ORAL PRESENTATION

S1 - What's new in neoadjuvant treatment of breast cancer?

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Neoadjuvant approach provides many benefits for patients with early breast cancer. Indication has to be provided by multidisciplinary team. Patients, candidates for neoadjuvant treatment and therapy regimens, have to be carefully selected. Therapy response has to be closely monitored. Surgery timing and radiotherapy extent have to be disscussed by the team.

In neoadjuvant treatment of early HER2 positive breast cancer, ER positive status is associated with lower response. Adding antihormonal therapy does not improve pCR, although it does not antagonize chemo- or targeted therapy efficiency. Chemotherapy based on taxane (without anthracyclines) with dual blockade (trastuzumab + pertuzumab) has high pCR rate, but unknown survival benefit. This TCPH regimen (docetaxel + carboplatin + pertuzumab + trastuzumab) can have significant toxicity and can be considered in stage II and III on individual level weighing pros and contras. Intrinsic Her2 subtypes (Her2 enriched) may be helpful in identifying responders to anti-HER2 therapy.

Carboplatin improves pCR, but has unknown survival benefit in triple negative breast cancer. Combining gene signatures (DNA repair, 70-gene signature assay) may help identifying those most likely to benefit from platinum compounds and PARP inhibitors.

Immune system is crucial for anti-cancer therapy. Tumor infiltrating lymphocytes (TILs) are associated with high pCR rates and may correlate with more aggressive behaviour. TILs can be induces what can imply relevant immunotherapy based regimens. Many ongoing clinical trials are currently using immunotherapy combination.

S2 - Genetic analysis in breast cancer

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Breast cancer is the most common malignant tumor in women. One in eight women during their lifetime will suffer from breast cancer, and each year more than 500,000 people die in the world. Adjuvant endocrine and chemotherapy treatment of breast cancer by surrogate subtypes has shown overall benefit in reducing the risk of disease relapse and death by about 15%. Is this a sufficient reason to apply severe cytotoxic therapy to a large number of patients, many of whom are pretreated?

The key role of genetic factors in breast cancer is the fact that mutations of some genes with their high penetrance can significantly increase the risk of developing cancer. Today, 30 of the genes that are of importance in breast cancer have been identified. Among them, the most common today are BRCA 1 and 2 genes, which when mutated carry almost 50% of the risk of developing breast cancer during lifetime.

Because of all of this, the paradigm of approach to breast cancer has changed completely in recent years. From a classical approach, where clinical decisions were based on cancer site, histology and disease stage, today we are talking about genomic drivers and decision-making based on complex genomic profiling. Today, with the development of molecular biology, it is possible to analyze the entire genome, using modern methods such as massive parallel sequencing (NGS).

Genetic tests can analyze individual locus in the gene to determine mutation, or analyze whole genes for the presence of mutations. Panel tests can simultaneously analyze several genes. Today, a variety of commercial tests for BRCA testing are in use. There are clear indications when it is justified and necessary.

Today, the most famous genomic tests are OncoTypeDX, MammaPrint, EndoPredict and ProSigna. OncoTypeDX is based on the RT PCR method, includes analysis of 21 genes, has prognostic and predictive value, and it is the only test specified in the NCCN / ASCO guidelines. MammaPrint uses the microarray method and analyzes 70 genes. The decision which test to use is not simple. Prospective clinical studies (TAILOR X, MINDACT) validated only the first two tests.

Comprehensive Genomic Profiling (CGP) is a molecular approach that analyzes multiple genomic alterations in a variety of genes. CGP brings benefit as initial diagnostics, when it can change the course of disease and treatment, but also in the progression of the disease. CGP has shown that over 90% of patients have active mutations, for which there are adequate target drugs in some of the clinical studies. CGP identifies mutations in about 80% of breast cancer. Foundation One is one of the most famous CGP tests in the world today, it is based on NGS and analyzes 315 genes. Molecular Intelligence Tumor Profiling is less known competitor to the previous test, a multiplatform method and analyzes over 600 genes.

In order to identify as many new useful markers, or successful target drugs, it is necessary to support and participate in new design studies, tailored for precision medicine, such as “umbrella” or “basket” designed studies.

