabrafenib and a standard dose of trametinib. Even so, pyrexia recurred in the third cycle, worsening to second-degree pyrexia with shivering. Treatment was again interrupted, and the dose of dabrafenib was once again reduced. This time trametinib dose was also reduced. Even after dose reduction of both drugs, second-degree pyrexia occurred again in the fourth cycle. We reduced the dose of dabrafenib for the third time. Fortunately, dose reductions did not affect treatment outcome and our patient continues to respond well to therapy to this day. He is also still regularly monitored by an ophthalmologist and so far no new ocular side-effects have developed.

Keywords: melanoma, targeted therapy, ophthalmopathy, pyrexia

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S36 – TREATMENT OF OLIGOMETASTATIC NON-SMALL CELL LUNG CANCER

CANJKO IVANA [1], Perić Luka [2, 1], Šambić Penc Mirela [2, 1], Flam Josipa [2, 1], Kovač Barić Maja [1], Krivdić Dupan Zdravka [3, 2], Kotromanović Darko [1]

[1] *University Hospital Center Osijek, Osijek, Croatia*
Department of Oncology
[2] *Faculty of Medicine, Osijek, Croatia*
University of J. J. Strossmayer Osijek
[3] *University Hospital Center Osijek, Osijek, Croatia*
Clinical Department of Diagnostic and Interventional Radiology

The oligometastatic disease is a stage between a localized and widespread metastatic disease that continues to be a controversial subject, both in terms of description and therapeutic options. It is characterized by a modest number of metastases with indolent biology, generally one to five.

Increasingly effective diagnostic technologies, including positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging of the brain (MRI of the brain), is leading to an increase in the number of newly diagnosed patients at this stage.

In lung cancer, the oligometastatic disease affects 20 to 50 percent of patients.

The brain, contralateral lung, lymph nodes, liver, and adrenal gland are the most common sites of metastasis.

Patients with oligometastatic disease have a better long-term prognosis than those with extensive metastatic disease, and they benefit from systemic therapy combined with local therapy (surgery/radiotherapy) at the metastasis site and, in certain situations, at the initial tumor site.

The classification of oligometastatic disease is based on the disease's initial appearance and the use of systemic treatment. The phrase synchronous or de novo refers to the appearance of a small number of metastases at the time of diagnosis, as opposed to the occurrence of new or metachronous metastases (oligo-recurrence) following final treatment of stable locoregional disease. Patients with disseminated disease at the time of diagnosis who partially respond to systemic treatment (disease stabilization) except for the development of a small number of metastases that progress (oligoprogression) or persist (oligoresistance) after systemic treatment are referred to as oligoprogression or oligoresistance.

Patients who receive targeted therapy frequently have oligoprogression and oligoresistance.

Surgical resection has generally been the primary therapeutic choice for oligometastatic patients, with about 55% of patients receiving surgery. However, in recent years, the use of less invasive ablative procedures, such as stereotactic radiosurgery (SRS) for brain metastases and stereotactic body radiation treatment (SBRT) for various extracranial locations, has expanded dramatically.

Which treatment option to choose (surgery or radiotherapy) depends on several factors: age, performance status, comorbidities, time of metastasis in relation to the primary tumor (metachronous metastases have a better prognosis), number of lesions (prognosis is better in patients with single metastases), localization of metastases (prognosis is better for metastases located in the brain, lungs and adrenal glands), size of primary tumor and involvement of mediastinal lymph nodes (better prognosis in stage N0 disease).

Numerous studies, including two randomized phase II trials, have shown that local treatment, such as radiotherapy or surgery for the primary tumor and metastasis, improves progression-free survival (PFS) and overall survival (OS) in patients with non-small cell (NSCLC) oligometastatic lung cancer at the time of diagnosis and in those who respond to initial systemic therapy.

Immunotherapy and targeted therapy, which are both more efficient and less toxic, have changed the therapeutic paradigm for patients with oligometastatic disease. Local therapy for progressive metastases is similarly linked to a longer PFS and OS in these patients, with the option of continuing the same treatment.

Major worldwide clinical recommendations urge a multimodal strategy in the treatment of individuals with oligometastatic disease while awaiting the outcomes of randomized phase III trials. According to current standards, systemic therapy should be used in conjunction with local treatment of metastases and, if necessary, the primary tumor. Treatment options (surgery vs. radiotherapy), with or without systemic treatment must be based on personalized prognostic considerations and considered as part of a multidisciplinary strategy.

The availability of molecular or microRNA profiles in the future will aid in the selection of patients who will benefit the most.

Keywords :oligometastatic disease,radiotherapy,surgery,systemic treatment, multimodal strategy.

