ORAL PRESENTATIONS

S1 – ROLE OF COMPREHENSIVE GENOME PROFILING (CGP) IN PROSTATE CANCER – A PRECISION ONCOLOGY VIEW

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Prostate cancer is among the most prevalent malignancies affecting men worldwide. In Croatia, prostate cancer is the most common malignancy in men and the fourth most common cause of cancer related death. Despite many advances in imaging and conventional biomarker analysis, the heterogeneity of prostate cancer continues to challenge effective patient management. This is primarily manifested in the limited response to each line of therapy in the long treatment trajectory of prostate cancer. In recent years, comprehensive genome profiling (CGP) has emerged as a transformative tool in oncology, enabling detailed characterization of genomic alterations and thereby paving the way for precision medicine. In the context of emerging therapies, CGP has the fundamental role in prostate cancer management as it enables personalized treatment strategies, improve prognostic assessments, and provide insights into mechanisms of inevitable therapeutic resistance.

The advent of next-generation sequencing (NGS) technologies has revolutionized our understanding of the genomic architecture of cancer. Comprehensive genome profiling—encompassing whole-exome sequencing, targeted gene panels, and RNA sequencing—allows for the simultaneous analysis of a broad range of genetic alterations, including point mutations, copy number variations, structural rearrangements, and fusion events.

A key area of interest is the androgen receptor (AR) signaling pathway, which plays a central role in prostate cancer biology. Alterations in the AR gene, including amplification, mutation, and the generation of splice variants, have been linked to the development of castration resistance. On the other hand, another unique genomic feature relates to defects in DNA repair mechanisms—particularly within homologous recombination repair (HRR) genes such as BRCA1, BRCA2, and ATM—which are present in approximately 15–25% of advanced cases. Specifically, advanced prostate cancer is enriched with genomic alteration compared to localized disease. HRR alterations not only confer a more aggressive phenotype but also offer actionable targets; for example, patients with HRR deficiencies may benefit from poly (ADP-ribose) polymerase (PARP) inhibitors. Additionally, CGP has shed light on aberrations in the PI3K/AKT/mTOR signaling axis and other pathways, further broadening the spectrum of potential therapeutic targets.

Integration of CGP into the clinical management of prostate cancer offers several key advantages. Foremost, it enhances patient stratification by providing a comprehensive molecular profile that can predict therapeutic response and overall prognosis. For instance, patients harboring AR pathway alterations may require alternative or combination therapeutic regimens to overcome resistance to androgen deprivation therapy (ADT), which remains the cornerstone of treatment for advanced disease. Conversely, the identification of HRR gene mutations through CGP can guide the use of PARP inhibitors, resulting in improved progression-free survival for selected patients. Moreover, emerging evidence suggests that CGP may have a role in predicting response to immunotherapy. Although prostate cancer has traditionally been considered a "cold" tumor with limited immunogenicity, the detection of high tumor mutational burden (TMB) or microsatellite instability (MSI) in a very limited subset of cases may identify patients who are likely to benefit from

immune checkpoint inhibitors. This represents a significant shift in therapeutic paradigms and underscores the importance of CGP in the evolving landscape of prostate cancer treatment.

Another crucial application of CGP is in disease monitoring. The heterogeneity of prostate cancer, especially in metastatic castration-resistant prostate cancer (mCRPC), relates to enhanced selection pressure therapies exhibited on prostate cancer clones. This means that prostate cancer evolves and gain resistance during the course of the treatment. Repeated genomic profiling, whether through tissue biopsies or less-invasive liquid biopsies (e.g., circulating tumor DNA [ctDNA] analysis), enables clinicians to track clonal evolution and identify emerging resistance mutations in real time. Such dynamic monitoring not only facilitates early intervention but also aids in the timely adjustment of therapeutic strategies to overcome resistance.

Despite the considerable promise of CGP, several challenges must be addressed before its widespread integration into routine clinical practice. One of the primary obstacles is cost-effectiveness. High-throughput sequencing platforms and the sophisticated bioinformatics infrastructure required to interpret complex genomic data remain resource-intensive. Additionally, variability in sequencing quality and the lack of standardized interpretation protocols can result in inconsistent data across different institutions.

Furthermore, translating genomic findings into actionable clinical insights requires multidisciplinary expertise and robust clinical decision support systems. There is a pressing need for standardized guidelines that bridge the gap between genomic discoveries and therapeutic interventions. In Croatia, the molecular tumor board is established, where discussion is being made for each individual patient, where potential targeted therapies are being considered based on CGP.

Additionally, the increasing use of liquid biopsy techniques is set to revolutionize the way clinicians monitor disease dynamics. By enabling serial assessments of tumor genomics in a non-invasive manner, liquid biopsies can capture real-time insights into tumor evolution and therapeutic resistance. This approach not only minimizes the risks associated with repeated tissue biopsies but also enhances the timeliness and accuracy of treatment modifications.

We have ample evidence from global PARP inhibitor trials (primers of personalized cancer medicine for prostate cancer) where CGP (both tissue and blood-based assays) failed in more than one third of recruited patients. This highlights the limitation of the broad clinical use of CGP in everyday clinical practice for prostate cancer patients.

Conclusion

Comprehensive genome profiling represents a paradigm shift in the management of prostate cancer. By elucidating the complex genomic landscape of the disease, CGP facilitates the identification of actionable molecular alterations and informs the development of personalized therapeutic strategies. Its application in detecting key alterations in the androgen receptor pathway, DNA repair deficiencies, and other critical signaling cascades have already demonstrated significant clinical impact, particularly in advanced and treatment-resistant prostate cancer. In Croatia, more than 300 patients with prostate cancer were tested so far using CGP tools (primarily Foundation One platform). Efforts are ongoing to analyze the impact of CGP on the care of patients with advanced prostate cancer in real life, with emphasis on the therapeutic interventions based on CGP results, in the context of therapy lines, toxicity and efficacy.

Keywords: prostate cancer, comprehensive genome profiling, precision oncology, DNA repair deficiency, PARP inhibitors, liquid biopsy

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S2 – HOW TO TREAT PATIENTS WITH MCRPC TREATED WITH TRIPLET THERAPY IN MHSPC?

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More than 300 000 men will be diagnosed with prostate cancer in 2025 and more than 35000 will die of it(1).

Androgen-deprivation therapy (ADT) remains the cornerstone of high risk localized, advanced or metastatic prostate cancer. Over the past 6 years, large clinical trials showed benefit of doublet and triplet therapies in the indication of metastatic hormone sensitive prostate cancer (mHSPC). The approved doublet therapies included ADT in combination with docetaxel, abiraterone acetate, apalutamide, enzalutamide, each displaying significant overall survival (OS) benefit. As the benefits of doublet therapies positioned these treatments in adequate patients' populations, interest in treatment intensification led to wide acceptance of triplet therapies in mHSPC (ADT+docetaxel (DOC) + abiraterone/apalutamide. The results of two practice-changing trials, ARASENS and PEACE-1 showed significant OS benefit in patients with mHSPC. PEACE-1 enrolled 1173 mCSPC patients with dual primary endpoints – radiologic progression-free survival (rPFS) and OS. After a median follow-up of 3.5 to 4.4 years, the addition of abiraterone to standard of care conferred an increase in rPFS from 2.22 to 4.46 years. Overall survival was similarly improved with reduction in the number of deaths from 268 to 228, with an improvement in median OS from 4.72 to 5.72 years, translating to a reduction in risk of death by 18% (adjusted HR for OS = 0.82, 95.1% CI = 0.69-0.98, P = .030)(2).

