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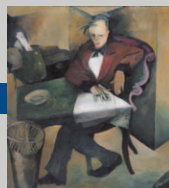
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Zagreb 2024

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nagovještajem novih mijena u prvoj polovici dvadesetog stoljeća preko Gecanovog *Cinika*, Junekovog *Maternite de Porte Royal* nastalog u Parizu, zatim intimističkog, mističnog i magičnog prizora u djelu *Stara ulica* Miljenka Stančića i Reiserove *Mrtve prirode* prema avngardi koja prati historiografski realitet aktivnosti staleške udruge noseći obilježja i mijene pojedine epohe, zrcaleći pozitivističko-modernistički pokret u dodiru znanosti i umjetnosti u djelu *Ultra A* Miroslava Šuteja.

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 - melanomom
 - tumorima središnjeg živčanog sustava, glave i vrata
 - ginekološkim tumorima
- Potporno i palijativno liječenje – sveobuhvatna skrb o onkološkom bolesniku
- Mogućnosti i značaj genskog profiliranja tumora
- Precizna onkologija
- Informatička podrška i praćenje ishoda liječenja
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HOTEL LONE, ROVINJ | 10 – 13. 10. 2024.

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Uvodna riječ | Introductory word

Poštovane kolegice i kolege, dame i gospodo, dragi prijatelji,

Veliko nam je zadovoljstvo pozvati vas na 16. kongres Hrvatskog društva za internističku onkologiju Hrvatskoga liječničkog zbora s međunarodnim sudjelovanjem, koji će se održati od 10. do 13. listopada 2024. godine u prekrasnom hotelu Lone u Rovinju.

U posljednjih nekoliko godina svjedoci smo značajnih pomaka u području onkologije. Unatoč tome, zloćudne bolesti i dalje predstavljaju vodeći zdravstveni izazov u Hrvatskoj, osobito među radno aktivnom populacijom mlađom od 65 godina. Naš cilj je kontinuirano unapređivati znanje i prakse kako bismo smanjili postojeću razliku u ishodima liječenja između Hrvatske i najrazvijenijih zemalja Europske unije.

I ove godine kongres će obuhvatiti najnovija saznanja i inovacije u dijagnostici, liječenju i rehabilitaciji onkoloških bolesnika. Posebno ćemo pažnju posvetiti nužnim promjenama na putu prema našem cilju – preciznoj onkologiji. Program je osmišljen tako da potiče interaktivne rasprave, razmjenu iskustava i suradnju među stručnjacima iz različitih disciplina. Kao i do sada, posebnu pažnju posvetiti ćemo uključivanju mladih stručnjaka, jer je njihova energija i inovativnost ključna za budućnost onkologije. Uz zdravstvene profesionalce raznih profila, poučeni lanjskim pozitivnim iskustvom, prostora za sudjelovanje će imati i oni najvažniji – naši bolesnici.

Uz bogat znanstveni i stručni program, osigurali smo i dovoljno vremena za neformalna druženja i umrežavanje, vjerujući da su i takvi trenuci ključni za jačanje naše zajednice i suradnje. Rovinj, sa svojim šarmom i ljepotom, pružit će nam savršenu pozadinu za ugodne i inspirativne dane kongresa.

Srdačno vas pozivamo da nam se pridružite u Rovinju i svojim prisustvom doprinesete uspjehu ovog važnog događaja.

Dobro došli na 16. Kongres Hrvatskog društva za internističku onkologiju HLZ-a s međunarodnim sudjelovanjem!

S poštovanjem,

Stjepko Pleština
Predsjednik Hrvatskog društva za internističku onkologiju
Hrvatskog liječničkog zbora (HDIO)



PROGRAM

14:00 - 20:00

REGISTRACIJA SUDIONIKA
Registration

15:00 - 16:00

SATELITSKI SIMPOZIJ ASTRAZENECA
SATELLITE SYMPOSIUM ASTRAZENECA

Panelisti/Panelists:

Zrna Antunac Golubić, Anuška Budisavljević, Snježana Dotlić, Višnja Matković, Marina Popović, Snježana Tomić

Lynparza: Desetljeće transformacije onkološkog liječenja
Lynparza: a decade of transforming the oncology landscape

16:00 - 16:10

OTVARANJE KONGRESA
CONGRESS OPENING

16:10 - 16:30

Mario Šekerija
Epidemiologija raka u Hrvatskoj
Cancer epidemiology in Croatia

16:30 - 16:50

Stjepan Gamulin
Personalizirana medicina i rak dojke, jučer, danas, sutra...
Personalized medicine and breast cancer, yesterday, today, tomorrow...

16:50 - 17:10

Eduard Vrdoljak
Zašto onkologija?
Why oncology?

17:10 - 17:30

Renata Kelemenić Dražin, Anuška Budisavljević
Izazovi onkologije kroz prizmu hrvatskih onkoloških profesionalaca - rezultati istraživanja

Challenges of oncology through the prism of Croatian oncology professionals – research results

17:30 - 17:45

PAUZA ZA KAVU I RAZGLEDAVANJE POSTERA
COFFEE BREAK AND POSTER VIEWING

17:45 - 18:45

PANEL RASPRAVA

Treba li Hrvatskoj akreditacija onkoloških ustanova, kako je i kada provesti, te kako pratiti ishode liječenja?

Does Croatia need accreditation of oncology institutions, how and when to implement it, and how to monitor treatment outcomes?

Predstavnici stručnih društava HR i SLO, MiZ, HZJZ, HZZO, udruge bolesnika

Representatives of professional societies of HR and SLO, MiZ, HZJZ, HZZO, patient association

18:45 - 19:00

Dragan Trivanović

Što je preostalo ciljati u tumorima pri kliničkom razvoju lijekova u budućnosti?

Drugging the 'undruggable' cancer targets

19:00 - 19:20

Scott Shepherd (UK)

Dešifriranje evolucijske dinamike raka za dobrobit pacijenata

Deciphering cancer evolutionary dynamics for patient benefit

19:20 - 19:50

SEKCIJA POTPORNE I PALIJATIVNE MEDICINE
SUPPORTIVE AND PALLIATIVE TREATMENT SESSION

Vjerujemo li u komplementarnu i integrativnu medicinu?
Do we believe in complementary and integrative medicine?
Nefarmakološke mjere u liječenju boli
Non-pharmacological measures in pain treatment

Sanja Pleština
Liječenje glazbom
Music therapy

Ivana Kukec
Liječenje kućnim ljubimcima
Pet therapy

20:00 - 21:00

DOMJENAK DOBRODOŠLICE
WELCOME DINNER

8:30 - 09:40

**SEKCIJA TUMORI SŽS, GLAVE I VRATA
CNS, HEAD&NECK SESSION**

**Moderatori/Moderators: Vesna Bišof, Ana Mišir Krpan,
Marija Skoblar Vidmar, Majana Soče, Ljubica Vazdar**

08:30 - 08:40

Maja Baučić

Konkomitantno ili sekvencijsko liječenje moždanih metastaza
Concomitant or sequential treatment of brain metastases

08:40 - 08:50

Marija Skoblar Vidmar

Recidivni gliomi: povezanost slikovnih i molekularnih biomarkera
Recurrent gliomas: association between imaging and molecular biomarkers

08:50 - 09:00

Ana Mišir Krpan

Ciljana terapija
Targeted therapy

09:00 - 09:10

Rasprava: tumori CNS – voditeljica Ana Mišir Krpan

Discussion: CNS tumors - moderator **Ana Mišir Krpan**

09:10 - 09:20

Majana Soče

Kako liječiti bolesnika s planocelularnim karcinomom glave i vrata nepodobnog za cisplatinu?
How to treat a patient with head and neck squamous cell carcinoma unsuitable for cisplatin?

09:20 - 09:30

Ljubica Vazdar

Ima li daljnjeg napretka u liječenju rekurentnog i/ili metastatskog planocelularnog karcinoma glave i vrata?

Are there any further advances in the treatment of recurrent and/or metastatic head and neck squamous cell carcinoma?

09:30 - 09:40

Rasprava - tumori glave i vrata: voditeljica Vesna Bišof
Discussion - head and neck tumors: moderator **Vesna Bišof**

09:40 - 11:10

SEKCIJA TUMORI PLUĆA LUNG TUMORS SESSION

Moderatori/Moderators: Marko Jakopović, Sanja Pleština, Miroslav Samaržija, Dragan Trivanović

Panelisti/Panels: Dorian Hiršl, Marko Jakopović, Tihana Pavić, Sanja Pleština, Miroslav Samaržija, Snježana Tomić, Dragan Trivanović

09:40 - 10:10

Paradigme liječenja raka pluća ranih stadija
Paradigms of early-stage lung cancer treatment

Marko Jakopović

Uvod i zaključci

Introduction and conclusions

Lidija Ljubičić, Jelena Viculin, Lela Bitar

Prikazi slučaja

Case presentations

10:10 - 10:40

Postaje li metastatski rak pluća kronična bolest?
Does metastatic lung cancer become a chronic disease?