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S37 – TREATMENT OF PENILE CANCER

REDŽOVIĆ ARNELA [1], Miletić Marija [2], Belac-Lovasić Ingrid [1]

[1] *Clinical Hospital Center Rijeka, Rijeka, Croatia*
Department of Radiotherapy and Oncology
[2] *Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Division of Radiotherapy and Oncology

Penile cancer (PC) is a rare disease. Most of penile cancer are squamous cell carcinoma. Multiple risk factors are involved, but most importantly, the high-risk human papillomavirus infection (especially HPV 16) is thought to be present in approximately 50% of cases. Several different subtypes of HPV-related and non-HPV-related penile cancers have been described, which also have different prognostic profiles. A 2019

meta-analysis estimated that 98.6% of PeIN 1–2 and 80.5% of PeIN 3 lesions were HPV positive. The genomic pathways relating to penile carcinogenesis and progression are not well understood and only the clinical aetiological risk factors and drivers, along with their mechanistic targets, have been identified. However, gene sequencing studies have increased our understanding about interaction of HPV E6 and E7 oncoproteins with cellular pathways induces cell immortalization. COX2 overexpression drives the overproduction of prostaglandins and thromboxanes, resulting in angiogenesis, proliferation and invasion via various molecular pathways common to HPV-related PC.

Various prognostic markers have been explored, but ingvinal lymph node (ILN) status remains the strongest predictor of clinical outcomes. Penile cancer is curable in all early stages with the appropriate treatment, but its prognosis depends crucially on the proper management of the regional lymph nodes. Most patients with high-risk advanced PC benefit from a multimodal treatment approaches. Patients with bulky, fixed, or bilateral inguinal lymphadenopathy typically will not benefit from up-front surgical treatment alone. Neoadjuvant systemic therapy for these patients is currently recommended as the preferred strategy by the NCCN and the EAU guidelines. The mainstay of systemic therapy for advanced PC is platinum-based chemotherapy, but response rates are poor (15–55%) and overall survival does not exceed 12 months. Unfortunately, there are currently no clinical or pathologic factors that can accurately predict a patient's benefit from neoadjuvant chemotherapy. The only strong predictor of better survival after therapy is achievement of a pathological complete response at the time of consolidative surgical treatment. The use of chemoradiotherapy in patients with PC have been reported with mixed results. For patients with T1 or T2 disease, concurrent chemoradiotherapy may be considered and similarly, for T3 or T4 disease or in patients with nodal involvement. Chemoradiotherapy can be an excellent choice for patients with high-risk features including metastases, extranodal extension, bilateral ILN involvement, and tumors in lymph nodes larger than 4 cm. Based on the limited data, chemoradiotherapy is a treatment option in select patients.

Penile cancer treatment may have a major adverse impact on urinary and sexual function but all these efforts have resulted in a remarkable improvement in patient quality of life.

Key words: human poapilloma virus, neoadjuvant chemoradiotherapy, penile cancer predicitive markers

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S38 – TREATMENT OF RARE PRIMARY MELANOMAS

SIMETIĆ LUKA [1], Blažičević Krešimir [1], Herceg Davorin [1]

[1] *University Hospital Center Zagreb, Zagreb, Croatia*
Department of Medical Oncology

Melanoma is a highly malignant melanocytic tumor, commonly located on skin. Different tissues or organs like eye (choroidal/ uveal melanoma) or mucosal parts of gastrointestinal, respiratory or genitourinary tract could be rare locations of primary melanomas.

Mucosal and uveal melanomas are biologically agressive than skin variants, resulting in low response rates to modern therapeutic options for advanced melanoma like immunotherapy or targeted therapies.

Majority of mucosal melanomas occur in head and neck region, predominanlty in older ager (median 70 years). Estimated 5 year survival rate is 25 % vs. 80% in skin variant. Only 13 % of mucosal melanomas harbour braf mutation vs. 52% in skin variant, limiting possibility to use braf and mek inhibitors as therapeutic option. Some melanomas arising from mucosal sites harbor activating mutations and amplification of the transmembrane receptor tyrosine kinase KIT. Treatment with *imatinib mesylate*, an multityrosine kinase inhibitor, results in significant clinical responses in that subset of patients.

The systemic treatment of advanced mucosal melanoma is challenhing. Future perspectives in mucosal melanoma treatment are directed towards combinations, like anti VEGF antibodies plus anti PD1 inhibitors. Study with *atezolizumab*, an anti PD -1 inhibitor and anti VEGF agent *bevacizumab*, or study with anti PD-1 inhibitor *toripalimab* with oral multi TK inhibitor *axitinib* showed promising results but further studies are needed.