ARASENS was a phase III trial on 1306 men with mCSPC randomized into 1 of 2 treatment arms, doublet therapy with ADT and DOC (n = 655) or triplet therapy with ADT plus DOC plus darolutamide (n = 651). The primary endpoint of OS was met with 62.7% of patients at 4-year for the triplet therapy arm

of ADT versus 50.4% in the doublet therapy arm. The reduction in the risk of death by 32.5% with triplet therapy, compared with the doublet of ADT plus DOC (HR = 0.68, 95% CI = 0.57-0.80,P < .0001)(3).

The ARASENS and PEACE-1 triplet therapy protocols serve as proof of concept that upfront systemic treatment intensification in the castration-sensitive setting helps metastatic prostate cancer patients live longer by delaying the development of castration-resistance.

But the clinical question remains: what can we offer to a patient who received triplet therapy in the mHSPC setting?

There are only limited data to answer this clinical question, since the level of clinical evidence is low, and the clinical utility is far from ubiquitous.

The main treatment options for patients with metastatic castration-resistant prostate cancer (mCRPC) after triplet therapy include cabazitaxel (based on the results from the CARD trial), PARP inhibitors (BRCA mutation carriers; based on the results from the Profound trial), and Lu-labeled prostate-specific membrane antigen (PSMA) radioligand therapy (o results from the VISION trial)(4,5,6). The results of the RADIANT study which evaluated radium-223 after docetaxel and ARPI treatment are not yet available. In the PEACE-1 study, 134 patients in the triplet arm experienced disease progression. At least one life-extending treatment was received by 92% of patients with disease progression. For cases progressing to mCRPC, the most probable treatment options include cabazitaxel, enzalutamide, docetaxel rechallenge, and abiraterone. Other, less feasible options following triplet therapy for mHSPC could include a second ARPI, with limited expected activity, and docetaxel rechallenge (again, the response rate is lower than in docetaxel-naïve CRPC). The intensification to triplet therapies in mHSPC has to be guided taking into consideration the biology of the disease, the volume, patient characteristics and expected survival.

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S3 – TREATMENT OF METASTATIC RENAL CELL CARCINOMA AFTER PROGRESSION TO FIRST-LINE THERAPY

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The introduction of vascular endothelial growth factor receptor – thyrosine kinases (VEGFR-TKIs) and immune checkpoint inhibitors (ICIs) have drastically altered the treatment landscape for kidney cancer. The doublet combination immunotherapy (IO/IO) or IO/VEGF-TKI now set as the standard frontline treatment for metastatic renal cell carcinoma (mRCC). Although frontline ICI-based combinations have improved overall survival (OS) relative to sunitinib, approximately two-thirds of patients will experience disease progression and require subsequent therapy. Despite continuous improvments in survival, multiple retrospective cohorts still suggest that up to one third of patients will not receive subsequent therapy at all. Thus, the therapeutic approach of patients who experience IO-based failure is an important question in clinical practice. Optimal management depends heavily on which therapy is used in the first-line setting. The need for standardized second-line therapy remains unmet.

VEGFR-TKIs remain effective in mRCC as second-line therapy. They were initially studied and approved in patients whose disease had progressed following frontline VEGFR-TKIs sunitinib or pazopanib. Axitinib and tivozanib were approved after showing median progression free survival (mPFS) benefit relative to sorafenib. Lenvatinib with everolimus was approved after showing mPFS benefit relative to everolimus. Only the CaboPoint study eveluated patients treated with second-line cabozantinib following progression on combination IO/IO (cohort A) or IO/VEGFR-TKI (cohort B). A higher overall response rate (ORR) was observed in VEGFR-TKI naive patients, but mPFS and OS were similar between both groups. This supports cabozantinib as a second-line therapy, particularly in patients who have never received VEGFR-TKI in the frontline setting. All current guidelines recommend that when IO-based combinations fail, clinicians should consider using a different TKI, including cabozantinib, axitinib, tivozanib or lenvatinib+everolimus. In the absence of head-to-head trials, there are some network meta-analyses to aid clinicians with salvage treatment decisions. One of them which included nine studies with a total of 4622 patients, but at a time when there was no IO-based combinations in the frontline, showed that all second-line therapies demonstrated some benefits over placebo. Based on OS i PFS, the lenvatinib+everolimus combination yielded superior followed by cabozantinib and lenvatinib monotherapy, but they were limited by a worse adverse events profile. In one systematic review which describe the available evidence on the use of VEGFR-TKIs after prior IO-based therapy, the most commonly prescribed TKI in both the trial and real-world settings was cabozantinib.

In the targeted therapy era, the CheckMate-025 trial established nivolumab monotherapy as one of the standards of care in previously treated mRCC. Today, multiple studies have examined salvage ICIs following IO-based combinations failure. IO/IO combination has limited response following IO. Also, IO/VEGFR-TKI combinations studies failed to meet benefit post-IO combination therapy. The CONTACT-03 trial evaluated atezolizumab+cabozantinib vs cabozantinib after progression on IO-based combination therapy. Atezolizumab+cabozantinib did not improve the median OS compared to cabozantinib monotherapy, but increased the rate of adverse events. Similarly, a recent update of TiNivo-02 study which compared nivolumab+tivozanib vs tivozanib alone in the second or third-line setting revealed that the trail failed to meet its primary endpoint of improved PFS.

The progress in research of ccRCC pathogenesis in which von Hippel-Linadu (VHL) gene loss results in hypoxia-inducible factor 2 alpha (HIF-2a) upregulation and increased VEGF expression, leading to angiogenesis, tumor progression and metastases, helped to the development of HIF-2a inhibitors. Belzutifan, a novel HIF-2a inhibitor, has demonstrated activity in mRCC clinical trials as a front– and later-line therapy and in combination with TKIs. It has been largely well tolerated, although anemia represents a common on-target side effect. First, it was approved for adult patients with VHL disease. Additionally, it received approval for mRCC after progression to IO and VEGFR-TKI therapy. Supporting date came from the LITESPARK-005 study that revealed that belzutifan reduced the risk of disease progression or death by 25% vs everolimus in adult patients with mRCC after progression to IO-based and VEGFR-TKI therapy. A subgroup analysis showed that belzutifan may be more appropriate for VEGFR-TKI naive patients. Many ongoing trials are investigating belzutifan in combination regimens in the refractory, frontline and adjuvant settings.

Metastasis-directed treatment (MDT) is also progressively expanding in the mRCC treatment, finding application both in cases of oligometastatic disease, whether synchronous or metachronous, and in oligo-progression during systemic therapy. Nowdays, personalized tailored treatments are the key, intergrating multimodal approach like metastesectomy, sterotactic body radiation therapy (SBRT) and systemic therapy.

Optimal therapeutic sequencing remains a challenge in mRCC after first-line IO combinations as multiple frontline regimens are now available. So far, strategies based on second-line TKIs that demonstrated improved outcomes in the preceding era will remain the mainstay for patients with refractory mRCC. Future research should focus on identifying biomarkers for treatment selection, optimizing therapy timing, and refining patient stratification to enhance outcomes.

Keywords: metastatic renal cell carcinoma; thyrosine kinases; immune checkpoint inhibitors; therapy sequencing

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S4 – LIQUID BIOPSY IN PATIENTS WITH LUNG CANCER

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Due to genomic complexity and the increasing number of targeted drugs related to specific genetic alterations, precise molecular diagnostics are today the basis for making treatment decisions for patients with NSCLC.

Although tissue diagnostics remains the gold standard in diagnostics and predictive biomarkers analysis in patients with lung cancer, its disadvantages include: the inability to biopsy the tumor due to localization, insufficient amount of tumor in the small tissue samples and sometimes false-negative results due to tumor heterogeneity, especially in patients who developed disease relapse during or after targeted treatment.