The results of genomic analyses gain the meaning through discussion on the Molecular Tumor Board, which has a task to thoroughly analyze the findings of the tests and transform them into practice, and so maximize the benefits for the patient.

S3 - News in the neoadjuvant therapy of rectal cancer

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Radiotherapy is beneficial in rectal cancer treatment, because of lower recurrence rates. It renders some tumours resectable. Long-course CRT is better than long-course RT. Radiotherapy does not increase sphincter preservation. It can preserve the organ. The question is which radiotherapy? The choice is: 1. Preoperative short-course RT (5x5 Gy) immediate surgery (or delayed?), 2. Preoperative long-course CRT (about 50 Gy with fluoropyrimidine). Three randomised studies with preoperative long-course RT+_ chemotherapy (two resectable bad, one non – resectable ugly tumours showed that CRT had fewer local recurrences, CRT is more toxic with more late adverse effects, there is no difference in survival unless non – resectable tumours. CRT with fluoropyrimidine is routine worldwide in stage II + III. Other presently current and subject to many trials are questions: Organ preservation?, An interval to surgery?, Neo-adjuvant chemotherapy? Postoperative CRT is indicated in max 1-2% patients with good MRI/MDT discussion, needed if the preoperative evaluation underestimated the stage and with no (C)RT given. Preoperative CRT is a method of choice for down-staging. „Intermediate risk" tumours may need treatment that kills subclinical deposits not removed by the surgery. Short-course RT is efficient, much simpler, less toxic and less resource demanding treatment. Local control has been much improved, but systemic control of disease hasn"t . We need better systemic tretment in neo-adjuvant administration. Randomised clinicas trials are ongoing: RAPIDO (n=920), Polish (n=515), Stellar (Chinesse, n=535). CRT (50 Gy with a floropyrimidine) in control arm in all, different neo-adjuvant shedules are used, shourt-course RT is used in the experimental arm. Three modern randomised studies were done with longer interval after CRT: Istanbul (153 patients) – no differences in pCR rate or other outcomes, Greccar (265 patients) – no increased pCR rate (15% vs.17.4%, p=0.5), Royal-Mardsen (237 pateints) increased pCR (9% vs. 20%), with no difference in reccurence rates (local, distant). Toxicity and complications were 2-3 times higher if CRT was done, but there were fewer postoperative complications with a delay – 40% vs 52% (statistically significant). The choice of treatment options of primary rectal cancer without distant metastases is based on TNM risk category. The early (good) ones, easily resectable (R0), very low local failure rates need operation directly. The bad ones, easily resectable (R0) have too high local failure rates – need pretreatment, but not downsizing/staging. SRT (direct surgery) is the „best", delayed surgery an option, particularly in surgical risk patients. The advanced (ugly) ones risk R1-2 surgery, previously „non resectable" must have pretreatment and downsizing/staging unless mutilating surgery. CRT is the „best" according to evidence, preoperative SCPRT (5x5 Gy) plus FOLFOX and a delay to surgery is an option. Clinical complete response and a „watch-and-wait" approach. Following CRT or SCPRT, a clinical complete response (cCR) can be obtained in 10% - 40% of patients when assessed after an interval of 12 weeks from the start of treatment. The significance of new diagostic methods (Diffusion MRI) has been pointed out in the assessment of the responses to neoadjuvant therapy. Diffusion MRI has shown bigger sensitivity (77%) in relatiion to the standard one (38%). cCR has only partial concordance with pCR. Dedicated centres have reported encouraging oncological and functional outcome results for selected patients treated with standardised CRT and a non-operative strategy. Such patients demand rigorous follow-up, where MRI surveillance is available, and more frequent than routine surveillance to ensure that surgical salvage is feasible and timely. Substantially more follow-up and larger numbers of patients treated within properly controlled prospective studies are needed to validate the *watch-and-wait* approach.

S4 - ESMO Highlights

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PACIFIC study examined effects of durvalumab (PD-L1 inhibitor) after radical radiochemotherapy (RCT) in stage III non-small cell lung cancer (NSCLC). Among those patients, the cure rates following RCT are typically less than 30%. By addition of durvalumab over 12 months after completion of RCT, significant progression free survival (PFS) prolongation was observed.