Unmet medical need, still is the best term describing uveal melanoma treatment. The incidence of uveal melanoma is low, but diagnosis is often made with significant delay due to its location (often locally advanced disease). Specific 5- year survival rate is 70-80%, but more than 50% of patients will develop distant liver metastasis. Prognosis is poor, with median survival rate of 2-15 months! Braf mutation in uveal melanoma is anecdotal (less than 1%), resulting in anecdotal usage of targeted therapies. According to our experience and UHC Zagreb database search, we found only one patient with metastatic uveal melanoma with biopsy proven (liver and lung) heterogeneous braf mut/wild type tumor cell populations. He was treated with braf and mek inhibitor, dabrafenib and trametinib, almost 12 months. Low tumor mutational burden (TMB) in uveal melanoma represents one more limiting factor in systemic treatment, resulting in low overall response rates (ORR) to immunotherapy; according to GEM-1402 study (ipilimumab+ nivolumab) ORR was 13% (CR and PR).

Current guidelines for systemic treatment for distant metastatic disease recommends clinical trial if available and clinically appropriate. Unfortunately, in daily practice, chemotherapy protocols based on

dacarbazine (or temozolamide) or polychemotherapy protocols like CVD or taxanes with platinum based regimens represent the standard of care. Liver directed therapies are preferred option for „liver only“ disease: Percutaneous Hepatic Perfusion (PHP) with melphalan, Isolated Hepatic Perfusion (IHP) with melphalan, Chemoembolization, Radioactive microspheres with Yttrium 90 etc. with mPFS 5,2 months and mOS 14,3 months (ASCO 2019.)

On January 25, 2022, the Food and Drug Administration approved tebentafusp, a bispecific gp100 peptide-HLA-directed CD3 T cell engager, for HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. Tebenbentafusp achieved a highly significant and clinically meaningful improvement in overall survival of metastatic uveal melanoma. This was the first investigational therapy in a phase III trial to improve overall survival in uveal melanoma. The survival benefit was seen in all subgroups of RECIST (Response Evaluation Criteria in Solid Tumors) responses even in patients without an objective response- PD.

Systemic treatment of mucosal and uveal melanoma is challenging. New therapeutic options are needed, especially for metastatic uveal melanoma.

Keywords: mucosal melanoma, uveal melanoma, systemic treatment

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S39 – WHAT IS NEW IN FIRST-LINE OVARIAN CANCER TREATMENT?

BORASKA JELAVIĆ TIHANA [1, 2]

[1] *University Hospital of Split, Split, Croatia*
Department of Oncology
[2] *University of Split, Split, Croatia*
Department of Health Studies

First-line ovarian cancer treatment is chemotherapy applied either adjuvantly- after maximal cytoreductive surgery which has a goal of complete macroscopic removal of the tumor, or neoadjuvantly, before interval cytoreductive surgery. Patients with initially disseminated disease in whom surgery is not indicated, are also treated with the same first-line chemotherapy protocols.

For the last twenty years first-line treatment is combination of platinum compound with paclitaxel, usually applied intravenously every three weeks. Alternative protocol is so called dose-dense chemotherapy, with either weekly application of both components of the schedule, platinum compound and paclitaxel, or weekly paclitaxel application with three-weekly carboplatin infusion.

Intraperitoneal administration of cisplatin and paclitaxel with intravenous paclitaxel, despite overall survival advantage in comparison to intravenous schedule, has not been widely accepted due to increased toxicity and demanding logistics.

A major step forward in prolongation of progression-free survival (PFS) in these patients was made with an addition of antiangiogenic agent, bevacizumab, to the standard first-line chemotherapy. The benefit of bevacizumab- chemotherapy combination and bevacizumab consolidation was greatest in patients with suboptimally debulked stage III, and stage IV disease.

Based on excellent treatment results with PARP (poly-ADP ribose polymerase) inhibitors in recurrent ovarian cancer, a substantial number of clinical trials investigating the impact of these drugs in front-line treatment has been conducted, mainly in patients with stage III and IV disease.

Three years ago, the results of SOLO-1 trial positioned as recommended schedule, consolidation therapy with olaparib, in patients with BRCA1 and 2 mutations who achieved response to front-line platinum based chemotherapy. After median follow-up of five years, sustained remarkable benefit in PFS prolongation was confirmed. Consolidation therapy with olaparib in first-line setting is approved in Republic of Croatia.

PRIMA study investigated consolidation therapy with niraparib, another PARP inhibitor, in all- comers population, after response to first-line therapy, with greatest PFS benefit achieved in population of patients with HRD (homologous recombination deficiency), of whom 30% had mutation in BRCA genes.