Liquid biopsy as a minimally invasive diagnostic method allows the use of an alternative sample for the analysis of tumor somatic changes, is minimally invasive, can be repeated multiple times and more easily detects genetic changes that occur through clonal evolution and lead to tumor heterogeneity. The main disadvantage of liquid biopsy is false negative results that may be due to the small volume of the tumor, the location of metastatic sites and the sensitivity and specificity of the methodology used to detect genetic changes.

Liquid biopsy uses different methodologies to analyze the different components: circulating tumor DNA (ctDNA), circulating tumor cells (CTC), extracellular vesicles (EV), tumor metabolites, tumor-associated antigens (TAA) and non-coding RNA (ncRNA).

In the past, ctDNA analysis in advanced or metastatic NSCLC was reserved for the assessment of EGFR mutational status, either in treatment-naïve patients with insufficient tissue for tumor genotyping or after acquired resistance to first or second -generation EGFR TKIs for *EGFR* exon 20 *T790M* mutation detection. Nevertheless, there is now robust evidence to support the clinical use of plasma ctDNA by a broad-based platform, such as NGS, in genotyping for multiple other actionable oncogene drivers.

Since the first publication of the International Agency for the Study of Lung Cancer (IASLC) in 2018, which defined the role of liquid biopsy in lung cancers, there has been significant technological progress in this area with an increase in the specificity and sensitivity of ctDNA detection, and a shift from the analysis of individual genes to the analysis of a large number of targetable gene alterations.

This resulted with a change in the testing algorithm for clinical decision-making and new guidelines published in 2021.

According to the recommended diagnostic algorithm, if a tissue sample is unavailable for tumor genotyping, genotyping of ctDNA from plasma is recommended (*plasma first approach*), and in case of a negative result, a repeat biopsy is suggested to obtain an adequate tissue sample. When tumor tissue sample is adequate for genotyping, ctDNA can be used for additional analyses that were not performed on the tumor sample (sequencing approach), and when tumor tissue is scant/of uncertain adequacy for genotyping, the so-called complementary approach is recommended in which concurrent tumor tissue sample and ctDNA genotyping is performed.

In clinical practice, if we do not have a suitable tissue sample, ctDNA analysis can enable a detailed analysis of genetic changes for treatment decision of newly diagnosed patients with lung cancer, as well as revealing resistance mechanisms in disease progression. The detection of ctDNA in blood after surgical

resection in patients with early clinical stages of the disease can identify patients at higher risk for disease recurrence, while the use of ctDNA for screening patients in early stages is still not a sufficiently sensitive and specific method for routine use.

Keywords: liquid biopsy, lung cancer

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S5 – OPTIMIZATION OF IMMUNOTHERAPY IN PATIENTS WITH RESECTABLE NON-SMALL CELL LUNG CANCER

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In the past few years, the checkpoint inhibitor immunotherapy has significantly changed and improved treatment of patients with resectable non–small cell lung cancer (NSCLC). Today we have positive phase III studies in the neoadjuvant (CheckMate 816), adjuvant (Impower010, KEYNOTE-091), and perioperative settings (AEGEAN, KEYNOTE-671, CheckMate 77T, Neotorch and Rationale-315). These studies included patients with stage I-III NSCLC, who would be candidates for adjuvant chemotherapy, indicated by tumor size ≥ 4 cm or nodal involvement. The results of the cited studies are difficult to translate into treatment decisions as they do not give answers to many clinically relevant questions. Consequently, in everyday clinical practice we often have to rely on indirect study comparisons and exploratory analyses.

For example, adding either neoadjuvant or adjuvant immunotherapy to chemotherapy improves treatment results. So far, we do not have a study in which these two treatment approaches have been compared. Therefore, we have to rely on indirect evidence which suggests that perioperative (neoadjuvant +/– adjuvant) immunotherapy should be preferred over adjuvant only immunotherapy.

If we opt for neoadjuvant approach, with the absence of studies comparing perioperative immunotherapy versus neoadjuvant immunotherapy alone, questions remain regarding the necessity of the adjuvant component. In cross trial comparisons, the widely similar event free survival (EFS) results seen in CheckMate 816, compared to the perioperative studies, certainly raise the question of whether the adjuvant component is providing any incremental benefit. Therefore, it is important to identify the subpopulation of patients who will most likely benefit from the adjuvant component. We have to establish whether the factors such as ctDNA (circulating tumor DNA) levels, major pathological response (MPR), complete pathological response can play a role in stratifying patients for the additional adjuvant treatment. Existing circulating tumor DNA-based minimum residual disease assays are specific, but not sensitive enough to guide any de-escalation decisions today. To the best of our current knowledge, the adjuvant part of the periopera-

tive immunotherapy regimen improves disease free survival across patients strata – possibly also in pCR subgroup. Positive ctDNA is an important negative prognostic factor, so these patients urgently need intensification strategies. We still need to find out how to intensify the treatment and at what point.

In the setting of metastatic and unresectable locally advanced NSCLC, high PD-L1 expression has been correlated with improved clinical benefit of immunotherapy. In the adjuvant setting, the value of PDL1 expression is not clear: in Impower010 study, PD-L1 expression influenced the efficiency of immunotherapy, while in Keynote-091 study it did not. Meta-analysis found that neoadjuvant chemoimmunotherapy was superior to neoadjuvant chemotherapy given that it was associated with improved efficacy (EFS and OS). However, OS benefit was restricted to the subgroup with a PD-L1 level of 1% or greater based on the current maturity of OS data.

Meta-analysis also showed that the positive impact of neoadjuvant chemoimmunotherapy is most expressed in patients with stage III disease. There are currently no uniform and widely accepted criteria defining resectability, especially in patients with N2 positive disease. In exploratory analysis of CheckMate77T study, perioperative nivolumab showed similar clinical benefit versus placebo in all patients with stage III NSCLC, regardless of N2 status (including patients with multistation N2 disease). Given these data, the question is whether we should move the bounderies of resectability, that is whether we should apply neoadjuvant immunotherapy to downstage patients with borderline resectable or unresectable disease into surgical candidates. Having no evidence that this approach is more efficient than the standard nonsurgical approaches (PACIFIC study), we should not be using it outside of a clinical trial.

About 20% of patients with resectable NSCLC who receive neoadjuvant chemoimmunotherapy do not get operated, and we need to define optimal treatment for this population.

Considering numerous treatment options and many open questions, the optimal treatment strategy for patients with resectable NSCLC must be defined on a multidisciplinary team.

Keywords: resectable non-small cell lung cancer, immunotherapy, treatment strategy, treatment outcomes

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S6 – MANAGEMENT OF PATIENTS WITH BRAIN METASTASES – AN INDIVIDUALIZED APPROACH

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At the time of diagnosis, approximately 10% of lung cancer patients have brain metastases and approximately 40-50% of all patients with brain metastases have primary lung cancer. There is a higher incidence of brain metastases in lung cancer patients with EGFR mutations and ALK rearrangements. Although these patients have longer survival, they will develop brain metastases during the course of disease and approximately 5% of patients will have leptomeningeal metastases.

Current therapeutic approaches in patients with brain metastases are surgical resection, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), systemic therapy (targeted therapy, immunotherapy, chemotherapy, combination of systemic therapies), corticosteroids and best supportive care. Optimal treatment approach is determined by tumor size and location, histology, extent of systemic disease, symptoms and functional status. Surgery or radiosurgery improves survival in selected patients with solitary or small brain metastases compared to whole brain radiotherapy. Surgery is rarely performed without postoperative hypofractioned SRS to the surgical cavity or whole brain radiotherapy due to a higher risk of recurrence, but it is recommended initially in patients with impending herniation and mass effect.

Recent progress in the development of new generation drugs with superior intracranial efficacy changed the treatment paradigm of patients with brain metastases.