FLAURA study has showed 37% risk reduction at the interim analysis with osimertinib in first line therapy in comparison with standard of care of EGFR mutated NSCLC.

MONARCH 3 study showed that addition of abemaciclib, a cyclin-dependent kinase (CDK) 4/6 to non-steroidal aromatase inhibitors (NSAIs) anastrozole or letrozole reduced the risk of progression or death by 46% compared with the NSAI alone for previously untreated patients with HER2-negative, HR-positive advanced breast cancer.

EXTENET trial showed some promising results as extented adjuvant therapy in triple positive (ER, PR and Her2 positive) early breast cancer.

In RANGE study promising result was observed in platinum resistant advanced urothelial cancer by treatment combination of docetaxel plus ramucirumab.

In KEYNOTE-059 study pembrolizumab showed a promising response rate in for both newly diagnosed and previously treated patients with metastatic gastric cancer. An overall objective response rate was observed in 12% of cases treated by pembrolizumab alone in the previously treated subgroup of patients who expressed programmed death-ligand 1 (PD-L1). In patients with newly diagnosed metastatic cancer, both the combination therapy (pembrolizumab and chemotherapy) and pembrolizumab alone were safe and showed some promising activity.

COMBI-AD trial combined dabrafenib plus trametinib as an adjuvant treatment for patients with high-risk *BRAF V600*-mutated melanoma after surgical resection significantly decreased the risk of death or recurrent disease.

In CheckMate 238 study was observed that patients with stage IIIb/IIIc or stage IV melanoma at high risk of recurrence following complete surgical resection had greater recurrence-free survival (RFS) with adjuvant nivolumab compared to adjuvant ipilimumab.

ARIEL 3 showed that maintenance therapy with rucaparib increases PFS in BRCA mutant recurrent ovarian cancer by 77%.

S5 - Logic in interpreting clinical trial results: Comparison between inductive and deductive reasoning

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Clinical trial results are often interpreted by inductive reasoning, in a trial design-limited manner, directed toward modifications of the current clinical practice. Deductive reasoning is an alternative in which results of relevant trials are combined in indisputable premises that lead to a conclusion easily testable in future trials.

S6 - News in the treatment of urogenital cancers

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This year, the results of several studies have been published that will have impact on practice changing in the treatment of prostate, kidney and bladder cancer.

The most important events in the prostate cancer treatment are the results from two studies LATITUDE and STAMPEDE in men with metastatic hormon-sensitive prostate cancer (mHSPC). They have shown that androgen deprivation (ADT) with abiraterone significantly improves survival compared with ADT alone. Until now the standard treatment for mHSPC has been ADT plus docetaxel and these recent data lead to question of whether ADT plus docetaxel is better than ADT plus abiraterone or may have a synergistic effect. No clinical data are currently available to answer this question, but multiple clinical trials are underway – STAMPEDE arm J, PEACE-1, ARCHES, ENZA-MET.

New date are set to change the standard first line treatment of metastatic renal cell carcinoma, after CHECKMATE-214 study showed improved overal survival with nivolumab plus ipilimumab in comparison to standard care with sunitinib.There were also some updated results from CABOSUN trial showed that cabozantinib provided statistically significant decrease in the rate of disease progression or death compared to sunitinib. The SURTIME study showed that upfront sunitinib and delayed nephrectomy is better than upfront nephrectomy. There was also an update from the adjuvant S-TRAC trial that tests adjuvant sunitinib for 1 year vs placebo and prolongs relapse-free but not overal survival. Immunotherapy trials are still the main topic, also in the adjuvant setting as KEYNOTE-564 study with pembolizumab.

Immunotherapy studies dominated in the bladder cancer treatment. Updates from KEYNOTE-052 and KEYNOTE-045 studies confirmed advanteges of pembrolizumab over chemotherapy in patients who cannot tolerate cisplatin or who have platinum-refractory disease in metastatic urothelial cancer. Some studies tested the combination of immunotherapy and chemotherapy. RANGE trial showed that adding angiogenesis inhibitor ramucirumab to docetaxel increased progression-free survival but not overal survival in patients who have progressed on platinum-chemotherapy. Immunotherapy is also the main topic in non-metastatic adjuvant setting. However, the greatest question is identification of patients most likely to benefit from certain therapy – looking for biomarkers.