VELIA study, which explored the usefulness of veliparib in front-line treatment of ovarian cancer patients, had slightly different design. Patients with stable disease could have been randomized also (and there were 28% of these patients), and veliparib was not applied only as a consolidation therapy (one arm), but also as a concomitant and consolidation therapy (the other arm) and compared with chemotherapy plus placebo arm. Veliparib containing arms achieved longer PFS in comparison to placebo arm, and it was shown for the first time that concurrent administration of PARP inhibitor with chemotherapy was safe.

Important question whether to combine two treatment strategies proved to prolong PFS has been raised in PAOLA 1 study. This study included patients with high grade serous or endometrial ovarian

cancer who received standard front-line chemotherapy with at least three cycles of bevacizumab and achieved objective response.

Patients were randomized in two treatment arms: consolidation with olaparib and bevacizumab vs placebo and bevacizumab in other arm. Patients who were treated with olaparib (2-years treatment) and bevacizumab had significantly longer PFS, and among them, especially patients with HRD. It is still not clear whether there is a true synergy between bevacizumab and olaparib (especially in BRCA mutation positive patients), since there was no treatment arm containing only olaparib.

ATHENA study, consisting of two parts, completed patient accrual: ATHENA mono which investigates consolidation therapy with rucaparib in patients responding to front-line chemotherapy, and ATHENA COMBO which explores a combination of rucaparib with nivolumab, an PD-1 inhibitor in the same setting. First results of ATHENA study are expected early in 2022.

All above mentioned studies, exploring consolidation strategies in first-line treatment, have included patients with high-grade serous (most of them included endometrioid type, also) ovarian, fallopian tube and primary peritoneal cancers. There is ongoing research of various consolidation treatments in rare ovarian tumor types, such as low-grade tumors (which show high hormonal receptor expression in majority of cases) or clear-cell tumors which tend to be chemoresistant (so pelvic irradiation has been explored).

In conclusion, first-line systemic treatment of majority of patients with high-grade ovarian cancer is based on chemotherapy consisting of platinum compound and paclitaxel, with bevacizumab used in high-risk patients. It is absolutely necessary to determine BRCA mutation status, and, if possible, HRD or LOH (loss of heterozygosity) status as soon after the diagnosis, since these patients have an outstanding benefit of PARP inhibitor consolidation therapy. In Republic of Croatia, olaparib is only approved PARP inhibitor as a consolidation therapy in first-line ovarian cancer treatment for patients with confirmed BRCA1 and 2 mutations.

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S40 – WHAT IS NEW IN THE TREATMENT OF OESOPHAGEAL AND GASTROESOPHAGEAL JUNCTION CANCERS?

BIŠOF VESNA [1]

[1] *University Hospital Center Zagreb, Zagreb, Croatia*

Oesophageal and gastroesophageal junction cancers are among sixth most common causes of cancer mortality in the world. Some progress has been made in the treatment of these tumours in recent years.

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is a standard of care for resectable, loco-regionally advanced oesophageal squamous cell carcinoma (SCC) and adenocarcinoma (AC) as well as for gastroesophageal junction adenocarcinoma (GEJ). However, the recurrence rate is still very high. The adjuvant treatment with nivolumab in case of residual pathological disease improved significantly disease-free survival (DFS) (median 22.4 vs. 11.0 months, HR 0.69) in a randomized, global phase 3 trial CheckMate 577. Besides, adenocarcinoma can be also treated with perioperative FLOT chemotherapy (CT). Preliminary results of phase 3 trial Neo-AEGIS found no difference in overall survival (OS) between nCRT and perioperative CT in adenocarcinomas, although pathological complete response (pCR) was more frequent in the nCRT group. But what is the most appropriate therapy for patients with a poor response to nCT? VESTIGE trial will answer to that question.

Although targeted therapy did not proved efficacy in combination with radiotherapy (SCOPE 1, RTOG 0436, SAKK 75/08, RTOG 1010) there is still an open question of potential efficacy of the addition of trastuzumab or trastuzumab and pertuzumab to perioperative CT in HER 2 positive adenocarcinoma. Randomized phase 3 trial INNOVATION is ongoing based on positive results of HER-FLOT (phase 2) and PETRARCA (phase 2/3) trials.

Several phase 3 trials with immunotherapy alone or in combination with CT in locally advanced inoperable or metastatic oesophageal and gastroesophageal cancer reported positive results leading thus to an improvement in the treatment outcomes of this group of patients (the first line: KEYNOTE 590, CheckMate 649, ATTRACTION-4, CheckMate 648, Keynote-811; the second line: ATTRACTION-3, KEYNOTE-181, RATIONALE 302; the third line: ATTRACTON-2).