Intracranial response rates of the new generation TKI with the most intracranial efficacy are 70-80%. Targeted therapy is recommended initially in patients with EGFR mutations and ALK rearrangements. In patients with ROS1 translocation, MET exon 14 skipping mutation, RET fusion and KRAS G12C mutation, a multimodal approach is recommended. If the lesion is located where even the slightest growth will affect the patient's quality of life, radiotherapy is the best option, while in other cases radiotherapy can be delayed.

Immunotherapy is the *standard of care* treatment of lung cancer patients without oncogenic driver mutations and in patients with brain metastases, in combination with radiotherapy, improves patient's outcome with a favorable safety profile.

Prophylactic intracranial irradiation (PCI) is the *standard of care* treatment of limited-stage small cell lung cancer patients who achieved complete or partial response to initial treatment modalities and it improves overall survival and reduces risk of brain metastases in these patients. It is also recommended in extensive-stage small cell lung cancer patients who sustained response to initial chemotherapy and immunotherapy.

Regarding the lung cancer patients with leptomeningeal metastases, currently there are no optimal treatment approach with definitive efficacy in these patients. However, many targeted drugs demonstrated efficacy in these patients, for example lorlatinib and alectinib in patients with ALK rearrangements and selpercatinib in patients with RET-fusion. In patients with EGFR mutation and leptomeningeal disease, osimertinib demonstrated significant intracranial activity at a dose of 80 to 160 mg daily.

Treatment approach in patients with brain metastases significantly changed in the past few years resulting in improved survival and local control but, also, there is a focus on preserving the patient's quality of life and cognitive functions.

Keywords: lung cancer, brain metastases, targeted therapy, radiotherapy, immunotherapy

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S7 – ADVANCES IN TREATMENT OF SMALL– CELL LUNG CANCER

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Small-cell lung cancer (SCLC) is an extremely aggressive disease with limited treatment advances and poor prognosis. For limited– stage (LS) SCLC, surgery is rarely an option, and the mainstay of treatment is chemoradiotherapy. Recently, durvalumab consolidation demonstrated improved OS versus placebo in phase III ADRIATIC trial, and has become the new standard of care. Trials with checkpoint inhibitors given concurrently with chemoradiotherapy are ongoing. The use of modern radiotherapy techniques also led to improvements in treatment outcomes. Recent data suggest that there is the OS benefit with high– dose hyperfractionated thoracic radiotherapy (54 Gy/30 fractions, twice– daily) concurrent with chemotherapy over standard radiotherapy for LS– SCLC (45 Gy/30 fractions, twice daily). Additionally, the role of prophylactic cranial irradiation with hyppocampal avoidance is currently being investigated vs. MRI surveillance.

The approval of checkpoint inhibitors atezolizumab and durvalumab combined with platinum/etoposide transformed outcomes for a subset (15-20%) of patients with extensive– stage (ES) SCLC, but there remains a clear need for new treatment strategies across the disease continuum. Lurbinectedin, RNA II polymerase inhibitor, outperformed standard chemotherapy (CAV, topotecan) in platinum– resistant disease, and got accelerated FDA approval; it is currently tested in phase III confirmatory trials as monotherapy and in combination with other agents.

In attempts to overcome immunotherapy resistance, many biomarker-driven therapies are under development; DLL3, B7-H3, TROP-2 and SEZ6 proteins seem the most promising targets. Two biomarker–driven agents recently got FDA– approval for treatment of later– line treatment of SCLC. Bispecific T– cell engager (BiTE) tarlatamab targeting DLL3 was tested in phase II DeLLphi– 301 trial and demonstrated a 40% ORR in patients with pretreated advanced SCLC. Toxicities are significant, with cytokine release syndrome in half of the patients. A phase III study comparing tarlatamab with topotecan or lurbinectedin, is ongoing, as well as other BiTEs targeting DLL3. Sacituzumab– govitecan (TROP-2 antibody– drug conjugate) showed marked response rates, as well as overall survival in TROPiCS– 03 trial and got approval for second– line treatment.

One of the challenges impeding personalization of therapy for advanced SCLC has been the failure to identify genomic drivers amenable to conventional targeted therapy. SCLC does not possess any of the genomic oncogenic driver mutations; instead, it is typically associated with the loss of tumor suppressor genes (almost universal dual loss of *TP53* and *RB1*). This is further complicated by the heterogeneity of SCLC, as recent molecular profiling has revealed four distinct subtypes based on the expression of key transcription regulators: ASCL1 (SCLC-A), NeuroD1 (SCLC-N), YAP1 (SCLCY) and POU2F3 (SCLC-P). The SCLC-I subtype was further described, including SCLC without expression of these transcription factors, and associated with an inflamed gene signature and mesenchymal characteristics. Retrospective data suggested that the SCLC-I subtype might benefit most from immunotherapy, but it might be only prognostic and harbors an insufficient predictive value. This classification is therefore not ready to set specific treatment recommendations. These transcriptional subtypes are highly plastic and exhibit significant intratumoral heterogeneity, complicating the development of targeted therapies. Additionally, they can evolve across the course of treatment and may be a potential source of therapeutic resistance.

In treatment of SCLC addressing toxicities is essential, as patients with SCLC typically have a significant smoking history and impaired performance status. Research on biomarkers and transformed SCLC, as well as understanding chemoresistance are highly needed. To help this, fostering research and international collaboration is an important approach.

Keywords: small– cell lung cancer, immunotherapy, biomarkers, transcriptional subtypes.

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S8 – SHORTER DURATION OF BREAST CANCER RADIOTHERAPY?

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Understanding of breast cancer biology, improvements in screening procedures and RT (radiotherapy) techniques open an opportunity to personalize postoperative RT management, rather than the *one size fits all* paradigm of breast conserving surgery and adjuvant standard fractionation whole breast RT.

Modern clinical trials have attempted to identify subsets of patients in whom recurrence rates are so low that RT can be safely omitted. Women of advanced age typically develop more biologically favorable breast cancers and given decreased overall life expectancy with age, may be less likely to benefit from adjuvant RT in their lifetime. CALGB 9343 randomized a subset of patients over the age of 70 with estrogen receptor (ER)-positive tumors less than 2 cm in size to adjuvant RT plus endocrine therapy versus endocrine therapy alone. PRIME II did the same with women over the age of 65 with ER-positive tumors less than 3 cm in size. Findings from CALGB 9343 demonstrated a reduction in 10-year LR rate from 10% to 2% with the addition of RT (10% and 1%, respectively, in PRIME II); however, no difference in overall survival (OS) was detected in either study. Given the small incremental local control benefit and lack of survival difference, endocrine therapy alone following BCS is an appropriate consideration in select women over the age of 65 with clinically node negative, ER-positive tumors less than 3 cm. Additional trials are investigating the omission of adjuvant RT in younger women with more favorable biology (low Ki67 and/or low Oncotype DX recurrence score).

Another subset of women in whom omission of RT may be considered is in patients with DCIS. RT has been shown to consistently decrease in-breast recurrence by 50% in the setting of DCIS. Recent studies attempted to identify subsets of patients with DCIS who are sufficiently low risk to consider omission of RT. ECOG E5194 prospectively studied omission of RT. The 12-year LR rate was 14% without RT, suggesting omission of RT may be acceptable in this select subset. RTOG 9804 was a randomized trial evaluating BCS versus BCS + RT among women with low–intermediate grade DCIS spanning less than 2.5 cm with negative (⩾3 mm) margins. The 15-year results demonstrated an in-breast recurrence risk reduction from 15.1 to 7.1% with the addition of RT, although overall recurrence risk was low in both arms. RT has not been associated with a survival benefit for DCIS and is intended to limit LR risk.