Sanja Pleština

Uvod i zaključci

Introduction and conclusions

Iris Vuković, Ana Bačelić Gabelica, Nikolina Vorkapić

Prikazi slučaja

Case presentations

10:40 - 10:55

Dragan Trivanović

ADC u raku pluća

ADC in lung cancer

Lidija Ljubičić

Prikazi slučaja

Case presentations

10:55 - 11:10

Ivana Mikolašević

Modulacija crijevne mikrobiote putem fekalne transplantacije i
uspjeh liječenja imunoterapijom kod raka pluća

Modulation of gut microbiota by fecal transplantation and
success of immunotherapy treatment in lung cancer

Lana Bolf

Prikazi slučaja

Case presentations

11:10 - 11:30

PAUZA ZA KAVU I RAZGLEDAVANJE POSTERA
COFFEE BREAK AND POSTER VIEWING

11:30 - 12:00

SEKCIJA POTPORNE I PALIJATIVNE MEDICINE
SUPPORTIVE AND PALLIATIVE TREATMENT SESSION

Moderator/Moderator: Sanja Pleština

**Toksičnost imunoterapije u bolesnika izliječenih od
maligne bolesti**

Surviving with immunotoxicity

Ana Bačelić Gabelica

**Kronične nuspojave imunoterapije u bolesnika s ranim
stadijima bolesti**

Long-term effects of immunotherapy in patients treated
with early stage of the disease

Jasmina Marić Brozić, Suzana Mladinov, Anela Novak

Panel diskusija

Panel discussion

12:00 - 12:30

SATELITSKI SIMPOZIJ Roche
SATELLITE SYMPOSIUM Roche

Moderator/Moderator: Miroslav Samaržija

Predavači/Lecturers: Sanja Pleština, Marko Jakopović

**Sva lica lijekova Tecentriq i Alecensa: kontinuirana učinkovitost
i sigurnost u liječenju raka pluća**

Exploring Tecentriq and Alecensa: Sustained Efficacy and
Safety in Lung Cancer Treatment

12:30 - 13:15

SATELITSKI SIMPOZIJ AstraZeneca
SATELLITE SYMPOSIUM AstraZeneca

Lela Bitar, Ivo Dilber, Sanja Pleština

Suvremeni pristup liječenju raka pluća u stvarnoj kliničkoj praksi
Modern approaches to lung cancer treatment in real clinical practice

13:15 - 14:00

SATELITSKI SIMPOZIJ MSD
SATELLITE SYMPOSIUM MSD

Panelisti/Panelists: Marko Jakopović, Sanja Pleština,
Dragan Trivanović

Keytruda® kao "gamechanger" u liječenju NSCLC-a
Keytruda® as gamechanger in NSCLC treatment landscape

12:00 - 12:30

SATELITSKI SIMPOZIJ MSD
SATELLITE SYMPOSIUM MSD

Predavač/Lecturer: **Stjepko Pleština**

Keytruda (pembrolizumab) u liječenju tumora probavnih organa
Keytruda (pembrolizumab) in the treatment of gastrointestinal tumors

12:30 - 13:15

SATELITSKI SIMPOZIJ Swixx
SATELLITE SYMPOSIUM Swixx

Moderator/Moderator: **Stjepko Pleština**

Predavači/Lecturers: **Juraj Prejac, Vesna Bišof, Snježana Tomić**

Nova prilika u liječenju GI tumora
New opportunity in GI treatment

13:15 - 14:00

SATELITSKI SIMPOZIJ AstraZeneca
SATELLITE SYMPOSIUM AstraZeneca

Moderator/Moderator: **Stjepko Pleština**

Panelisti/Panelists: **Tajana Filipec Kanižaj, Luka Novosel, Juraj Prejac, Mislav Rakić**

Karcinomi hepatobilijarnog sustava - jučer, danas i sutra
Hepatobiliary Carcinoma – Yesterday, Today and Tomorrow

14:00 – 15:00

RUČAK
LUNCH

15:00 - 15:30

SATELITSKI SIMPOZIJ Johnson & Johnson
SATELLITE SYMPOSIUM Johnson & Johnson

Predavači/Lecturers: Marko Jakopović, Sanja Pleština, Snježana Tomić

Prvi leptir je poletio: PAPILLON
First butterfly is out: PAPILLON

15:30 - 15:50

SATELITSKI SIMPOZIJ Pfizer
SATELLITE SYMPOSIUM Pfizer

Najnoviji petogodišnji podaci praćenja iz ispitivanja CROWN uz stručnu perspektivu kliničkog učinka
Latest 5-year follow-up data from the CROWN trial with expert perspective on the clinical impact

Sanja Pleština

Lorlatinib u 1L ALK+ NSCLC - 5 godina kasnije...
1L lorlatinib in ALK+ NSCLC – 5 years later...

Suzana Mladinov

Promjena razgovora u 1L ALK+ NSCLC: donošenje odluka o liječenju
Changing the conversation in 1L ALK+ NSCLC: treatment decision-making

15:50 - 16:20

SATELITSKI SIMPOZIJ Medison Pharma
SATELLITE SYMPOSIUM Medison Pharma

Predavači/Lecturers: Marko Jakopović, Sanja Pleština

Cemiplimab u liječenju raka pluća nemalih stanica – kome i kada?

Cemiplimab in the treatment of non-small-cell lung cancer – for whom and when?

15:00 - 15:30

SATELITSKI SIMPOZIJ Genesis Phama
SATELLITE SYMPOSIUM Genesis Phama

**Predavači/Lecturers: Borislav Belev, Nikša Librenjak,
Anamarija Kovač Peić**

**Qinlock (ribretinib) u liječenju odraslih bolesnika s
uznapredovalim gastrointestinalnim stromalnim tumorom (GIST)**
Qinlock (ribretinib) in the treatment of adult patients with
advanced gastrointestinal stromal tumor (GIST)

15:30 - 15:50

SATELITSKI SIMPOZIJ Servier
SATELLITE SYMPOSIUM Servier

**Precizna medicina: od ranog otkrivanja do poboljšanja ishoda
u bolesnika s IDH mutacijama**
Precision Medicine: from early detection to improved outcomes
in patients with IDH mutations

Stjepko Pleština

IDH: Rijetka mutacija u rijetkim tumorima: kolangiokarcinom
IDH: A rare mutation in a rare cancer: Focus on
Cholangiocarcinoma

Jasna Radić

IDH: Česta mutacija u rijetkim tumorima: gliomi
IDH: A common mutation in a rare cancer: Focus on Glioma

DVORANA A
HALL A

PETAK / FRIDAY
11. 10. 2024.

15:50 - 16:20

SATELITSKI SIMPOZIJ Amgen
SATELLITE SYMPOSIUM Amgen

Napredak u mKRK: Personalizirani pristupi liječenja
Advancements in mCRC: Personalized treatment approaches

Moderator/Moderator: Borislav Belev

Borislav Belev

Personalizirana strategija liječenja mKRK
Personalised mCRC treatment strategy

Juraj Prejac

Optimalno liječenje bolesnika s mKRK
Optimal treatment of mCRC patients

Nikša Librenjak

Naša iskustva liječenja mKRK
Our experiences of mCRC treatment

DVORANE 5 & 6
MEETING ROOMS 5 & 6

PETAK / FRIDAY
11. 10. 2024.