In the KEYNOTE-590 patients were randomized to pembrolizumab versus placebo plus 5-fluorouracil and cisplatin (CF). Three-quarters of patients had SCC and the rest AC. Although pembrolizumab plus CT improved progression-free survival (PFS) and OS in all patients, SCC, SCC PD-L1 CPS ≥ 10, the OS benefit was most marked in SCC patients with PD-L1 CPS ≥ 10 (median OS 13.9 vs. 8.8 months, HR 0.57). In the CheckMate 648 trial nivolumab plus CT (CF) and nivolumab plus ipilimumab improved OS in SCC patients compared with CT alone both in patients with tumour cell PD-L1 expression ≥ 1% and overall population (nivolumab + CT: median OS 15.4 vs.9.1 months, HR 0.54; 13.2 vs. 10.7 months, HR 0.74, respectively; nivolumab + ipilimumab: median OS 13.7 vs. 9.1 months, HR 0.64; 12.7 vs. 10.7 months, HR 0.62, respectively). Furthermore, two trials proved the efficacy of the addition of nivolumab to CT (oxaliplatin with fluoropyrimidine) in HER2 negative AC in comparison to CT alone. CheckMate 649 was a global trial, while ATTRACTION-4 was an Asiatic trial. In CheckMate 649 OS was improved in overall population, in population with CPS ≥ 1 but the greatest benefit was found in patients with CPS ≥ 5 (median OS 14.4 vs. 11.1 months, HR 0.71). Although OS was not improved in ATTRACTION-4, progression-free survival (PFS) was significantly better for nivolumab plus CT arm in comparison to CT (10.5 vs. 8.3 months, HR 0.68). Maintenance durvalumab after first-line platinum-based CT in GEJ carcinoma did not prolong PFS

and OS (PLATFORM, phase 2 trial). In HER2 positive AC pembrolizumab with trastuzumab and CT provided 22.7% improvement in objective response rate (ORR) in comparison to trastuzumab and CT (KEYNOTE-811).

In the ATTRACTION-3 trial, at three-year follow-up nivolumab continued to show improved OS over CT in the second line treatment of SCC patients (24 months OS 20.2% vs. 13.5%). Pembrolizumab also prolonged OS compared to CT in SCC patients with CPS ≥ 10 (median OS 9.3 vs. 6.7 months, HR 0.69) with fewer grade 3-5 treatment-related adverse events (18.2% vs. 40.9%) (KEYNOTE-181). Tislelizumab improved OS over CT in both overall SCC population (median OS 8.6 vs. 6.3 months, HR 0.70 and SCC CPS ≥ 10 (median OS 10.3 vs. 6.8 months, HR 0.54).

At 2-year update OS was longer in the patients with AC treated with nivolumab versus placebo in the third line therapy (ATTRACTION-2).

In patients with HER2 positive tumours trastuzumab deruxtecan improved ORR both in the third line (DESTINY-Gastric 01, phase 2 trial, Asian population) and the second line treatment (DESTINY-Gastric 02, phase 2 trial, Western population).

However, the improvement in understanding both oesophageal cancer and gastroesophageal junction cancers at the molecular level has led to still mostly unmet need for the biomarker driven treatments. Heterogeneity between and within tumours makes the issue even more complex. But some progress has been made. Bemarituzumab improved median OS in HER2 negative, FGFR 2b+ adenocarcinoma by 5.7 months in combination with CT compared to CT alone while zolbetuximab with CT provided longer PFS and OS in patients with tumours expressing claudin 18.2 versus CT alone.

Therefore, the improvement in treatment of oesophageal and gastroesophageal junction cancer is slow but obvious and we look forward to the results of numerous ongoing studies

Keywords: oesophageal cancer, gastroesophageal cancer, immunotherapy, HER2

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S41 – WHAT IS NEW IN THE TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

TEČIĆ VUGER ANA [1], Šeparović Robert [1, 2]

[1] *University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
Division for Medical Oncology
[2] *Juraj Dobrila University of Pula, Pula, Croatia*
Division for Medical Oncology