Newer technique represents accelerated partial breast irradiation (APBI) which rationale is that microscopic cells are most likely to be in the surgical bed and thus restricts RT exposure to a narrow margin around the lumpectomy site. In addition to limiting dose to organs at risk, APBI also allows for abbreviated courses of RT, typically ranging between 1 and 10 fractions. To be a candidate for APBI, selected pathologic and anatomic criteria ideally should be met. There are a variety of techniques to deliver APBI including intraoperative RT (IORT), intracavitary or interstitial brachytherapy, or external beam RT. IORT is currently recommended only in the context of clinical trials given inferior outcomes published in randomized trials. Intracavitary and interstitial brachytherapy are well-established options for the delivery of APBI; however, external beam APBI, which is less operator dependent and more widely available, has been the greater focus in recent randomized phase III trials. The University of Florence, RAPID, and NSABP B39/RTOG 0413 trials all evaluated APBI versus WBI, however differed in RT technique and fractionation schema. In the NSABP B39/RTOG 0413, after 10 years, the authors were unable to claim non-inferiority between APBI and WBI. In Florence Trial, 10-year statistical equivalence was reported between

the two arms. Furthermore, APBI was associated with less acute and late toxicity, as well as improved cosmesis. The ASTRO consensus guideline defines eligibility criteria: age ⩾ 50, negative surgical margins ⩾ 2 mm, Tis, or T1 disease.

Modern efforts have attempted to improve the convenience of RT by increasing the dose per fraction while reducing the number of total fractions to maintain a biologically effective dose. Four randomized trials with 10 years of follow-up have established the equivalence of a 3-week hypofractionated course of WBI to the standard fractionation regimen of 5 weeks. The comparable cosmetic outcomes between the two fractionation regimens without compromise in oncologic outcomes led ASTRO to update clinical guidelines in 2018, and strongly recommend hypofractionation as the new standard for all patients receiving breast RT.

Investigators also questioned whether the number of fractions can be further reduced, yet maintain safety, cosmesis, and therapeutic quality. The concept of ultrahypofractionation was investigated in UK FAST trial studied cosmetic outcome as the primary endpoint in patients receiving ultrahypofractionation to 28.5 Gy or 30 Gy in five once weekly fractions; and concluded a total dose of 28.5 Gy had less breast edema and shrinkage after RT ($p < 0.05$). At 10-year follow-up, breast induration was the only notable difference for patients receiving 28 Gy (compared to 50 Gy in 25 fractions; $p < 0.05$). The FAST-Forward Trial studied 26 Gy or 27 Gy in five daily consecutive fractions with the primary endpoint being IBTR. Inclusion criteria were broad (pT1-3N0-1, age ⩾ 18, negative margins). Approximately one-third of patients were deemed 'high risk' (age < 50 and/or grade 3). At 5-year follow-up, local control, regional control, distant relapse, and OS were statistically equivalent across all three arms. Interestingly, women receiving 27 Gy in 5 fractions were found to have more breast distortion, shrinkage, induration, telangiectasias, and edema (compared to 40 Gy in 15 fractions; $p < 0.05$); however, 26 Gy in 5 fractions was more comparable to 40 Gy in 15 fractions in regard to toxicity with statistically significant, but numerically minimal differences in breast induration and edema. These results support ultrahypofractionation (26 Gy in 5 consecutive daily fractions) to be an appropriate regimen with excellent local control and acceptable cosmesis at 5-year post-RT.

To shorten RT course simultaneous integrated boost is under investigation. Initial data from the IMPORT HIGH trial suggest broadly similar cosmetic outcomes between the two boost techniques. Preliminary results of RTOG 1005 trial evaluating conventional WBI with sequential boost versus hypofractionated WBI with SIB, suggest non-inferiority between the two arms with respect to ipsilateral breast recurrence and toxicity.

The delivery of adjuvant RT evolved into a different option of variable dose, fractionation and treatment volumes. In the setting of WBI planning, several technologic leading to greater dose homogeneity and conformality (ie prone breast treatment, deep inspiratory breath hold, multifleaf collimators,…) Dose homogeneity techniques include field in field and electronic compensation.

In the post-mastectomy setting, standard fractionation remains the standard of care. The reluctance to adopt hypofractionation in this setting is primarily due to concerns over increased toxicity to organs at risk. Few randomized trials evaluating the efficacy and toxicity of hypofractionated postmastectomy RT are ongoing.

General movement in the field of radiation oncology to increase dose per fraction safely and effectively, shorten RT treatment time, and minimize toxicity have been applied in breast cancer during the current era. This has resulted in modernized treatment paradigms which have widely been accepted as standard of care.

Keywords: breast cancer, radiotherapy, short course

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S9 – LOCOREGIONALLY ADVANCED CERVICAL CANCER; IS THERE A GENERALLY ACCEPTED STANDARD OF TREATMENT?

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Cervical cancer is the fourth most common cancer in women and the leading cause of cancer-related death in underdeveloped countries(1).Human papillomavirus (HPV) infection is the primary cause of cervical cancer, responsible for 90-100% of cases. Locally advanced disease is diagnosed in 37% of cervical cancer patients(2).

For the past two decades, chemoradiotherapy has been the standard treatment for locally advanced cervical cancer, supported by five randomized clinical trials showing a 30–50% reduction in mortality compared to radiotherapy. A meta-analysis confirmed this benefit, reporting a 5-year overall survival rate of 66% with chemoradiotherapy versus 60% with radiotherapy, yielding an absolute survival benefit of 6%.(3).

Despite this, 35% of patients experience disease relapse after chemoradiotherapy, highlighting the need for new treatment strategies to improve outcomes. Key areas of investigation include modern radiation techniques, adjuvant chemotherapy, and two landmark studies INTERLACE and KEYNOTE A-18 published last year that are reshaping clinical practice. The INTERLACE study explored neoadjuvant chemotherapy, while the KEYNOTE A-18 study assessed chemoradiotherapy combined with pembrolizumab immunotherapy concurrently and as consolidation therapy.

Modern radiation techniques have been extensively studied through the EMBRACE program, whit the aims to enhance local disease control, minimize treatment side effects, and improve outcomes. The EMBRACE-I prospective multicenter study reported that chemoradiotherapy combined with MRI-guided adaptive brachytherapy (MRI-IGABT) achieved a 92% local disease control rate with acceptable late treatment-related side effects(4).

The OUTBACK study, the largest trial investigating adjuvant chemotherapy, found no survival benefit with adjuvant chemotherapy over chemoradiotherapy alone(5). However, it had several limitations:

one-third of patients had early-stage FIGO IB2–IIA disease with a favorable prognosis, most participants were from well-developed countries, 22% did not receive adjuvant chemotherapy, and the chosen chemotherapy regimen was debatable. Patients received taxol and carboplatin, despite evidence that carboplatin is less effective than cisplatin in chemotherapy-naive patients with metastatic cervical cancer.

INTERLACE study showed that neoadjuvant chemotherapy with weekly taxol and carboplatin significantly improved progression free interval and overall survival compared to chemoradiotherapy, with an absolute survival benefit of 8%(6). Subgroup analysis showed the greatest benefit in FIGO stage I–II patients. The KEYNOTE A-18 study demonstrated that adding pembrolizumab to chemoradiotherapy and adjuvant immunotherapy improved survival, with an 8% absolute overall survival benefit(7). The greatest benefit was in patients with FIGO stage III–IVA disease.

In conclusion, the INTERLACE and KEYNOTE A-18 studies have introduced new treatment approaches for locally advanced cervical cancer. The choice of treatment in locally advanced cervical cancer depends on available resources, and further studies are needed to determine the most effective approach.