15:00 – 16:00

RADIONICA „Tumorska genetika u svakodnevnoj praksi“
WORKSHOP „Tumor genetics in routine clinical practice“

Marina Popović, Ivana Rako, Kristina Gotovac Jerčić,
Natalija Dedić Plavetić

16:20 - 16:35

PAUZA ZA KAVU I RAZGLEDAVANJE POSTERA
COFFEE BREAK AND POSTERS

16:35 - 18:05

SEKCIJA PROBAVNI TUMORI
DIGESTIVE TUMORS SESSION

Moderatori/Moderators: Borislav Belev, Janja Ocvirk, Stjepko Pleština

16:35 - 17:05

Novosti u imunoterapiji tumora gornjeg dijela probavnog trakta
News in immunotherapy of tumors of the upper part of the digestive tract

Domina Kekez

Prikaz slučaja

Case report

Panelisti/Panelists: Zlatko Marušić, Juraj Prejac, Jasna Radić

17:05 - 17:35

Periampularni karcinom – pristup liječenju
Periampullary carcinoma – treatment approach

Nikša Librenjak

Prikaz slučaja

Case report

Panelisti/Panelists: Ana Marija Alduk, Pave Markoš, Nikša Librenjak, Zlatko Marušić, Jurica Žedelj

17:35 - 18:05

Rijetki tumori
Rare tumors

Tatjana Ladenhauser

Prikaz slučaja

Case report

DVORANA A
HALL A

PETAK / FRIDAY
11. 10. 2024.

Borislav Belev
GIST – “State of art”

18:15 - 19:00

SKUPŠTINA HDIO (članovi HDIO)
HDIO ASSEMBLY (HDIO members)

08:10 - 08:30

SATELITSKI SIMPOZIJ NOVARTIS
SATELLITE SYMPOSIUM NOVARTIS

TAFINLAR + MEKINIST – kombinacija koja vam pruža pouzdanje
za život pun mogućnosti

TAFINLAR + MEKINIST- with confidence comes a life full
of possibilities

Luka Simetić

1st to 10 – Prva i jedina ciljana terapija sa 10-godišnjim
podacima u adjuvantom liječenju melanoma stadija III

1st to 10 – First and only targeted therapy for stage III
adjuvant melanoma with 10-year data

Jasmina Marić Brozić

Tafinlar + Mekinist u liječenju metastatskog melanoma – neka
Vas vodi Vaše kliničko iskustvo

Tafinlar+ Mekinist in metastatic melanoma- let your clinical
experience guide you

08:30 - 09:30

SEKCIJA MELANOM, MEZENHIMALNI I RIJETKI TUMORI
MELANOMA, SARCOMA AND RARE TUMORS SESSION

MELANOM
MELANOMA

Moderatori/Moderators: **Daška Štulhofer Buzina, Luka Simetić**
Panelisti/Panelists: **Daška Štulhofer Buzina, Nina Dabelić,**
Luka Simetić, Krešimir Blažičević

08:30 - 08:45

Daška Štulhofer Buzina

Melanom - nova, stara WHO klasifikacija
Melanoma- new, old WHO classification

08:45 - 09:05

Nina Dabelić

Novosti u liječenju melanoma – ESMO 2024.

Novelties in melanoma treatment – ESMO 2024

09:05 - 09:10

Diskusija

Discussion

09:10 - 09:20

Krešimir Blažićević

Naša prva iskustva s kombinacijskom imunoterapijom s ipilimumabom i nivolumabom u metastatskom melanomu

Our first experiences with combination immunotherapy with ipilimumab and nivolumab in metastatic melanoma

09:20 - 09:30

Kata Međugorac

Prikaz slučaja – Kompletni odgovor na kombinacijsku imunoterapiju s ipilimumabom i nivolumabom kod metastatskog mukozalnog melanoma

Case report – complete response to combination immunotherapy with ipilimumab and nivolumab in metastatic mucosal melanoma

09:30 - 10:15

SATELITSKI SIMPOZIJ MSD
SATELLITE SYMPOSIUM MSD

Panelisti/Panelists: Janja Ocvirk, Jasmina Marić Brozić, Luka Simetić

Promjena paradigme liječenja melanoma stadija IIB, IIC, ili III uz lijek Keytruda

Changing the treatment paradigm for stage IIB, IIC, or III melanoma with Keytruda

10:15 - 10:45

SATELITSKI SIMPOZIJ Medison Pharma
SATELLITE SYMPOSIUM Medison Pharma

Nina Dabelić

Melanom uvee i melanom kože: jedna bolest, 2 različita lica
Uveal melanoma and skin melanoma: one disease,
2 different faces

Luka Simetić

Tebentafusp: iskustva KBC Zagreb u liječenju melanoma uvee
Tebentafusp: KBC Zagreb experience in the treatment
of uveal melanoma

09:30 - 10:15

SATELITSKI SIMPOZIJ Eli Lilly
SATELLITE SYMPOSIUM Eli Lilly

Diskusija eksperata o izboru CDK4/6i u metastatskom
i ranom raku dojke
Expert Discussion on the CDK4/6i Choices in MBC & EBC

Moderator/Moderator: **Stjepko Pleština**

09:30 - 09:35

Stjepko Pleština
Uvodna riječ moderatora
Opening words from moderator

09:35 - 09:45

Matteo Lambertini
Talijansko iskustvo s abemaciclibom u metastatskom
i ranom raku dojke
Italian Experience with Abemaciclib in MBC and EBC

09:45 - 10:15

**Eduard Vrdoljak, Natalija Dedić Plavetić, Matteo Lambertini,
Stjepko Pleština**
Diskusija eksperata: sličnosti i razlike hrvatskih
i talijanskih iskustava
Open Panel Discussion: Similarities and Differences between
Croatian and Italian Experience

10:15 - 10:45

SATELITSKI SIMPOZIJ Pfizer
SATELLITE SYMPOSIUM Pfizer

Krenimo na putovanje usmjereno na pacijenta
Embarking on a patient-centric journey

Ljubica Vazdar

Ishodi liječenja u starijih bolesnika s mBC-om koji su primali palbociclib

Treatment outcomes in older patients with mBC receiving palbociclib

Natalija Dedić Plavetić

Trenutačni obrasci i izazovi u liječenju bolesnika s mTNBC-om

Current treatment patterns and challenges in the treatment landscape of mTNBC patients

Mario Nalbani

Priča o 'Mari' – naše iskustvo s talazoparibom

Story about 'Mara' – our experience with talazoparib

10:45 - 11:00

PAUZA ZA KAVU I RAZGLEDVANJE POSTERA
COFFEE BREAK AND POSTER VIEWING

11:00 - 13:15

SEKCIJA RAK DOJKE
BREAST CANCER SESSION

**Moderatori/Moderators: Anuška Budisavljević,
Natalija Dedić Plavetić, Tajana Silovski**

11:00 - 11:05

Uvod u sekciju
Introduction to the Session

11:05 - 11:25

Mario Nalbani
Pregled novosti SABCS, ESMO BREAST, ASCO i ESMO
Overview of SABCS, ESMO BREAST, ASCO and ESMO news

11:25 - 11:45

Matteo Lambertini (Italy)
Onkofertilitet u eri nove adjuvantne terapije raka dojke
Oncofertility in the era of novel adjuvant therapeutics for breast cancer

11:45 - 12:15

Panel diskusija: Nude li kliničke studije odgovore na ključne di(tri)leme u multimodalitetnom liječenju ranog raka dojke?
Panel discussion: Do clinical studies offer answers to key di(tri)lemmas in the multimodality treatment of early breast cancer?

Novi standardi u pristupu aksili u ranom raku dojke
New standards in treatment of axilla in early breast cancer

Moderatorica/Moderator: Anuška Budisavljević

Anđela Nadinić
Predstavljanje slučaja
Case report

**Panelisti/Panelists: Marina Popović,
Ivana Božović Spasojević (Srbija),
Maria Cristina Leonardi (Italija),
Katarina Antunac, Ivan Milas, Ivan Marković (Srbija)**

12:15 - 12:45

**Panel diskusija: HR+ eBC: Gužva u 16-stercu, izazovi
sekvenciranja terapije HR+ eBC: CDK4/6i, PARP-ovi i inhibitori
kontrolnih točaka**

Panel discussion: Crowd in penalty area, challenges of
sequencing HR+ eBC therapy: CDK4/6i, PARPs and checkpoint
inhibitors

Moderatorica/Moderator: Tajana Silovski

Katarina Čular
Predstavljanje slučaja
Case report

**Panelisti/Panelists: Marijana Jazvić, Nikolina Lonjak,
Snježana Tomić, Ljubica Luetić Cavor, Ivan Milas,
Marko Granić**

12:45 - 13:15

**Panel diskusija: eTNBC: Terapija ranog trostruko negativnog raka
dojke, eskalacija i deeskalacija, kada je manje – više?**

Panel discussion: Tailoring therapy for early triple negative
Breast Cancer, Escalation and De-escalation,
When is less – more?