We can conclude that this year in urooncology we had some practice changing studies in the prostate and kidney cancer treatment and that immunotherapy is still the main topic.

S7 - Personalised therapy of hepato-pancreato-biliary malignancies

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Pancreatic ductal adenocarcinoma (PDAC) is among the most devastating human malignancies with aggressive biology and resistance to multiple therapeutic modalities. Through whole-genome and deep-exome sequencing, genomic multiplicities of PDAC, such as copy number alterations, point mutations and indels, chromosomal aberrations and epigenetic changes have been identified. Pancreatic and duodenal homeobox 1 (PDX1) promotes tumorigenesis and it is a promising therapeutic target for PDAC. Oncogenic *KRAS* is found exclusively in cancer cells with up to 90% of pancreatic cancer cells possessing the mutation, but so long, no effective therapy is found. PDAC is uniquely associated with desmoplastic stroma that accounts for 80% of tumor mass. Sonic hedgehog (SHh) signaling was recognized as one of the key regulators of tumor epithelia–stromal interaction in PDAC. Understanding the biology of stroma can also aid the discovery of innovative strategies for eradicating this lethal cancer in the future. Immunotherapies for PDAC have not yet yielded much clinical benefit when administered as single agents. Transforming growth factor-β (TGF-β) signaling plays a dual role in both pro-tumorigenic and tumor suppressive of pancreatic cancer. Developing therapies for advanced PDAC is much more complicated than targeting only the cancer cells.

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide. Aberrant expression of cancer-related genes is one of the hallmarks of cancer cells and plays a role in hepatocarcinogenesis. The most common molecular anomalies in this malignancy are mutations in the TERT promoter, TP53, CTNNB1, AXIN1, ARID1A, CDKN2A and CCND1 genes. PTEN loss at the protein level is also frequent. Genomic portfolios stratify by risk factors as follows: (i) CTNNB1 with alcoholic cirrhosis; and (ii) TP53 with hepatitis B virus-induced cirrhosis. Activating mutations in CTNNB1 and inactivating mutations in AXIN1 both activate WNT signaling. Alterations in this pathway, as well as in TP53 and the cell cycle machinery, and in the PI3K/Akt/mTor axis (the latter activated in the presence of PTEN loss), as well as aberrant angiogenesis and epigenetic anomalies, appear to be major events in HCC.

Immune response(s) of the body may be potentiated by immunomodulation of various effector cells such as B-cells, T-cells, Treg cells, natural killer cells, dendritic cells, cytotoxic T-lymphocytes, and other antigen-presenting cells; cellular components such as genes and microRNA; and molecules such as proteins, proteoglycans, surface receptors, chemokines, and cytokines. 82% of patients express PD-L1 (immunohistochemistry) and response rates to anti-PD-1 treatment are about 19%, and include about 5% complete remissions as well as durable benefit in some patients.

Biliary tract cancers represent heterogenous malignant group of tumors that include gallbladder cancers (GBC) and IH and EH cholangiocarcinomas that are frequently detected in the locally advanced or metastatic setting. The literature reveals alterations in ARID1A, BRAF, CDKN2A/B, EGFR, ERBB2-4, HKN-RAS, PIK3CA, PBRM1, and TP53. Biliary tract cancers represent a potentially attractive target for immune-based therapies given the background association with chronic inflammation and conditions such as cholecystitis sclerosing cholangitis and primary biliary cirrhosis. Recognition that an activated tumour microenvironment exists in biliary cancers encourages a focus also on adoptive therapy.