Keywords: cervical cancer, locally advanced, radiotherapy, chemotherapy, chemoradiotherapy, immunotherapy

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S10 – ENDOMETRIAL CANCER: THE ROLE OF PRECISE DIAGNOSTICS AND THERAPY

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The incidence of endometrial cancer (EC) is rising due to increased obesity and aging of the population. In Croatia, it is the fourth most common cancer in women with 817 new cases in 2022. A significant improvement in diagnosing and treating ECs over the last decade has been the development of a molecular classification system. The Cancer Genome Atlas (TCGA) provides a comprehensive classification and four different molecular subclasses have been identified: POLE ultramutated (POLEmut), microsatellite-unstable or mismatch repair deficient (MSI-H or dMMR), copy-number high (p53 positive) and copy-number low (no specific molecular profile or NSMP). Each molecular subgroup has a different prognosis and the PORTEC 3 trial also reported their predictive value. Patients in the POLE-mutant subgroup have an excellent prognosis with only occasional relapse, regardless of receiving adjuvant treatment. Copy-number high patients have the worst prognosis and generally benefit from adjuvant chemotherapy. Patients in the MSI/dMMR subgroup or the NSMP subgroup with an estrogen receptor (ER) positive status have intermediate prognosis and little benefit from adjuvant chemotherapy. Patients with the ER negative NSMP subgroup have a poorer prognosis and also benefit from adjuvant chemotherapy. The new ESGO-ESTRO-ESP guidelines have included molecular classification as a factor in determining adjuvant therapy in the early stages of the disease.

The ongoing PORTEC4a, TAPER and the TransPORTEC RAINBO trials will determine the value of integrating molecular parameters in adjuvant treatment.

The combination of chemotherapy drugs paclitaxel and carboplatin has long been the standard of care for women with advanced or recurrent disease. The new standard of care for patients with dMMR/MSI-H tumors is combination of chemotherapy and checkpoint inhibitor (pembrolizumab, dostarlimab or durvalumab), and for patients with microsatellite-stable or mismatch repair proficient (MSS or pMMR) tumors, immunotherapy with/without PARP inhibitor may be considered in addition to chemotherapy. For patient with serous EC overexpressing human epidermal growth factor receptor 2 (HER2), addition of trastuzumab to front line chemotherapy and continuing it as maintenance therapy is an option. For some patients with metastatic or recurrent disease, endocrine therapy is a reasonable alternative to chemotherapy, especially for low-grade tumors that are positive for estrogen and progesterone receptors.

There is no standard second line therapy. New therapies have been investigated, and molecular profiling of the tumor is being used to try to find new predictive biomarkers for targeted therapy.

Current evidence supports the use of checkpoint inhibitors in patients with dMMR/MSI-H tumors after failure of first-line chemotherapy if they are ICI naïve. Pembrolizumab and dostarlimab are PD-1 inhibitors that have been approved for these patients. Single agent immunotherapy is less effective in tumors that are MMR proficient (pMMR) or microsatellite stable (MSS). In these patients, the combination of lenvatinib and pembrolizumab is an effective option.

In hormone receptor positive tumors, the combination of endocrine therapy and mTOR inhibitor has been shown to be effective, especially in chemotherapy-naive patients. Another new combination with hormone therapy that has made recent advances is the cyclin dependent kinase (CDK) 4/6 inhibitors. Tumors in the copy number low group have a high proportion of hormone receptor positivity.

Patients with a TP53 mutated tumor have the poorest outcomes. In this group, therapy with PARP inhibitors has been investigating. In patients with recurrent serous uterine cancer, an oral Wee1 inhibitor (adavosertib) has shown clinical activity and reduction in disease progression.

In patients with a TP53 wild type subgroup, the results of selinexor maintenance therapy are promising.

Antibody-drug conjugates (ADCs) are a novel class of anti-cancer therapeutic agents. Trastuzumab deruxtecan has been shown to be effective in overtreated patients with EC overexpressing HER2, and many other ADCs are currently being investigated.

With increasing knowledge of the molecular alterations of EC, their prognostic and predictive value, it is expected that treatment decisions will be based on molecular characteristics of the tumor.

Keywords: endometrial cancer, molecular subtype, targeted therapy, immunotherapy

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S11 – NEW ADVANCES IN THE THERAPY OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Head and neck squamous cell carcinoma (HNSCC) is a common and aggressive malignancy with a poor prognosis and low survival rates. It's associated with invasion of surrounded structures and high rates of regional lymph node metastases as a first step of metastatic process allowing further distant spread. Despite advances in surgical and non-surgical interventions (radiotherapy, systemic therapy, targeted therapy, immunotherapy) survival rate remains low due to high rates of locoregional recurrence and resistance to systemic therapy. This review explores recent advances in therapeutic strategies for HNSCC, focusing on novel therapy which could potentially improve poor outcomes and reduce toxicity in HNSCC subjects. In this review we have identified three studies with potential impact on current clinical practices. The PATHWAY study demonstrated prolonged progression-free survival (PFS) in patients with resected HNSCC at high-risk for recurrence receiving adjuvant pembrolizumab for 1.5 year compared to placebo. Long term follow-up of de-escalation study E3311 demonstrated that it is safe to reduce radiation dose to TD 50Gy in patients with resected intermediate risk HPV-associated oropharyngeal cancer with omission of irradiation in those with low-risk disease. In a phase III study, intensity-modulated proton therapy (IMPT) proved to be superior in terms of toxicity (lower rates of G-tube insertion and weight loss) compared to standard photon-beam radiotherapy without compromising survival. Despite advances in treatment and de-escalation strategies of HNSCC there is need for more efficient therapeutic options especially in terms of HPV-negative disease, definitive and metastatic setting.

S12 – OPTIMIZATION OF ADVANCED GASTRIC CANCER TREATMENT IN THE ERA OF BIOMARKERS

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Despite a decline in the incidence and mortality of gastric cancer in developed countries, it remains the fifth most common malignant solid tumor worldwide and the fifth leading cause of cancer-related deaths globally. Unfortunately, gastric cancer is often diagnosed at an advanced stage, with an average five-year overall survival (OS) rate of only 20-30%. Comprehensive molecular characterization of gastric adenocarcinoma has significantly improved our understanding of the disease, paving the way for the development of novel therapies and the identification of new biomarkers that offer the potential for enhanced therapeutic efficacy and reduced side effects. Although advancements in the treatment of advanced gastric cancer (AGC) have been relatively slow compared to other tumor types, recent years have witnessed clinically meaningful and statistically significant improvements. However, intra-tumoral and inter-tumoral heterogeneity, as well as resistance mechanisms, contribute to the complexity of treatment.

Several biomarkers have been recognized and validated in phase III trials, including human epidermal growth factor receptor 2 (HER2), programmed cell death ligand-1 (PD-L1), claudin 18.2 (CLDN18.2), and deficient mismatch repair or high microsatellite instability (dMMR/MSI-H). Additionally, fibroblast growth factor receptor (FGFR) has emerged as a promising new biomarker, while others, such as MET, EGFR, ALK, and PIK3CA, are under investigation.

Fifteen years ago, the addition of trastuzumab to standard chemotherapy (a platinum and fluoropyrimidine-based doublet) for patients with HER2-positive AGC (which accounts for 15–20% of cases) extended median OS to 13.8 months. More recently, the introduction of immune checkpoint inhibitors (ICIs), particularly inhibitors of programmed death-1 (PD-1), has further improved outcomes for AGC patients with PD-L1-positive tumors. In the KEYNOTE-811 clinical trial, the combination of chemotherapy, trastuzumab, and pembrolizumab in first-line treatment for HER2-positive, PD-L1 combined positive score (CPS) ≥ 1 patients improved median OS by 4.4 months (20.1 vs. 15.7 months). The phase III CheckMate-649 trial demonstrated that first-line chemotherapy combined with nivolumab significantly improved OS by 3.3 months (HR 0.70) and progression-free survival (PFS) by 2.2 months (HR 0.71) in HER2-negative, PD-L1 CPS ≥ 5 patients. OS also improved in the overall population (HR 0.78), as did PFS (HR 0.79), though to a lesser extent. Pembrolizumab, sintilimab, and tislelizumab have also demonstrated efficacy in combination with chemotherapy (KEYNOTE-590, KEYNOTE-859, ORIENT-16, RATIONALE-306). Additionally, high tumor mutational burden (TMB) and Epstein-Barr virus positivity have been identified as predictive biomarkers for ICI therapy in clinical trials.