Moderatorica/Moderator: Natalija Dedić Plavetić

Martina Mladinović
Predstavljanje slučaja
Case report

Panelisti/Panelists: **Simona Borštnar** (Slovenija),
Matteo Lambertini (Italija), **Stela Bulimbašić**,
Marko Petrovečki, **Anto Dujmović**, **Berisa Hasanbegović** (BiH)

13:15 - 13:30

Josip Joachim Grah (Austria)

Radioterapija/reiradijacija inoperabilnog raka dojke uz primjenu površinske hipertermije

Radiotherapy/reirradiation of inoperable breast cancer using surface hyperthermia

13:30 - 14:00

SEKCIJA POTPORNE I PALIJATIVNE MEDICINE
SUPPORTIVE AND PALLIATIVE TREATMENT SESSION

Moderator/Moderator: **Sanja Pleština**

Trebaju li bolnicama odjeli akutne palijativne medicine?
Do hospitals need acute palliative medicine units?

13:30 - 13:45

Maja Ebert Moltara

Akutni palijativni odjel u tercijarnom centru OI Ljubljana

Acute palliative department at the Ljubljana Oncology Institute

13:45 - 14:00

Panel diskusija/Panel discussion: **Maja Ebert Moltara**,
Marin Golčič, **Ivana Kukec**, **Gordana Štirjan Marković**,
Ilijan Tomaš, **Tomislav Omrčen**

14:05 - 15:00

RUČAK
LUNCH

15:00 - 15:45

SATELITSKI SIMPOZIJ AstraZeneca
SATELLITE SYMPOSIUM AstraZeneca

Tajana Silovski, Matteo Lambertini

Liječenje HER2+ i HER2Low metastatskog karcinoma dojke
Treatment of HER2+ and HER2Low mBC

15:45 - 16:45

SEKCIJA MLADIH
SESSION OF YOUNG ONCOLOGISTS

Moderator/Moderator: Martina Mladinović

Alternativna medicina - "Doktore, smijem li ja to uzimati?"
Alternative medicine – „Doc, can I take this?“

15:45 - 15:57

Lea Ledinsky

Alternativna medicina - Jesmo li spremni na izazove?
Alternative medicine - Are we ready for challenges?

15:57 - 16:12

Dominik Strikić

Farmakologija alternative: od začina do atmosfere
Pharmacology of alternatives: from spices to atmosphere

16:12 - 16:42

Panel rasprava/Panel discussion

Moderator/Moderator: Iva Nikles

**Panelisti/Panelists: Teo Buhovac, Andrea Brajković,
Dominik Strikić, Ida Čepulić Maravić**

16:42 - 16:45

Martina Mladinović

Zaključak

Conclusion

16:45 - 17:30

SATELITSKI SIMPOZIJ Swixx

SATELLITE SYMPOSIUM Swixx

Natalija Dedić Plavetić, Tajana Silovski

Novi standard preživljavanja kod HER2+ metastatskog
raka dojke

New standard for survival in HER2+ metastatic breast
cancer

15:00 - 15:30

SATELITSKI SIMPOZIJ Johnson & Johnson
SATELLITE SYMPOSIUM Johnson & Johnson

Proširimo horizonte u liječenju uznapredovalog raka prostate
Getting ahead of advanced prostate cancer

Milena Gnjidić

Paradigme u liječenju mHORP-a
Paradigms in the treatment of mHSPC

Renata Kelemenić-Dražin

Osigurajmo budućnost bolesnicima s mKRRP-om
pozitivnih BRCA1/2 mutacija
The future is clear with Akeega

16:45 - 17:15

SATELITSKI SIMPOZIJ Astellas
SATELLITE SYMPOSIUM Astellas

Moderator/Moderator: **Borislav Belev**

Pomicanje granica u liječenju urotelnog karcinoma
i raka prostate

Breaking new ground in treatment of urothelial carcinoma
and prostate cancer

Dora Niedersüß-Beke

Novi modaliteti: Optimiziranje 1L liječenja LA/mUC
Emerging modalities: Optimizing 1L treatment of LA/mUC

Milena Gnjidić

Krenimo na novo putovanje u liječenju raka prostate
EMBARK to new journey in prostate cancer

DVORANA B
HALL B

SUBOTA / SATURDAY
12. 10. 2024.

17:15 - 17:35

SATELITSKI SIMPOZIJ Bausch Health
SATELLITE SYMPOSIUM Bausch Health

Borislav Belev

Uloga Cabometyxa u liječenju bolesnika s uznapredovalim
karcinomom bubrežnih stanica

The role of Cabometyx in the treatment of patients with
advanced renal cell carcinoma

DVORANA 6
MEETING ROOM 6

SUBOTA / SATURDAY
12. 10. 2024.

17:15 - 17:45

Astellas SASTANAK SA STRUČNJAKOM
Astellas MEET THE EXPERT

Marijana Jazvić, Dora Niedersüß-Beke

Uvidi u klinička iskustva s lijekom PADCEV u 2L LA/mUC
Insights in clinical experiences with PADCEV in 2L LA/mUC

17:30 - 17:45

PAUZA ZA KAVU I RAZGLEDAVANJE POSTERA
COFFEE BREAK AND POSTER VIEWING

17:45 - 18:30

SATELITSKI SIMPOZIJ Novartis
SATELLITE SYMPOSIUM Novartis

**Natalija Dedić Plavetić, Eduard Vrdoljak, Stjepko Pleština,
Ljubica Vazdar, Tajana Silovski, Anuška Budisavljević**

Proširimo vidike i mogućnosti liječenja HR+/HER2- ranog
raka dojke ribociklibom

Let's expand the horizons and treatment options for
HR+/HER2- early breast cancer with ribociclib

18:30 - 19:00

SATELITSKI SIMPOZIJ Medicopharmacia
SATELLITE SYMPOSIUM Medicopharmacia

Izazovi u liječenju TNBC-a

Challenges In the treatment of TNBC

Branka Petrić Miše

Izazovi u liječenju TNBC-a – što bi bio napredak?

Challenges in the treatment of TNBC – what would be
the progress?

Tajana Silovski

Život s metastatskim TNBC-om – prikaz slučaja

Living with metastatic TNBC – a case report

Rasprava

Discussion

19:00 - 19:30

MEDICINSKI SIMPOZIJ Roche
SATELLITE SYMPOSIUM Roche

Predavači/Lecturers: Natalija Dedić Plavetić, Ljubica Vazdar

Nova mogućnost ciljanog liječenja bolesnica s HR+ rakom dojke
New option for targeted treatment of HR+ BC patients

21.00 - 22:00

KONGRESNA VEČERA
CONGRESS DINNER

08:15 - 09:00

SATELITSKI SIMPOZIJ Merck
SATELLITE SYMPOSIUM Merck

Jure Murgić, Milena Gnjidić

Bavencio u liječenju karcinoma urotela s našim iskustvima
Bavencio in the treatment of urothelial carcinoma with our experiences

09:00 - 10:30

SEKCIJA UROGENITALNI TUMORI
UROGENITAL TUMORS SESSION

Moderatori/Moderators: Borislav Belev, Filip Grubišić Čabo

09:00 - 09:40

Novosti u liječenju karcinoma prostate
Innovations in prostate cancer treatment
Liječenje lokalnog visokorizičnog karcinoma prostate
Treatment of high-risk local prostate cancer

Lea Toula

Prikaz slučaja
Case report

**Panelisti/Panelists: Mladen Solarić, Maja Baučić,
Lana Jajac Bručić, Tomislav Kuliš**

Kako sekvencionirati liječenje u mCRPC?
How to sequence treatment in mCRPC?