S8 - News in gastrointestinal oncology

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There are significant advances all over the field of gastrointestinal oncology, including neurondocrine tumors and gastrointestinal stromal tumors, in the past few years. Considering colorectal carcinoma (CRC), looking back from 2014 our view has been changed dramaticaly in the way we started to understand more profound the pathogenesis of disease based on molecular profiling. Starting from RAS/BRAF testing, understanding tumor location as a key driver of treatment decision, all to new biomarkers like MSI and Consensus molecular subtype (CMS) classification which intergrates multiple molecular markers in CRC. There was also discussed a question of duration of adjuvant treatment in CRC. According to data we have today, for high risk stage III colon cancer it is recommended 6 months of FOLFOX-protocol treatment, for low risk stage III CRC it is probably enough 3 months of CAPOX. Regarding advanced gastric cancer, one of the most significant news is update of KEYNOTE-059 study, showing promising clinical activity of pembrolizumab in 3 cohorts: pembrolizumab after 2 or more prior lines of therapy (cohort 1), combination of pembrolizumab and chemotherapy (cohort 2) with overall response rate (ORR) of about 60% and pembrolizumab as a single first-line agent. All three cohorts are very promising but role in early lines and in combination with chemotherapy has to be clarified and established as well as optimal combination and sequence. Pembrolizumab was examined also in pNET tumors and provided clinically meaningful antitumor activity in some patients. It was about 36% of carcinoids and pNETs positive for PD-L1 detection and the most of patients achieved stable disease (60%). It is also important to mention that it was mad a PanNETassigner gene signature as a first step to molecular characterisation of NETs. Fourt-eight patients had isolated RNA from fresh frozen tumor samples for immune gene expression profilling using microarray. There are 3 subtypes of were defined - metastasis-like-primary (MLP), intermediate and insulinoma-like type.

S9 - Metabolomics-metabolic phenotype of cancer

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Cancer is a heterogeneous disease with profound changes in intracellular and extracellular metabolism. These changes are related to direct or indirect effects of mutations in tumor suppressor genes and oncogenes, and influenced by epigenetic factors as well. Otto Warburg was the first scientists who observed metabolic changes in tumors during 1920s. These changes include fast synthesis and usage of nutrients for tumor maintenance and growth. Metabolomics is a systemic analysis of chemical fingerprints of metabolites that result from biological processes in cells, tissues and organs. Metabolome comprises all metabolites in an organism of low molecular mass (80-1500 Da). Changes in the metabolome are result of effects of by environmental and genetic factors, changes in gut microbiome and changes in enzyme content and activity. These changes are part of tumor biology and tumor phenotype. During last ten years there is intensive development of metabolomics due to advances in analytical methodology and instruments such as nuclear magnetic resonance (NMR), gas chromatography mass spectrometry(GC-MS) and liquid chromatography mass spectrometry (LC-MS). Samples in which metabolomics can be analyzed are cells, body fluids and tissues. Intracellular and extracellular metabolic changes have impact on gene expression and on differentiation and proliferation of tumor cells. Cancer metabolomics can be applied for identification of diagnostic and predictive biomarkers, changes in metabolic pathways in normal and tumor cells, evaluation of therapeutic efficacy, assessment of drug toxicity, etc. Metabolomics approach in precision medicine may provide important information to the clinician regarding cancer diagnosis and treatment.

S10 - Emerging importance of Thrombospondin-1 and Endothelin-1 in cancer development and growth

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Similar expression patterns of mRNA profiles for Endothelin 1 (ET-1) and Thrombospondin 1 (TSP-1) from GeneAtlas U133A, gcrma, suggest that these two mediators are dominantly synthesized in the myocard and lungs. They are both linked to tissue remodelling and fibrosis.

Thrombospondin-1 (TSP-1) is a inhibitor of angiogenesis that attenuates tumor progression and metastasis. Small peptide mimetics of TSP-1 show activity against several malignancies (head and neck cancer, non-small cell lung cancer, lymphoma, renal cell carcinoma and soft tissue sarcoma). TSP-1 related ADAMTS enzymes seem crucial in cancer progression via extracellular matrix remodelling.

Endothelin-1 is a ubiquitous regulatory peptide produced by various tissues. The precursor cells of many tumor types secrete endothelins. ET-1 protein expression was detected in situ in all tested prostate cancers as well as in normal prostate tissue. The majority of hepatocellular carcinomas produce ET-1, while ET-1 is secreted by the normal hepatic stellate cells. Human breast cancer cells often produce immunoreactive ET-1.