Triple - negative breast cancer (TNBC) is nowadays still clearly an unmet need, when compared to results achieved in the field of luminal or HER2 positive breast cancer treatment. Today, we still see TNBC as 15% of early stage breast cancer patients being at high risk of developing fatal disease,and as around 20% of metastatic disease patients dieing in no more than 1.5 year from diagnosis. In the times when we consider using synonims such as "chronic disease" for some of the patients living long lifes, with other two types of breast cancer, there is an urge to find a better way and a better target to provide better outcomes for these patients as well. When it comes to the early TNBC treatment, benefits of neoadjuvant approach, ie preoperative systemic treatment, are well established. It is an *in vivo* experiment, giving straight information on the responsiveness of the disease, it serves as window of opportunity for a plethora of approaches and agents, and facilitates an optimal surgical approach. Evidence showing noninferiority of the neoadjuvant approach in comparison to adjuvant was reassuring and that one very needed information, for the neoadjuvant approach to become the well accepted standard. Nevertheless, nowadays we discuss some new data arriving, that might even suggest superior outcomes for the neoadjuvantly treated patients. From a medical oncology point of view, neoadjuvant approach gives the opportunity for a patient to be treated more aggressively, introducing some additional drugs and protocols, that are only evidence based and supported by results, when applied in the neoadjuvant/postneoadjuvant setting. When considering chemotherapy backbone, new data show that, beside the standard anthracycline - taxane sequence, we should also consider introducing carboplatinum as a regular part in the taxane sequence of the preoperative chemo protocol. Further, newest data on immunotherapy (IO) is possibly bringing us pembrolizumab joined to chemotherapy, as a new standard in the neoadjuvant treatment of a stage II/III TNBC, regardless of the biomarker status. There are still some important questions to be answered, when considering introduction of pembrolizumab in clinical practice in this setting, above all whether it really should be used also in the postneoadjuvant setting, and what about the patients with germline BRCA mutation, who received immunotherapy joined to chemotherapy preoperatively, and did not reach a pCR. With that we proceed to the postneoadjuvant setting, and the fact that a small but very specific proportion of these patients, ie those with germline BRCA mutation, are finally experiencing some greater progress towards personalized approach to their disease. Olaparib, when used postneoadjuvantly in TNBC patients that did not reach pCR, significantly reduced the risk for these patients and this undoubtedly puts it in the calculation, by not forgetting what a major driver germinal BRCA mutation is for these patients. Third option for postneoadjuvant escalation of treatment is the longest known so far, the capecitabine monotherapy. Either during six months, or as a metronomic therapy during one year postneoadjuvantly, capecitabine demonstrated benefit in the non – pCR TNBC population, that even reflected in the OS advantage. Yet, we can not forget that the results with capecitabine are derived from trials that did not consider addition of platinum, or immunotherapy preoperatively. Treatment of the metastatic TNBC in the last few years clearly pointed to the direction of the biomarker guided attempts. Among many mostly aborted

attempts of targeting different molecular pathways and spots, such as PIK3CA/AKT/mTOR, CCNE1/CDK, EGFR, CK, JAK/STAT3, c-KIT/PDGFRA, MET/EMT, FGFR1 etc., the BRCA mutation and the immunogenicity, or the immuno-status arised as the ones with the result. When treating metastatic TNBC, the IO must be combined with chemotherapy backbone. Today, we have results from atezolizumab, in combination with nab-paclitaxel, as a way of circumventing the neccessity of corticosteroids with the regular solvent paclitaxel. Clinically clearly relevant atezolizumab results are, however, compromised by the officially negative statistics of the trial, and therefore are today even excluded from some of the official recommendations, such as the American gudielines. Additional question emerged with the negative results of the paclitaxel – atezolizumab trial (ImPassion 131), that did not, even close, confirm the results of the trial with nab-paclitaxel as chemotherapeutic partner to IO (ImPassion 130). On contrary, pembrolizumab added to chemotherapy in the treatment of these patients undoubtedly demonstrated statistically significant and clinically relevant survival benefit, and that even regardless of the chemo partner, posing additional questions on the difference among the IO agents themselves. Finally, it should be noted that the IO only works in the "immuno – rich", ie PDL1 positive population of patients, and the newest data reveal a gradual increase in benefit of pembrolizumab, according to the CPS level. PARP inhibitors, such as olaparib and talazoparib made the difference in the disease control for the metastatic TNBC patients with the germline BRCA mutation, although without the OS benefit. However, these drugs were not faced to a platinum chemotherapy as a standard chemotherapy choice for these patients, and we know that harbouring the germline BRCA mutation is a signal for a superior platinum results to be expected, in comparison to the otherwise standard choice of taxane chemotherapy. Nowadays we are whitnessing a new era of the antibody- drug – conjugates (ADCs) for the treatment of breast cancer. A prototype and a very powerful agent is sacituzumab – govitecan, that demonstrated PFS and OS superiority in a heavily pretreated population of patients, and enlighted the future for these patients. Lastly, a small proportion of TNBC patients is actually HER2 low population, and a plethora of antiHER2 (low) agents is emerging, such as already antiHER2 proven agent trastuzumab – deruxtecan, as well as datopotamab – deruxtecan etc. In the end, when fighting such an ugly enemy, as heterogeneous TNBC, we should never give up on further molecular dissecting and finding a pattern to be targeted with a particular precision oncology approach, especially through including our patients in the clinical trials.