Ivan Vičić

Prikaz slučaja
Case report

**Panelisti/Panelists: Tomislav Omrčen, Iva Nikles,
Mislav Čonkaš**

09:40 - 10:10

Novosti u liječenju urotelnog carcinoma
New developments in the treatment of urothelial carcinoma

Antonija Salamun

Prikaz slučaja
Case report

**Panelisti/Panelists: Marijana Jazvić, Zrna Antunac-Golubić,
Mirko Bakula, Anamarija Kovač Peić**

10:10 - 10:30

Rijetki tumori - adrenalni karcinom (ACC)
Rare tumors - adrenal carcinoma (ACC)

Predavač/Lecturer: Ana Koši Kunac

**Panelisti/Panelists: Darko Kaštelan, Vivian Milotić,
Stela Bulimbašić, Milena Gnjidić**

10:30 - 10:45

PAUZA ZA KAVU I RAZGLEDAVANJE POSTERA
COFFEE BREAK AND POSTER VIEWING

10:45 - 11:30

SATELITSKI SIMPOZIJ AstraZeneca
SATELLITE SYMPOSIUM AstraZeneca

**Panelisti/Panelists: Kristina Katić, Marko Klarić,
Marija Milković Periša**

DUO-E: Novi smjer u liječenju raka endometrija
DUO-E: setting a new course in endometrial cancer

11:30 - 12:30

SEKCIJA GINEKOLOŠKIH TUMORA
SESSION OF GYNECOLOGICAL TUMORS

Moderator/Moderator: Višnja Matković
Panelisti/Panelists: Marija Milković Periša,
Branka Petrić Miše, Jasna Marušić, Josip Kuharić

11:30 - 11:40

Maja Kolak

Novosti u liječenju lokalno uznapredovalog karcinoma vrata maternice – INTERLACE studija

News in the treatment of locally advanced cervical cancer – INTERLACE study

11:40 - 11:50

Branka Petrić Miše

Ne-epitelni karcinomi jajnika – liječenje

Non-epithelial ovarian cancers – treatment

11:50 - 12:00

Ana Magličić

Liječenje sarkoma uterusa

Treatment of uterine sarcoma

12:00 - 12:15

Marina Popović

Uloga ambulante za genetsko savjetovanje u ginekološkoj onkologiji

The role of the outpatient clinic for genetic counseling in gynecological oncology

12:15 - 12:30

Panel rasprava

Panel discussion

12:30 - 13:30

BEST OF HDIO - Proglašenje najboljih radova i zatvaranje Kongresa

BEST OF HDIO - Poster Awards and Closing Word

SEKCIJA ZA PACIJENTE
SESSION FOR PATIENTS

**„Partnerstvo za bolje
ishode liječenja“**

**„Partnership for Better
Treatment Outcomes“**

15:00 - 15:05

Stjepko Pleština

Otvaranje Sekcije za pacijente

Session opening

15:05 - 15:30

Dragan Trivanović

Promocija ESMO vodiča za pacijente „Kako rak može utjecati na zdravlje kostiju?“

Promotion of the ESMO patient guide „How can cancer affect bone health?“

15:30 - 15:50

Nikolina Lonjak

Praćenje oboljelih nakon završenog inicijalnog liječenja

Follow-up of patients after completion of initial treatment

15:50 - 16:10

Iva Skočilić i Marin Golčić

Kvaliteta života onkoloških bolesnika

Quality of Life of Oncology Patients

16:10 - 16:30

Gordana Kuterovac Jagodić

Psihoonkologija u službi boljih ishoda i kvalitete života bolesnika

Psycho-Oncology in Support of Better Outcomes and Quality of Life for Patients

16:30 - 17:00

PAUZA ZA KAVU

COFFEE BREAK

17:00 - 17:20

Luka Simetić

Precizna medicina i personalizirano liječenje

Precision Medicine and Personalized Treatment

17:20 - 17:40

Mario Nalbani

Prediktivni testovi u liječenju raka dojke

Predictive Tests in Breast Cancer Treatment

17:40 - 18:30

Okrugli stol - Ishodi onkološkog liječenja

Round Table - Outcomes of Oncology Treatment



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HDIO 2024

SAŽETCI PREDAVANJA | LECTURE ABSTRACTS

IZAZOVI ONKOLOGIJE KROZ PRIZMU HRVATSKIH ONKOLOŠKIH PROFESIONALACA – REZULTATI ISTRAŽIVANJA

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• Odjel za hematologiju, onkologiju i kliničku imunologiju i alergologiju

² Opća bolnica Pula

• Odjel za internističku onkologiju s hematologijom

Uvod: Nakon istraživanja Europskog društva za medicinsku onkologiju (ESMO W4O) iz 2016. i 2021. koja su pokazala kako postoji rodni jaz u onkološkoj karijeri proveli smo istraživanje u hrvatskoj onkološkoj zajednici s ciljem identificiranja izazova s kojima se onkološki profesionalci susreću u svojoj karijeri.

Materijali i metode: Putem Google forms *online* ankete dizajnirane analizom sadržaja literature provedeno je istraživanje s pitanjima o utjecaju političke pripadnosti, seksualne orijentacije, vjere i spola na razvoj karijere. Rezultati su analizirani prema spolu i dobi ispitanika.

Rezultati: Prikupljeno je 206 odgovora od čega je 74% ispitanika bilo ženskog, a 26% muškog spola. U istraživanje su bili uključeni svi profesionalci koji se bave onkologijom. Najviše, 55% je bilo internističkih onkologa i onkologa radioterapeuta, potom slijede specijalisti patologije i citologije (15%), kirurški onkolozi (5%), radiolozi (4%) i ostali. Značajan udio ispitanika (41%) je imao ≤ 40 godina i nalazi se u ranoj fazi svoje karijere (18% specijalizanata, 43% ispitanika se onkologijom bavi manje od 10 godina). Ispitanici su gotovo jednako podijeljeni između rada u kliničkim bolničkim centrima (42%) i općim/županijskim bolnicama (39%), a 19% ispitanika radi u farmaceutskoj/biotehnološkoj tvrtki. Spol je u trećine ispitanika imao umjeren (22%) ili velik utjecaj (10%) na razvoj karijere, za razliku od političke ili vjerske pripadnosti ili seksualne orijentacije. Ispitanici kao glavne prepreke za postizanja ravnopravnosti spolova navode: nedostatak ravnoteže između poslovnog i privatnog života (69%), društvene pritiske (46%), nesvjesnu pristranost (44%) i nedostatak razvoja vodstva za žene (33%). 35% ispitanika je izjavilo kako je zbog spola doživjelo diskriminaciju na radnom mjestu dok je 34% ispitanika navelo spol i kao diskriminirajući faktor u interakciji s pacijentima. Čak 38% ispitanika je doživjelo uznemiravanje ili je svjedočilo (47%) uznemiravanju na radnom mjestu, ali ga je prijavilo samo 11% ispitanika (znatno manje u odnosu provedeno istraživanje ESMO W4O; 2016. 41%, 2021. 50%). Iako je većini ispitanika (80%) važno napredovanje u karijeri čak trećina ispitanika (34%) je tek djelomično zadovoljno ili uopće nije zadovoljno napredovanjem u svojoj karijeri. Također se većina ispitanika (86%) suočila s preprekama u napredovanju u karijeri pri čemu je najčešća pronalaznja ravnoteže između posla i obiteljskog života (56%), a čak 28% ispitanika je kao prepreku navelo neprijateljsko okruženje na radnom mjestu i mobing. 59% ispitanika smatra kako je značajno opterećeno administracijom. U prilog opterećenosti onkologa govori i podatak kako 61% ispitanika radi više od 8 radnih sati dnevno, a samo 14% ispitanika ne radi vikendom ili slobodnim danima.

Zaključak: Spol ostaje glavna prepreka napredovanju u karijeri u onkologiji, kako u onkološkoj zajednici u svijetu, tako i u Hrvatskoj. Spol je također značajan diskriminirajući faktor na radnom mjestu, ali i u interakciji s pacijentima. Nedostatak ravnoteže između poslovnog i privatnog života najveći je izazov u karijeri i glavna prepreka za postizanje ravnopravnosti spolova. Zabrinjava visoka stopa uznemiravanja na radnom mjestu i niska stopa prijavljivanja neprikladnog ponašanja. Administracija uz prekovremeni rad te rad vikendom i slobodnim danima predstavlja značajno opterećenje onkologa. Rezultati istraživanja pružaju nove dokaze i naglašavaju područja za buduće intervencije za podršku jednakosti i raznolikosti u onkološkom razvoju karijere.

Cljučne riječi: rodni jaz, onkologija, anketa, karijera, uznemiravanje na radnom mjestu

CHALLENGES OF ONCOLOGY THROUGH THE PRISM OF ONCOLOGISTS – RESEARCH RESULTS

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Background: Following the 2016 and 2021 European Society for Medical Oncology (ESMO W4O) surveys, which showed a gender gap in the oncology career, we surveyed the Croatian oncology community to identify challenges facing oncology professionals.

Materials and methods: Through an online Google Forms survey designed by analyzing the content of the literature, research was conducted with questions about the influence of political affiliation, sexual orientation, religion and gender on career development. The results were analyzed according to the gender and age of the respondents.