S11 - Novel treatment strategies in breast cancer

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Breast cancer is the most commonly diagnosed cancer in female population worldwide. Advances in understanding tumor biology, particularly signaling pathways, have led to the development and approval of novel therapeutic agents, especially in HER2 positive and hormone receptor positive subtypes. To date, there are no approved targeted therapies specifically for triple-negative breast cancer (TNBC).

A promising field of clinical research in breast cancer is the use of immune checkpoint inhibitors. By blocking inhibitory molecules or, alternatively, activating stimulatory molecules, these treatments are designed to enhance pre-existing anti-cancer immune responses. Several studies investigating checkpoint inhibitors are currently enrolling breast cancer patients. According to results from KEYNOTE-086 study, stromal tumor infiltrating lymphocytes (sTIL) levels act as a surrogate of preexisting antitumor immunity and can identify patients with metastatic TNBC with a greater chance of responding to pembrolizumab monotherapy. Priming with radiotherapy RT and chemotherapy CT followed by boost with nivolumab is an effective strategy in metastatic TNBC. PARP inhibitors confirmed new active agents in BRCA mutated mBC.

Endocrine therapy (ET) is the preferred option for hormone receptor positive disease mBC, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance. Recent advances in treatment of HR+ HER2 – with addition of the CDK4/6 inhibitors palbociclib and ribociclib to an aromatase inhibitor, as 1st line therapy, for post-menopausal patients provided a significant improvement in PFS. The addition of CDK4/6 inhibitor palbociclib or abemaciclib to fulvestrant, beyond 1st line therapy, for pre/peri/post-menopausal patients, provided significant improvement in PFS (about 5 months), with an acceptable toxicity profile.

Novel approach to neoadjuvant treatment of HR+ HER2 – tumors is integratingPI3K and CDK 4-6 inhibitors together with aromatase inhibitors. LORELEI study met its primary endpoint. This is the first randomized study to demonstrate a significant increase in ORR measured by centrally assessed MRI upon treatment with a PI3K selective inhibitor + endocrine therapy in HR+ HER2 – early BC patients. The addition of taselisib to letrozole increases the ORR in the overall and PIK3CA- mutated population.

Escalating adjuvant therapy in HER2+ early BC is the most significant novel approach for that subgroup of patients. The 5-year analysis of the ExteNET trial confirms sustained benefit with extended adjuvant neratinib. Also, APHINITY is the first trial to prove the superiority of dual HER2 blockade in the adjuvant setting over the existing standard of care. At this time, patients with higher risk of recurrence, such as lymph node-positive or hormone receptor-negative disease, appear to derive the most benefit.

S12 - Dose Dense Chemotherapy in Adjuvant Treatment of Early Breast Cancer - Pro Arguments

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For several decades, the benefit of adjuvant cytotoxic therapy in reccurence risk reduction and overall mortality reduction for early breast cancer has been well-known.

The concept of dose dense chemotherapy consists of applying the same dose of cytotoxic agent in a shorter interval between cycles than the standard ones, reducing the recovery time of tumour cells. Application of (peg)filgrastim is obligatory after each dose dense cycle.

Several trials have ben conducted with comparison of standard and dose dense protocols in high risk breast cancer patients. The results of CALBG 97-41 study were published in 2003 and stand in favour of dose dense chemotherapy: after the median follow-up od 3 years, the disease free and overall survival are longer in dose dense patient groups, while grade IV neutropenia is more frequent in standard protocol groups.

Systemic review and meta-analysis of randomised controlled studies published in 2010 extracts the results of ten dose dense studies and concludes that dose dense chemotherapy provides better overall survival and disease-free survival, in particular in women with estrogen-receptor negative disease. Similar benefit was found also in GIM-II trial from 2013 which had median follow-up of 5 years.

Distinct form od dose dense protocol is intensive dose dense protocol. It has been compared to standard protocol in high risk patients with 4 and more positive axillar lymph nodes and 42% patients with more than 10 positive lymph nodes in AGO-iddETC trial. Its results from 2012 represent the longest so far known 10-year survival of 69% for such high risk patient group.