Keywords: triple negative breast cancer, neoadjuvant approach, chemotherapy, immunotherapy, PARPi, ADCs

S42 – YOUNG WOMAN WITH METASTATIC BREAST CANCER – PROBLEMS AND NEEDS: A CASE REPORT

BUHOVAC TEO [1], Marijanović Inga [1]

[1] *University Clinical Hospital Mostar, Mostar, Bosnia and Herzegovina*
Department of Oncology

Breast cancer is the most common malignancy in women. According to some data, only 4% of women with breast cancer is diagnosed before the age of 40 years. However, breast cancer incidence rates are slowly increasing among younger women. Metastatic breast cancer is a special entity that is considered as incurable disease. The goal of the treatment is to prolong survival and to maintain a good quality of life (QoL). 5-10% of newly diagnosed breast cancer patients have metastatic breast cancer and 20-30% of women with early breast cancer eventually develop metastatic disease. 5-year survival rate for women diagnosed with early breast cancer in Europe is 96% and for women diagnosed with metastatic breast cancer only 38%.

Young women with breast cancer, especially metastatic breast cancer, are a specific group of patients with unique problems and needs. According to some results, patients with metastatic breast cancer in age groups <30 years and between 30 and 39 years had inferior survival outcomes compared to patients aged 40-49 years and 50-59 years. Some data suggest a higher proportion of more aggressive phenotypes of breast cancer in younger women. Young women with more favorable luminal-type tumors have worse outcomes than older women with the same type of tumors. Also, hereditary breast cancer is more frequent in younger population. Every young woman with breast cancer should be offered genetic counseling.

Diagnosis and treatment of metastatic breast cancer in women <40 years affects multiple dimensions of life and has a negative impact on QoL. Focus of the treatment switches to prolonging survival, symptom control and improving QoL. Multidisciplinary approach that includes personalized psychosocial support is mandatory in this setting. Metastatic breast cancer diagnosis and treatment can result in physical and emotional distress. Young women are in particular risk of adverse mental health outcomes. The most clinically prevalent symptom is anxiety. Communication about diagnosis of metastatic breast cancer and treatment expectations is difficult challenge for both patients and physicians. Metastatic breast cancer diagnosis has an impact on the family of young woman. Younger patients reported higher concerns about mortality, uncertainty, financial and interpersonal concerns. Psychosocial challenges in patients with metastatic breast cancer are different than in patients with early breast cancer.

Our case is a 39-year-old woman with metastatic breast cancer. Married, mother of three children, with no comorbidities, family history positive for malignant disease – mother and aunt had breast cancer.

She was diagnosed with early breast cancer when she was 33-year-old and underwent a left radical mastectomy in August 2016. The histopathological examination revealed invasive ductal adenocarcinoma of the breast measuring 4.5cm in longest diameter. Estrogen receptors (ER) and progesterone receptors (PR) were negative and human epidermal growth factor receptor 2 (HER-2) status was positive. Ki-67 proliferation index was higher than 20%. Cancer cells were found in two out of ten resected axillary lymph nodes.

The patient was then referred to an oncologist. She was treated with adjuvant chemotherapy with AC-T regimen, adjuvant immunotherapy with trastuzumab and adjuvant locoregional radiotherapy. Adjuvant immunotherapy treatment with trastuzumab finished in April 2018 and after that patient was under close surveillance. The patient gave a birth to a third child in 2020

In August 2021, patient reported lower back and rib cage pain. CT scans of thorax, abdomen and pelvis revealed suspect bone metastases. Metastatic disease was confirmed by PET/CT scan. Biopsy of the lesion showed ER and PR negative, HER2 positive metastatic breast cancer. Patient was then treated with palliative radiation therapy, six cycles of chemotherapy with docetaxel, immunotherapy with pertuzumab and trastuzumab and bisphosphonates.

After confirmed diagnosis of metastatic breast cancer patient wanted to know as much as possible about her disease, treatment options and prognosis. She reported anxiety and was referred to psychologist. Psychological assessment showed high levels of anxiety and depression. Patient was worried about impact of her diagnosis of metastatic cancer on communication and future relationships with her children, husband and parents. She was particulary unsure about finding the right balance between telling the truth about her diagnosis and protecting her children. She feared that her disease would cause disruptions in her expected life roles and responsibilities. Patient also reported work-related challenges. After returning to work, she faced difficulties in incorporating her disease-related obligations in work timetable. Patients' distress and psychosocial needs were regularly assessed by oncologist, psychologist and social worker and adequate interventions were proposed. Problems of sexual functioning and body-image concerns were also discussed.