Results: 206 responses were collected, of which 74% were women and 26% were men. All oncology specialists were involved in the research. At most, 55% were medical oncologists and radiation oncologists, followed by specialists in pathology and cytology (15%), surgical oncologists (5%), radiologists (4%) and others. A significant proportion of respondents (41%) were ≤40 years old and were in the early phase of their career (18% of residents, 43% of respondents have been working in oncology for less than 10 years). Respondents are almost equally divided between working in a Clinical Hospital Center (42%) and a General/County Hospital (39%), and 19% of respondents work in a pharmaceutical/biotechnology company. Gender had a moderate (22%) or large (10%) influence on career development for a third of respondents, in contrast to political or religious affiliation or sexual orientation. Respondents cited as the main obstacles to achieving gender equality: lack of balance between work and private life (69%), social pressures (46%), unconscious bias (44%) and lack of leadership development among women (33%). 35% of respondents state that they have experienced discrimination in the workplace because of their gender, while 34% of respondents state that gender is a discriminatory factor in their interactions with patients. 38% of respondents experienced harassment or witnessed (47%) harassment in the workplace, but only 11% of respondents reported it (significantly less compared to the ESMO W4O survey; 41% in 2016, 50% in 2021). Although career advancement is important to the majority of respondents (80%), a third of respondents (34%) are only partially or not at all satisfied with their career advancement. Also, the majority of respondents (86%) encountered obstacles in career advancement, the most common of which was finding a balance between work and family life (56%). 28% of respondents cited a hostile workplace environment and mobbing as an obstacle. 59% of respondents believe that they are significantly burdened by the administration. In support of the workload of oncologists is the fact that 61% of respondents work more than 8 working hours a day, and only 14% of respondents do not work on weekends or days off.

Conclusions: Gender remains the main obstacle to advancement in the oncology career, both in the oncology community in the world and Croatia. Gender is also a significant discriminating factor in the workplace, but also in interaction with patients. The lack of balance between work and private life is the biggest challenge in a career and the main obstacle to achieving gender equality. The high rate of harassment in the workplace and the low rate of reporting inappropriate behavior is a concern. Administration along with overtime work and work on weekends and days off represents a significant burden for oncologists. The research findings provide new evidence and highlight areas for future interventions to support equity and diversity in oncology career development.

Keywords: gender gap, oncology, survey, career, workplace harassment

SEKCIJA POTPORNE I PALIJATIVNE MEDICINE / SUPPORTIVE AND PALLIATIVE TREATMENT SESSION

TERAPIJA KUĆNIM LJUBIMCIMA U OSOBA S RAKOM

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Terapija kućnim ljubimcima (engl. PET therapy; Animal-assisted therapy, AAT) koristi trenirane životinje, najčešće pse, za pružanje terapijskih interakcija koje mogu ublažiti bol i poboljšati emocionalnu dobrobit bolesnika.

AAT se pokazala korisnom u smanjenju boli kod pacijenata s rakom kroz smanjenje anksioznosti i stresa, što može umanjiti percepciju boli. Terapija životinjama potiče otpuštanje hormona poput oksitocina i endorfina, što doprinosi osjećaju opuštenosti i smanjenju boli. Studije su pokazale da pacijenti uključeni u AAT programe ponekad trebaju manje lijekova protiv bolova, što naglašava potencijal ove terapije kao komplementarne metode u liječenju boli.

AAT dovodi i do poboljšanje emocionalnog stanja pacijenata, smanjuje umor i osjećaja depresije, smanjuje emocionalni distress, te poboljšava kvalitetu života u osoba s rakom.

AAT može se primjenjivati u onkološkim odjelima, dnevnim bolnicama, hospicijima i odjelima za palijativnu skrb.

Zaključno, terapija uz pomoć životinja nudi obećavajući pristup u upravljanju boli kod osoba s rakom, uz minimalne nuspojave i potencijalno smanjenje upotrebe lijekova protiv bolova.

Ključne riječi: terapija životinjama, bol, onkološki pacijenti, suportivna terapija

PET THERAPY IN PERSONS WITH CANCER

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Pet therapy (also known as Animal-assisted therapy, AAT) involves using trained animals, most commonly dogs, to provide therapeutic interactions that can alleviate pain and improve patients' emotional well-being.

AAT has proven beneficial in reducing pain in cancer patients by lowering anxiety and stress levels, which can decrease the perception of pain. Animal therapy stimulates the release of hormones such as oxytocin and endorphins, contributing to relaxation and pain relief. Studies have shown that patients participating in AAT programs sometimes require less pain medication, highlighting the potential of this therapy as a complementary method in pain management.

AAT also leads to an improvement in patients' emotional state, reduces fatigue and feelings of depression, decreases emotional distress, and enhances the quality of life in persons with cancer.

AAT can be applied in oncology wards, day hospitals, hospices, and palliative care units.

In conclusion, animal-assisted therapy offers a promising approach to pain management in cancer patients, with minimal side effects and the potential to reduce the use of pain medication.

Keywords: pet therapy, pain, cancer patient, supportive therapy

SEKCIJA TUMORI SŽS, GLAVE I VRATA / CNS, HEAD AND NECK SESSION

RECURRENT GLIOMA: A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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Molecular biomarkers have fundamentally changed the understanding of glioma over the last decade. Accordingly, the fifth edition of the World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5) incorporates numerous molecular biomarkers with clinicopathologic utility that are important for more accurate classification of CNS neoplasms. Molecular biomarkers also improve diagnostic accuracy and influence the course of treatment by changing treatment recommendations. A marker of particular importance is isocitrate dehydrogenase (IDH). Mutations in genes encoding *IDH* are known to play a crucial role in the classification of gliomas. IDH mutant (IDHm) glioma generally exhibits a better disease outcome than IDH wild type (IDHwt). In adults, diffuse gliomas have been divided into three types according to the new classification: (1) astrocytoma, IDHm; (2) oligodendroglioma, IDHm and 1p/19q-codeleted; and (3) glioblastoma, IDHwt.

The treatment of gliomas includes maximal surgical resection, possibly followed by radiotherapy (RT) and chemotherapy with either procarbazine/lomustine/vincristine (PCV) or temozolomide (TMZ). Due to the proliferative, radioresistant, and chemoresistant nature of the gliomas and high levels of intratumoral heterogeneity, the disease often recurs, and the possibilities of additional treatment are very limited.

The evaluation of treatment response remains a challenge in glioma cases because the neuro oncological therapy can lead to the development of treatment-related changes (TRC) that mimic true progression (TP). Positron emission tomography (PET) using O-(2-[¹⁸F] fluoroethyl)-L-tyrosine (¹⁸F-FET) has been shown to be a useful tool for detecting TRC and TP.

The results of our published study indicated that the diagnostic value of static and dynamic biomarkers of ¹⁸F-FET PET for discrimination between TRC and TP depends on the IDH mutation status of the tumor. Dynamic ¹⁸F-FET PET acquisition proved helpful in the IDHwt subgroup, as opposed to the IDHm subgroup, providing an early indication to discontinue dynamic imaging in the IDHm subgroup.

Keywords: glioma, isocitrate dehydrogenase, positron emission tomography, biomarkers

CILJANA TERAPIJA

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Ozbiljnije poglavlje o ciljanoj terapiji tumora mozga počinje 2022. odobravanjem BRAF/MEK inhibitora temeljem *BRAF* V600E mutacije neovisno o primarnom sijelu tumora. U gotovo 90% pedijatrijskih glijalnih tumora dolazi do alteracije u MAPK signalnom putu s time da je u većine prisutna *BRAF* fuzija (35%), potom *BRAF* V600E mutacija (17%) i *NFI* alteracija (17%). U adolescenata i mladih odraslih mutacija *BRAF*V600E prisutna je u oko 10% bolesnika. Temeljem studija ROAR, NCI MATCH i CTMT212X2101 uočena je visoka stopa odgovora od 33% za gliome visokog gradusa i 50% za gliome niskog gradusa. BRAF/MEK inhibitori od iznimne su važnosti u djece, bolesnika s difuznim gliomima gdje resekcija nije moguća, gdje je zračenje velikog volumena povezano s nuspojavama i kod leptomeningealnih tumora. U bolesnika s progresijom bolesti u travnju 2024. odobren je lijek tovorafenib koji djeluje kao pan-RAF inhibitor uz ukupnu stopu odgovora od 51% (FIREFLY-1). Gliomi niskog gradusa pojavljuju se u mlađim dobnim skupinama, prosječno između 30. i 50.

godine. Većina glijalnih tumora niskog gradusa ima *IDH1* mutaciju u kodonu R132, a 10–15% oboljelih mlađih od 55 godina imaju *IDH2* mutaciju u kodonu R172. Posljedica mutacija je intracelularno nakupljanje 2-hidroksiglutarata, metabolita koji potiče proliferacijsku aktivnost stanice. Gliome niskog gradusa dijelimo na tumore niskog i visokog rizika. Tumori visokog rizika nadalje su predmet radioterapije i kemoterapije. Kako tumori niskog rizika imaju dulje očekivano trajanje života veća je briga o akutnim i kasnim posljedicama zračenja i kemoterapije koje smanjuje kvalitetu života. INDIGO je randomizirana studija faze 3 koja pozicionira vorasidenib u prvu liniju liječenja IDH mutiranih glijalnih tumora gradusa 2. Primarni cilj studije PFS je 27,7 mjeseci u odnosu na 11,1. mj u skupini koja je dobivala placebo (HR 0.39, $P=0,000000067$). Ključni sekundarni cilj studije je vrijeme do sljedeće intervencije i statistički značajno favorizira vorasidenib (HR, 0,26, $P=0,000000019$). Registracijski postupak je u tijeku.