On grounds of these and other trials, dose dense adjuvant protocols are listed in NCCN guidelines as „preferred protocols“ for HER-2 negative high risk early breast cancer due to 26% disease recurrence reduction and 31% mortality risk reduction.

The ESMO guidelines from 2015 also recommend dose dense adjuvant protocols, especially in highly proliferative tumours.

S13 – Dose dense chemotherapy, is there a catch?

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Dose dense chemotherapy has recently become a standard adjuvant treatment for women with high risk breast cancer. Although one can not dispute the benefits of dose dense in selected patients, we should always bear in mind possible side effects and risks of this treatment.

Several trials proved efficiency of dose dense chemo regimen. In the CALGB 9741 trial dose dense patients received: doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles followed by paclitaxel. Granulocyte colony stimulating factor (G-CSF; filgrastim) was originally administered in the study with AC protocol, from 3rd till 10th day of each AC cycle. The DFS and OS were significantly better for the group of patients receiving AC every 2 weeks than those on the conventional schedule.[1,2]

On the other hand, women that receive dose dense chemo are more exposed to possible side effects of chemotherapy and G-CSF applied. In the mentioned CALGB 9741 study there was no increase in haematological toxicity due to use of filgrastim in the dose dense regimens. However, dose dense patients have greater risk of complications known for G-CSF application. Besides common side effects such as bone pain and pain in extremity there are several more uncommon but serious adverse effects. Spleen rupture, allergic reactions/hypersensitivity, including anaphylaxis and pulmonary toxicities mainly manifesting with ARDS could also be expected.[4]

The other important issue to be considered when applying G-CSF with chemotherapy is possible stimulation of malignancy. A systematic review of trials of cancer chemotherapy with G-CSF reports small but increased risk of AML and MDS when the use of G-CSF with chemotherapy, but all-cause mortality is decreased in patients receiving chemotherapy with G-CSF support. Greater reductions in mortality were observed with greater chemotherapy dose-intensity.[3] Finally, dose dense chemo regimen is considerably more expensive than standard regimen. The cost of dose dense versus standard treatment, if pegylated G-CSF is administered, is increased approximately by eight hundred per cent.

Working in the General hospital in Pula I would like to point out two main problems we face when it comes to dose dense chemo. Firstly, our hospital covers the whole Istrian region and some patients are situated 50 km from the hospital, which means it takes two hours drive per day minimally 7 days in a row in order to receive G-CSF with AC regimen, if classic filgrastim over pegylated filgrastim is used. Organising those trips sometimes represents quite a problem for a patient. Secondly, as listed by Croatian Health insurance company (HZZO), pegylated filgrastim should only be given in General Hospitals if prescribed and recommended by a Clinical Hospital and approved by General Hospital's Drugs Committee. This process of getting approval to prescribe pegylated filgrastim unnecessarily prolongs the start of the treatment in all general hospitals.

To conclude, dose dense chemotherapy is a mainstay regimen in the adjuvant setting for women with high-risk breast cancer. By reasonably selecting candidates for this kind of treatment, benefits of dose dense chemotherapy should outweigh the possible risks.

S14 - Surgery after neoadjuvant treatment for rectal cancer

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Neoadjuvant approach to treatment of locally advanced rectal cancer is a standard of care today. The response to neoadjuvant treatment has been shown to correlate with the long-term prognosis of the disease and may serve as a predictive marker in the decision on further adjuvant treatment. Surgery after completed neoadjuvant treatment is currently the preferred option in all relevant guidelines for rectal cancer treatment. Given that the surgical intervention in the area of the small pelvis carries with it significant morbidity and impact on the quality of life, experts in the field are trying to identify a group of patients who might possibly be spared such treatment. Patients with complete clinical response to neoadjuvant treatment are population in which intensive monitoring modality is currently being investigated, without the use of a surgical treatment. The most important factor in tracing a patients in whom intensive follow-up comes into consideration are the limitations of the currently available radiological methods for assessing the response to neoadjuvant treatment. It has been shown that no available radiologic method can safely evaluate a complete clinical response because in 15-20% of patients operated after a radiologically verified complete clinical response postoperative pathohistological analysis proved metastases in locoregional lymph nodes. Available studies on „watch and wait“ approach were conducted on small numbers of patients and with relatively short follow-up period, which is why their results should be taken with the reserve. Results of larger observational studies are needed to consider “watch and wait” approach as a routine treatment for patients with complete clinical response. Taking into account all of the above mentioned, surgery after a neoadjuvant treatment remains the treatment of choice for a majority of patients.