For patients with CLDN18.2-positive (defined as ≥ 75% of tumor cells with moderate-to-strong membranous CLDN18 expression), HER2-negative tumors, zolbetuximab significantly improved OS by 2.16-2.69 months and PFS by 1.48-1.94 months, though without an improvement in overall response rate (ORR) (GLOW, SPOTLIGHT trials). ICIs are recommended for the treatment of dMMR/MSI-H AGC patients (KEYNOTE-059/061/062).

In the GASFOX-PRODIGE 51 phase III trial, adding docetaxel to FOLFOX significantly improved PFS, OS, and ORR in first-line treatment of triple-negative (HER2-, PD-L1-, and CLDN18.2-negative) AGC, though with reduced benefit in patients ≥ 65 years old, those with poorer ECOG performance status, and those with non-diffuse tumor type per Lauren classification.

In the phase II FIGHT trial, the addition of bemarituzumab, a monoclonal antibody that selectively binds FGFR2b, to standard chemotherapy in patients with immunohistochemistry (IHC) score 2+ or 3+ in ≥ 10% of tumor cells substantially improved OS (25.4 vs. 11.1 months, HR 0.41). Phase III trials are ongoing.

Antibody-drug conjugates represent an exciting new class of therapeutics for AGC. Trastuzumab deruxtecan (T-DXd) has already demonstrated efficacy as a second- or third-line treatment for HER2-positive tumors in the DESTINY-Gastric 01 and DESTINY-Gastric 02 trials. In the phase 1b/2 DESTINY-Gastric 03 trial, a combination of T-DXd, chemotherapy, and pembrolizumab showed promising efficacy but was associated with a high incidence of grade ≥ 3 adverse events. The phase III DESTINY-Gastric 04 trial is ongoing. Another promising antibody-drug conjugate, disitamab vedotin, is in early-stage clinical trials and has shown potential efficacy even in low-HER2 and low-PD-L1 expression tumors.

Several other novel therapeutic strategies are under investigation, including bispecific antibodies—among which zanidatamab appears particularly promising—adoptive immune cell therapies, and tumor vaccines. Emerging technologies, such as artificial intelligence-driven biomarker analysis and multi-omics profiling, are expected to further refine patient stratification and enhance treatment personalization. Bio-

marker-driven approaches are revolutionizing AGC treatment, enabling more effective and personalized therapeutic strategies. Continued research, clinical trials, and biomarker validation will be essential for optimizing outcomes for AGC patients in the era of precision medicine.

Keywords: advanced gastric cancer, biomarkers, therapy

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S13 – YOUNG-ONSET COLORECTAL CANCER

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Young-onset colorectal cancer (YO-CRC) refers to colorectal cancer occurring in individuals under the age of 50. The incidence has been increasing globally, predominantly in the distal part of the colon, and it is expected to account for 11% of colon cancers and 23% of rectal cancers by 2030. This trend is observed in different parts of the world and both sexes. In 20% of YO-CRC cases, hereditary cancer syndrome is found as the underlying cause; however, in most cases, no genetic predisposition is present.

Due to the lack of screening, YO-CRC is often diagnosed at an advanced stage. Symptoms include abdominal pain, rectal bleeding, and changes in bowel habits. Treatment involves a combination of surgery, systemic therapy, and radiotherapy. The approach is personalized based on the patient's medical fitness, disease stage, and tumor characteristics. Long-term treatment-related complications should be considered in these younger patients, making the more traditional sequential approaches of drug therapy not always the most appropriate option.

Lifestyle factors such as antibiotic use, low physical activity, and obesity, which affect the gut microbiome, are believed to play a significant role in YO-CRC development. Furthermore, the interplay between gut dysbiosis and gut immunity might also have a key role in CRC pathogenesis and YO-CRC development. However, which changes in the intestinal microbiota contribute to the development of CRC and YO-CRC and which prevent or protect against their development are currently unknown. Given the preventive and therapeutic potential of interventions targeting the gut microbiota, further research on antibiotic use and its effect on the gut microbiota is needed.

Assessing whether CRC risk is reduced after eliminating risk factors, such as smoking, consumption of alcohol, highly saturated fats, high-sugar beverages, red meat, and low physical activity, is of interest but is also challenging to address. Interventional prospective studies might provide some insights, but confounders owing to differences between individuals at risk of CRC should be considered. The additional effect of environmental factors on CRC risk in patients with a hereditary syndrome is also not fully elucidated. For this group of patients, several extensive prospective cohort studies are underway, and the datasets from these studies could be integrated to increase patient numbers and the validity of findings. A better understanding of the pathogenetic mechanisms underlying YO-CRC will enable tailored screening and targeted interventions. It might also provide new insights leading to the development of new therapies, which could eventually result in improved clinical outcomes for this group of young patients.

Emerging data indicate that YO-CRC may have distinct genomic and epigenetic characteristics compared to older-onset CRC. Genomic studies have revealed differences in the mutation profiles of tumors from younger patients. For instance, younger patients with CRC are more likely to have gene alterations such as TP53 and CTNNB1, while older patients more commonly exhibit mutations in APC, KRAS, and BRAF. These differences suggest that the molecular mechanisms driving tumor development may vary between age groups. Epigenetically, YO-CRC may also differ from older-onset CRC. Research has shown that early-onset tumors are less likely to develop along the CpG Island Methylator Phenotype (CIMP) pathway, associated with specific DNA methylation patterns. Additionally, YO-CRC may have distinct histological features, such as higher tumor grade and mucinous or signet ring histology. These genomic and epigenetic differences highlight the need for tailored treatment approaches and further research to understand the unique biology of YO-CRC.

Of note, data on environmental factors and YO-CRC risk are mainly derived from cross-sectional cohort studies, which can only detect associations but not infer causality. To better understand the underlying mechanisms and define the relationships between environmental factors, changes in the gut microbiota and YO-CRC development, and life-long risk, long-term prospective studies collecting detailed lifestyle, antibiotic use, and dietary data from childhood are needed. Although it will take some time before the outcomes of these long-term prospective studies become available, progress toward implementing these studies should not be impeded. This strategy will probably also elucidate other relationships between risk factors, the gut microbiota, and any other disease occurrence.

Treatment approaches for YO-CRC must address the unique challenges faced by younger patients. These patients often experience significant life disruptions, maintaining multiple work, family, and social roles while undergoing treatment. They may require more intensive psychosocial support to cope with the emotional and psychological impact of their diagnosis and treatment. Personalized care is crucial, as their tumors may have distinct genomic and epigenetic characteristics that require tailored treatment strategies. This involves upfront germline genetic testing and next-generation sequencing (NGS) genomic profiling to identify targeted therapeutic options.

Early detection through screening and awareness campaigns can improve outcomes by identifying the disease at an earlier, more treatable stage. Research is also critical to understanding the underlying biological mechanisms, risk factors, and potential preventive measures. Collaborative scientific discovery and innovation efforts are needed to develop novel therapies and improve the overall management of this growing patient population.

S14 – THE ROLE OD RADIATION ONCOLOGY IN THE TREATMENT OF GASTROINTESTINAL CANCERS

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Radiotherapy is one of the most important treatment modalities in gastrointestinal cancer. Recent advances in imaging, radiotherapy planing and delivery tehniques have made it possible to more precisely targeting tumors while sparing normal tissues. Today, we are using intensity-modulated radiotherapy for many GI tumors (esophagus, pancreas, liver, anus). Stereotactic body radiotherapy is an emerging treatment option for patients with primary and metastatic liver lesions as well as locally advanced pancreatic cancer.