Ključne riječi: gliomi, BRAF, izocitrat dehidrogenaza, ciljana terapija

TARGETED THERAPY

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BRAF/MEK inhibitors are approved based on the *BRAF* V600E mutation, regardless of the primary tumor site. In almost 90% of pediatric glial tumors there is an alteration in the MAPK signaling pathway, with *BRAF* fusion, *BRAF* V600E mutation, and *NF1* alteration present in the majority. In adolescents and young adults, the *BRAF* V600E mutation is present in about 10% of patients. Based on the ROAR, NCI MATCH, and CTMT212X2101 studies, a high response rate of 33% for high-grade gliomas and 50% for low-grade gliomas (LGG) was observed. In patients with disease progression, a pan-RAF inhibitor tovorafenib was approved in April 2024. Overall response rate is 51% (FIREFLY-1).

LGG appears in younger patients, between the ages of 30 and 50. Most LGG have an *IDH1* mutation in codon R132, and 10–15% of patients under the age of 55 have an *IDH2* mutation in codon R172. LGG are divided into low- and high-risk tumors. High-risk tumors are further subject to radiotherapy and chemotherapy. Since low-risk tumors have a longer life expectancy, there is greater concern about the consequences of radiation and chemotherapy. In these tumors, efforts are made to postpone radiotherapy and chemotherapy, and start targeted therapy. Vorasidenib is an *IDH1* and *IDH2* inhibitor with significantly better distribution and a 1:1 ratio between plasma and brain parenchyma. INDIGO is a randomized phase 3 study that positions vorasidenib in the first-line treatment of IDH-mutated grade 2 glial tumors. The primary objective of the study is PFS 27.7 months compared to 11.1. month in the placebo group (HR 0.39, $P=0.000000067$). The key secondary objective of the study is the time to the next intervention and statistically significantly favors vorasidenib (HR, 0.26, $P=0.000000019$). The registration procedure is in progress.

Keywords: glioma, *BRAF*, isocitrate dehydrogenase, targeted therapy

IMA LI DALJNJEG NAPRETKA U LIJEČENJU REKURENTNOG I/ILI METASTATSKOG PLANOCELULARNOG KARCINOMA GLAVE I VRATA?

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Promjena paradigme u liječenju rekurentnog/metastatskog (R/M) karcinoma skvamoznih stanica glave i vrata (HNSCC) s uvođenjem inhibitora imunoloških kontrolnih točaka (anti-PD1) sa ili bez kemoterapije, u početku u okruženju otpornom na platinu, a zatim u prvoj liniji R/M bolesti dovela je do poboljšanja u preživljenju. Unatoč ovom terapijskom napretku, samo 15%–19% bolesnika doživi četiri godine te postoji nezadovoljena potreba za novim terapijama za R/M HNSCC. Nove terapijske mogućnosti uključuju terapijska cjepiva, bispecifična protutijela, fuzijske proteine, multitargetirane inhibitori kinaza te konjugate protutijela i lijeka (ADC).

Nove imunoterapijske strategije uključuju terapijska cjepiva koja ciljaju epitope specifične za humani papiloma virus (HPV), cjepiva koja nisu usmjerena na HPV te personalizirana neoantigenska cjepiva. Od 2011. provedena su brojna klinička ispitivanja terapijskih cjepiva kao monoterapije ili u kombinaciji s drugim lijekovima, najčešće inhibitorima imunoloških kontrolnih točaka usmjerenih na PD1, a HPV je glavna terapijska meta. Cjepiva su pokazala značajnu kliničku dobit u ispitivanjima faze II i III.

ISA 101 cilja epitope E6 i E7 virusnog proteina i inducira CD4+ i CD8+ T-stanične odgovore. U ispitivanju faze II, u kombinaciji s nivolumabom postignuta je objektivna stopa odgovora (ORR) od 33% s medijanom PFS-a 10,3 mjeseca. PDS0101 u kombinaciji s pembrolizumabom u prvolinijskom liječenju, ispitivanje VERSA-TILE 002, dovelo je do smanjenja tumora u 67,6% bolesnika s medijanom PFS-a 10,4 mjeseci, a jednogodišnji OS bio je 87,1%. U ispitivanju su i druga kombinacijska cjepiva usmjerena na HPV, u kombinaciji s pembrolizumabom BNT113, CUE-101, HB-200 te INO-3112 u kombinaciji s durvalumabom.

Terapijska cjepiva koja nisu usmjerena na HPV kao UV1 koje je usmjereno na reverznu transkriptazu ljudske telomerase (hTERT), odnosno ribonukleoproteinski enzim koji može produžiti telomere i igra značajnu ulogu u napredovanju raka. U tijeku je ispitivanje FOCUS – randomizirano ispitivanje faze II, UV1 s pembrolizumabom u usporedbi sa samim pembrolizumabom u prvolinijskom liječenju bolesnika s PD-L1-pozitivnim HNSCC-om. Personalizirano cjepivo, MVX-ONCO-1, kombinira ozračene autologne tumorske stanice s kolonijom granulocitnih makrofaga, pokazalo je ohrabrujući odgovor u prethodno liječenih i otpornih na nivolumab s medijanom OS-a 11,4 mjeseci, a stope OS-a od 12 i 18 mjeseci bile su 49,2% i 31,6%. Terapijska cjepiva imaju povoljan sigurnosni profil u kojemu dominira umor, artralgije i infuzijske reakcije.

Druga nova oružja, uključujući bispecifična protutijela, fuzijske proteine i multitargetirane inhibitore kinaza, iskorištavaju istodobno višestruke mete i modulaciju mikrookruženja tumora kako bi se iskoristio antitumorski imunitet i inhibicija protumorigenih signalnih putova s novim obećavajućim rezultatima. Petosemtamab, IgG1 je bispecifično protutijelo za EGFR i transmembranski receptor LGR5, prisutan u 89% stanica raka glave i vrata. Bolesnici koji su napredovali ili nisu podnosili anti-PD-(L)1 i terapiju baziranu na platini pokazali su ORR od 37%, s medijanom trajanja odgovora od 6 mjeseci. BCA 101 je bifunkcionalan fuzijski protein, monoklonsko protutijelo usmjereno na EGFR i transformirajući faktor rasta beta, u kombinaciji s pembrolizumabom u prvoj liniji liječenja ima ORR 46%.

Inhibitori multikinaza kao što je lenvatinib u kombinaciji s pembrolizumabom u odnosu na pembrolizumab, faza III ispitivanja LEAP-010, u prvolinijskom liječenju PD-L1 CPS ≥ 1 , ima ORR-u 46,1% vs 25,4 % i poboljšanje medijana PFS-a sa 2,8 na 6,2 mjeseca uz više stope nuspojava povezanih s liječenjem, stupnja ≥ 3 (61,4% vs 17,8%), veće stope prekida liječenja zbog nuspojava (28% vs 8%) i brojčano više stope smrtnih slučajeva povezanih s liječenjem. OS nije poboljšán s ovom kombinacijskom terapijom. U tijeku je ispitivanje LEAP-009 koje procjenjuje lenvatinib sa ili bez pembrolizumaba u odnosu na standardnu kemoterapiju nakon progresije na inhibitoru PD-1 i kemoterapiju na bazi platine. Cabozantinib u kombinaciji s pembrolizumabom u populaciji PD-L1 CPS ≥ 1 , u prvoj liniji liječenja pokazuje ORR od 52%, medijan PFS-a 12,8 mjeseci, 2-godišnji PFS 32,6% i 2-godišnji OS 54,7 %. U tijeku je ispitivanje STELLAR-305, kombinacije zanzalintiniba i pembrolizumaba, također u prvolinijskom liječenju u PD-L1 pozitivnom R/M HNSCC.