S15 - Watch and wait approach to rectal cancer

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Standard treatment for stage II and III rectal cancer includes neoadjuvant chemoradiation (CRT) followed by radical surgical resection (SR) and total mesorectal excision. However, SR carries significant acute morbidity as well as substantial long-term alteration of bowel function and some degree of urologic and sexual dysfunction, so minimizing surgery has the potential to benefit patients significantly.

Considering that 50-60% of patients are downstaged following neoadjuvant therapy

with 18-26% showing absence of viable malignant cells, known as complete pathological response (pCR), the watch and wait approach has been proposed as a reasonable alternative to surgery. A retrospective review of 725 patients with rectal cancer found that 5-year recurrence free survival rate is 90.5% for patients with CR and distant metastases and local recurrences also correlated with the level of response. CR confirmed by clinical and radiographic evaluation is known as complete clinical regression (cCR). The patients with cCR are followed with physical examinations, endoscopy, and imaging. An article by Habr-Gama et al. was the first to seriously raise the possibility of avoiding SR altogether through use of CRT. No significant difference was found between 71 patients who were observed without surgery compared with those of patients with pCR at surgery. Further studies, including 867 patients, with median follow-up of 12–68 months found no significant difference between patients managed with watch and wait after a cCR and patients with pCR identified at resection in terms of non-regrowth recurrence, cancer-specific mortality, disease-free survival, or overall survival.

In conclusion, the consequences of a proctectomy, can lead to very extensive comorbidities, such as the need for a permanent colostomy, fecal incontinence, sexual and urinary dysfunction, and even mortality. Contemporary data is shifting the current paradigm of rectal cancer management towards nonoperative therapy and thus the question arises in colorectal surgery whether do patients really benefit from radical surgery after an adequate response to CRT.

S16 - Role of Family medicine physician in treatment of oncologic patients

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The importance of family medicine practitioner in treating oncologic patients as a part of multiprofessional and multidisciplinary team is increasing, but the role is not well defined. There is a need for a better understanding of division of assignments and responsibilities between oncology specialists, family medicine practitioners and other healthcare providers who come in contact with cancer patients.

As oncologic diseases become more and more chronic, and as field of oncology develops, management of patients' needs is becoming more complex. It is important to notice that family medicine in Croatia is a big decentralized system and coordination between colleagues has specific problems. There are around 2350 family medicine practitioners in Croatia and their work conditions can be very different. Working in a small village is largely different from urban environment as secondary healthcare can be hard to reach and social conditions that patients face are often difficult. On the other hand, smaller social clusters can be beneficial as family medicine practitioner has a unique role in being part of community and can get to know their patients surrounding, lifestyle and social connections better than a specialist could. Another important but not often discussed role in patient care comes down to public pharmacist, as patients often approach pharmacists even before primary care physicians.

When patient comes to their family medicine practitioner there can be several decisions and treatment options available. Family medicine physician must strike a balance between not delaying diagnostic procedures and possible treatment, but at the same time serve as a filter for secondary and tertiary healthcare admission. After the initial contact with patient and as they start the treatment for their oncologic disease, family medicine practitioner has a great role in coordinating their hospital visits, observing adherence to therapy, treating side effects of drugs and some symptoms of primary disease, giving psychological support and caring for the needs of patients' family and close ones. Prevention to minimize chances for a disease to occur as well as follow up, or palliative care, after treatment options have been exhausted, also heavily relies on family practitioner. It is therefore crucial that communication and collaboration between everyone included in patients' care improves. There are many areas in which patients themselves are not sure who to contact with questions or how to ask for help.

As new therapies emerge and evolve, there is a constant need for education of family practitioners in order to adequately fulfill their many roles in providing best possible care. Good example of educating and communicating between oncology specialists and primary physicians are guidelines issued by, as an example, Croatian Society for Medical Oncology.