Diagnosis of metastatic disease, psychological stress and disease and treatment-related symptoms such as pain, nausea, vomiting, fatigue and sleep disruptions had a negative impact on her quality of life and psychological well-being. According to our patient, psychological interventions, pharmacotherapy, advised physical activity and nutritional counseling helped to minimise those negative effects.

Patient is currently under treatment with maintenance immunotherapy with pertuzumab and trastuzumab and bisphosphonates. She has no physical symptoms related to her disease. Her main concerns are about disease progression, mortality and interpersonal relations. She also reported that she is worried about availability of treatment modalities in case of disease progression (standard second-line therapy for HER2 positive metastatic breast cancer is not available in our country at the moment).

In conclusion, young women with metastatic breast cancer are special patient population with unique problems and needs. Multidisciplinary care and holistic approach are needed to address specific physical, psychosocial and sexual issues of these patients.

Keywords: breast neoplasms, neoplasm metastasis, young adult, quality of life, psycho-oncology

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S43 – IMMUNOTHERAPY IN GASTROINTESTINAL CANCER – UNFULFILLED AIM IN CROATIA

BELEV BORISLAV [1]

[1] *University Hospital Center Zagreb, Zagreb, Croatia*
Department of Oncology and Radiotherapy

Gastrointestinal (GI) cancers represent a variety of malignancies, each with a unique interplay between the tumor and local immune microenvironment. The successes that immunotherapy, particularly immune checkpoint inhibition, achieved in some other tumor types, has not yielded the same benefits to majority of GI-cancer-patients. Nevertheless, small subsets of cancers, such as DNA mismatch repair deficient (dMMR)/microsatellite instable (MSI) cancers, among others, seem to benefit from treatment with immune checkpoint inhibition. Routine testing for the rare molecular features that can predict response should be implemented in clinical routine for all GI tumors, and large scale clinical trials to identify predictive biomarkers are needed. It is now clear that some patients with GI-cancer are suitable for immunotherapy and as such, they change standard paradigms and guideline protocols known up to recent days. Various phase I-III trials focusing on immunotherapies for GI tumors have found only moderate to unsatisfactory objective response rates (ORR), ranging between 10 % and 25 %. The approval of several PD-1/PD-L1 and CTLA-4 inhibitors radically changed the treatment landscape in many cancer types and established immune-oncology as a new treatment strategy against cancer. Several immunotherapies for the treatment of GI tumors have recently emerged; however, checkpoint inhibition has not yet shown similar success in GI malignancies compared to other solid tumors. Some of the recent data might be practice changing - the updated KEYNOTE-590 data lend greater weight for the use of pembrolizumab plus che-

motherapy as first-line standard of care in advanced esophageal cancer (includede squamous cell carcinoma, adenocarcinoma and Siewert type 1 esophagogastric junction adenocarcinoma, regardless of PD-L1-status). Progression-free survival (PFS) and overal survival (OS) were superiro for CPS≥10 for combination treatment.(HR 0.59, 0,64, 0,73).A novel dual immunotherapy regimen significantly improved overall survival compared to a standard of care in patients with advanced, unresectable hepatocellular carcinoma (HCC) in the large phase 3 HIMALAYA trial. The novel regimen, dubbed STRIDE (Single T Regular Interval D), comprised a single priming dose of the investigational agent tremelimumab followed by regular doses of durvalumab. Patients on this regimen experienced a 22% lower risk of death than patients treated with sorafenib, which at the time the trial began was the only approved frontline standard of care for patients with advanced HCC. Adding the checkpoint inhibitor durvalumab to chemotherapy significantly improved overall survival in patients with advanced biliary tract cancer, as compared to chemotherapy alone, according to interim results from the TOPAZ-1 trial. According to results of TOPAZ-1, the risk of death for those taking durvalumab plus chemotherapy was 20% lower than for patients on chemotherapy alone. At 18 months, overall survival was 35.1% in the durvalumab group vs 25.6% for chemotherapy alone. By 2 years, overall survival was 24.9% vs 10.4%. TOPAZ-1 is the first phase 3 trial to show that adding immunotherapy to standard chemotherapy can increase survival in biliary tract cancer, and importantly, does so without inducing any new serious side effects.

In the near future, innovative techniques with thoughtful treatment combinations, adoptive cell therapy, CAR-T cells, as well as novel predictive biomarkers are needed to bring the benefits of immunotherapy to the majority of patients with GI malignancies.

Key words: GI-cancer, immunotherapy, check-point inhibitors, clinical trials