Radiotherapy has an important part in the comprehensive treatment of esophageal carcinoma. For operable esophageal squamous carcinoma, surgery after neoadjuvant chemoradiotherapy is the standard treatment. For inoperable esophageal squamous carcinoma, radical chemoradiotherapy is the only treatment option, and postoperative adjuvant radiotherapy can improve local control and survival rates in selected cases. Standard total dose is 50.4 Gy in 28 fractions, and according to ARTDECO study and CONCORDE (PRODIGE-26) study radiation dose escalation up to 61.6 – 66Gy did not result in a significant increase in local control and locoregional progression free survival over 50.4 Gy. Radioherapy alone should generally be reserved for palliation or for patients who are medically unable to receive chemotherapy**.** An emerging RT technique that may offer further sparing of normal tissues is proton beam therapy (PBT). The proton plans decreased dose to various volumes of the heart and lungs in comparison to the IMRT and 3D-CRT plans. But, data regarding PBT are early and evolving and recommendation is that PBT in esophageal cancer can be used within a clinical trial.

The role of radiotherapy in the treatment of gastric cancer is still controversial, especially in the neoadjuvant setting, and it is unclear whether preoperative chemoradiotherapy is superior to preoperative chemotherapy alone in terms of survival. Current standard of care for locally advanced gastric cancer remains perioperative chemotherapy, although phase II single-arm studies have shown promising results for chemoradiotherapy.

For many years, preoperative RT has widely been accepted as standard of care for locally advanced rectal cancer, with either standard fractionated chemoradiation (50-50.4 Gy in 25-28 fractions) or short-course Rt (25 Gy in 5 fractions). RT can reduce local recurrence, but we have incosistent survival effect of RT. In the context of organ preservation, RT is the treatment cornerstone. We are witnessing an increase in the incidence od rectal cances in the younger population. Therefore, the role of organ preservation will be increasing and possible with total neoadjuvant approach.

Current standard of care for anal canal cancers is chemoradiotherapy (45-50.4 Gy, plus boost to 59Gy in very selected cases). Cancers of the anal canal are rare, but its incidence has been increasing over the past several decades, particularly among women. Management of very early stage anal margin cancer is best by wide local excision or radiotherapy alone, similar to the management of skin cancer (60-65 Gy). Current standard of care for anal canal cancers is chemoradiotherapy (45-50.4 Gy, plus boost to 59Gy in very selected cases). Dose escalation above 60 Gy did not showed benefit in local control, colostomy-free survival or overal survival. IMRT is clinically associated with decreased acute toxicity, especially dermatologic and GI toxicity. The role of dose-descalation is also being assesed, in T1-T2 tumors, but only in ongoing studies.

Stereotactic body radiation therapy (SBRT) is a technique that allows a high dose of radiation to be delivered to a highly conformal treatment volume in a short amount of time. SBRT improving local tumor control, but also can increase tumor immunogenicity. Today, SBRT is mainly used in the treatment of oligometastatic disease, for local control of metastases in the lungs, liver, brain, bones and lymph nodes. We have a lack of randomized studies otherwise with SBRT, so the conclusions are mostly from smaller retrospective studies. Most existing data regarding oligometastatic upper GI cancers are consolidative RT in advanced esophageal squamous cell carcinoma. In ESO-Shanghai 13 trial (phase 2 randomized trial) showed that addition of local treatment for metastases could significantly improve progression-free survival among patients with oligometastatic oesophageal squamous cell carcinoma being treated with systemic therapy. Future perspectives there are no randomized trials supporting the use od SBRT for patients with colorectal liver metastases. However, a meta-analysis of 656 patients across 18 studies demonstrated a 2-year OS rate of 56.5% and favorable toxicity. Current expert recommendations support the consideration of SABR when surgery or ablation is not an option. Several retrospective studies including only patients with pulmonary mets from colorectal cancer showed that 2– or 3-year local control and overall survival rates were 60–70% and 50–64%. Also, local failure of irradiated metastases has been reported to have a correlation with worse OS. Prospective cohort study by O'Cathail et al. showed patients having SBRT for nodal oligometastases have better survival outcomes, relative to those treated for visceral metastases. The excellent local control (at 1 year was 90%) achieved with SBRT in nodal disease translated into an improved time to progression (19 vs 9 months) and sustained into an OS benefit.

Future perspectives are combination of different treatment modalities, especially in metastatic disease, such as radiotherapy and immunotherapy/targeted therapy.The treatments of oligometastatic GI cancers are exceedingly complex. Multidisciplinary approaches to patients with oligometastatic cancers remain crucial for the development of personalized treatment plans that maximize survival and quality of life.

Keywords: esophageal cancer, gastric cancer, rectal cancer, anal cancer, SBRT

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S15 – CASE REPORT OF A BRCA-2 MUTATED BREAST CANCER PATIENT

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Introduction: The incidence of breast cancer is increasing rapidly worldwide. Early triple negative breast cancer is effectively treated with neoadjuvant immunotherapy and chemotherapy showing significant improvement in pathological complete response, event-free survival and overall survival(1,2). BRCA mutation testing is indicated in all patients with triple negative breast cancer and treatment with adjuvant PARP inhibitor is available(3,4).

Case report: A 37-year old female patient with no history of previous disease and family history of prostate cancer presented with the lump in the left breast in October 2023. A breast ultrasound revealed a tumor in the upper inner quadrant of the left breast, measuring 25x26x18mm with no suspicious lymph nodes in the left axilla. Core needle biopsy was performed and the titanium marker was placed in the tumor. The histopathological diagnosis was invasive breast cancer, no special type, nuclear grade 3, ER negative, PR negative, HER2=0, Ki67=70%. A breast MRI confirmed the ultrasound findings. A pretreatment CT-scan of thorax, abdomen and pelvis was performed and showed no signs of metastatic disease. The patient received neoadjuvant chemotherapy and immunotherapy from November 2023 until June 2024. She received four cycles of pembrolizumab (at the dose of 200 mg per cycle) every three weeks plus paclitaxel and carboplatin (weekly paclitaxel 80mg/m^2 weekly and carboplatin AUC 5 every three weeks) and additional four cycles of pembrolizumab with four cycles of doxorubicine-cyclophosfamide (60 mg/m^2 and 600 mg/m^2) every three weeks(5). After four cycles of therapy, an ultrasound of the breast was completed which showed a tumor of size 6x5x5mm. There were no significant side effects and no dose reduction or postponements were needed. In May 2024, a blood sample was sent to BRCA 1 and 2 mutation analysis. In June 2024, a skin-sparing mastectomy of the left breast with reconstruction and sentinel biopsy of left axilla was performed. Histopathological exam showed a complete pathological response (pCR) with RBC 0 (residual cancer burden zero). The patient continued with adjuvant pembrolizumab treatment. In September 2024, gene testing was performed and showed the presence of BRCA 2 gene c.3744_3747 del (Ser1248fs) mutation. Researches done by today showed significant activity of PARP inhibitors in treatment of early BRCA mutated breast cancer. Even though our patient had significant mutation and was suitable for treatment with a PARP inhibitor, due to late gene testing results, the decision was to complete the adjuvant immunotherapy with pembrolizumab.

Conclusion: Early triple negative breast cancer is effectively treated with neoadjuvant chemotherapy and immunotherapy. In cases of positive response to treatment, in adjuvant setting it is possible to continue with adjuvant immunotherapy. PARP inhibitors are also available in the adjuvant setting and it is necessary that genetic tests are performed on time for treatment decision making. Further investigations are needed to optimize treatment strategies in this aggressive cancer subtype.

Keywords: triple negative breast cancer, immunotherapy, BRCA mutation

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