Od konjugata protutijela i lijeka (ADC) objavljeni su preliminarni podaci za tisotumab vedotin (TV), enfortumab vedotin (EV) i SGN-B6A, u pretretiranih bolesnika s najmanje dvije linije prethodne sustavne terapije sa ORR oko 20%, medijanom PFS-a 4 mjeseca i OS-a oko 9 mjeseci. Sacituzumab govitekan (SG) je Trop-2-usmjereni ADC, ispitivan je u TROPiCS-03 (faza II) u 43 bolesnika otpornih na platinu i inhibitore kontrolnih točaka, 68% je primilo ≥ 2 linije sustavne terapije u metastatskom okruženju. ORR je bio 16% s medijanom PFS-a od 4,2 mjeseca. Nuspojave povezane s liječenjem stupnja ≥ 3 zabilježene su u 44% bolesnika, od kojih najčešće gastrointestinalne, s jednim smrtnim slučajem septičkog šoka, koji se smatrao povezanim s liječenjem.

Trenutačni podaci o ADC-ima u bolesnika s HNSCC-om usmjereni su na bolesnike koji su otporni na platinu i imunoterapiju, a rani rezultati su ohrabrujući. Za populaciju koja je prethodno intenzivno liječena stope odgovora su varirale od 16% do 40% uz relativno dobru podnošljivost. Međutim, regulatorne agencije nisu odobrile nijedan od ovih lijekova za liječenje HNSCC-a iako višestruka klinička ispitivanja trenutno procjenjuju različite ADC-e za ovu populaciju.

Uz rano oduševljenje novim terapijama u R/M HNSCC-u, željno se očekuju rezultati većih randomiziranih ispitivanja u R/M HNSCC-u.

Ključne riječi: planocelularni karcinomi glave i vrata, konjugati lijeka i protutijela, imunoterapija, antitumorska cjepiva

IMPROVEMENTS IN THE TREATMENT OF RECURRENT AND/OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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The paradigm shift in the treatment of recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (HNSCC) with the introduction of immune checkpoint inhibitors (anti-PD1) with or without chemotherapy, initially in platinum-refractory settings and later in the first line of R/M disease, has led to improved survival. Despite this therapeutic improvement, only 15%–19% of patients survive four years, underlining the unmet need for new therapies for R/M HNSCC. New therapeutic options include therapeutic vaccines, bispecific antibodies, fusion proteins, multitargeted kinase inhibitors, and antibody-drug conjugates (ADC).

New immunotherapeutic approaches include therapeutic vaccines targeting epitopes specific to human papillomavirus (HPV), non-HPV-targeted vaccines, and personalized neoantigen vaccines. As the primary therapeutic target, HPV has been the subject of multiple clinical trials since 2011 involving therapeutic vaccinations either as monotherapy or in combination with other medications, most frequently immune checkpoint inhibitors targeting PD1. These vaccines have shown significant clinical benefits in phase II and III trials.

ISA 101 targets the E6 and E7 viral protein epitopes, inducing CD4⁺ and CD8⁺ T-cell responses. In a phase II trial, a median progression-free survival (PFS) of 10.3 months was attained with an objective response rate (ORR) of 33% when in combination with nivolumab. In the VERSATILE 002 study, PDS0101 plus pembrolizumab as first-line treatment resulted in tumor decrease in 67.6% of patients, with a median progression-free survival (PFS) of 10.4 months and a one-year overall survival (OS) of 87.1%. Other HPV-targeted combination vaccines in trials include pembrolizumab with BNT113, CUE-101, HB-200, and INO-3112 with durvalumab.

Human telomerase reverse transcriptase (hTERT), a ribonucleoprotein enzyme that can lengthen telomeres and is substantial in cancer development, is the target of non-HPV-targeted therapeutic vaccinations like UV1. The FOCUS trial is a randomized phase II study that compares pembrolizumab alone to UV1 plus pembrolizumab as first-line therapy for patients with PD-L1-positive HNSCC. With a median overall survival (OS) of 11.4 months and OS rates of 49.2% and 31.6% at 12 and 18 months, respectively, the personalized vaccine MVX-ONCO-1, which combines irradiated autologous tumor cells with a granulocyte-macrophage colony, has demonstrated an encouraging response in previously treated and nivolumab-resistant patients. Therapeutic vaccines have a favorable safety profile, with fatigue, arthralgia, and infusion reactions being the most common side effects.

With encouraging new results, other novel medicines like fusion proteins, bispecific antibodies, and multi-targeted kinase inhibitors use several simultaneous targets and tumor microenvironment modification to harness anticancer immunity and disrupt protumorigenic signaling pathways. Petosemtamab, an IgG1 bispecific antibody for EGFR and the transmembrane receptor LGR5, present in 89% of head and neck cancer cells, showed an ORR of 37%, with a median duration of response of 6 months in patients who progressed on or could not tolerate anti-PD-(L)1 and platinum-based therapy. BCA 101, a bifunctional fusion protein, a monoclonal antibody directed at EGFR and transforming growth factor beta, in combination with pembrolizumab in first-line treatment, has an ORR of 46%.

In first-line treatment for PD-L1 CPS ≥ 1 , multikinase inhibitors such as lenvatinib in combination with pembrolizumab showed an ORR of 46.1% versus 25.4% and an improvement in median PFS from 2.8 to 6.2 months in the phase III LEAP-010 trial. There were also higher rates of treatment-related adverse events of grade ≥ 3 (61.4% vs 17.8%), higher rates of treatment discontinuation due to adverse events (28% vs. 8%), and numerically higher rates of treatment-related deaths. OS was not improved with this combination therapy. In the ongoing LEAP-009 trial, lenvatinib in combination with or without pembrolizumab is being compared to conventional chemotherapy following progression on PD-1 inhibitor and platinum-based chemotherapy. Cabozantinib in combination with pembrolizumab in a PD-L1 CPS ≥ 1 population in first-line treatment showed an ORR of 52%, median PFS of 12.8 months, 2-year PFS of 32.6%, and 2-year OS of 54.7%. The STELLAR-305 trial of zanza-lintinib and pembrolizumab combination in first-line treatment in PD-L1-positive R/M HNSCC is ongoing.

Preliminary data have been published for antibody-drug conjugates (ADCs) such as tisotumab vedotin (TV), enfortumab vedotin (EV), and SGN-B6A in pre-treated patients with at least two lines of prior systemic therapy, with ORR around 20%, median PFS of 4 months, and OS of about 9 months. In TROPiCS-03 (phase II), sacituzumab govitecan (SG), a Trop-2-targeted ADC, was investigated in 43 platinum- and checkpoint-resistant patients; 68% of these patients received at least two lines of systemic therapy in the context of metastatic disease. The ORR was 16%, with a median PFS of 4.2 months. Treatment-related adverse events of grade ≥ 3 were reported in 44% of patients, most commonly gastrointestinal, with one treatment-related death from septic shock. The patients with HNSCC resistant to immunotherapy and platinum are the focus of current data on ADCs, and the initial findings are promising. Response rates for the population that received extensive pretreatment have ranged from 16% to 40%, with a generally acceptable level of tolerability. However, regulatory agencies have not yet approved any of these medications for the treatment of HNSCC, even though numerous clinical trials are presently assessing different ADCs for this demographic.

Larger randomized trials in R/M HNSCC are widely anticipated, given the early enthusiasm for potential therapeutics in this condition.

Keyword: head and neck squamous cancer, antibody drug conjugate, immunotherapy, cancer vaccines

SEKCIJA PROBAVNI TUMORI / DIGESTIVE TUMORS SESSION

AVAPRITINIB U ČETVRTOJ LINIJI LIJEČENJA METASTATSKOG GASTROINTESTINALNOG STROMALNOG TUMORA – PRIKAZ SLUČAJA

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Uvod: GIST je najčešći mezenhimalni tumor probavne cijevi, ali samo 1–2% svih probavnih tumora. Cajalove stanice mišićnog sloja odgovorne za peristaltiku najvjerojatnije su ishodište. GIST uzrokuju aktivirajuće mutacije u *KIT* i *PDGFRA* genima za receptore tirozinskih kinaza. Najčešća je mutacija *KIT* u egzonu 11 (60–70%).

PDGFRA D842V u egzozu 18 prisutna je kod 10–15% slučajeva. Avapritinib je peroralni TKI registriran za liječenje uznapredovalog *PDGFRA* egzoz 18 mutiranog GIST-a i za sistemske mastocitoze.

Prikaz slučaja: Kod muškarca, 1948. godište, bez značajnih komorbiditeta, je u svibnju 2021. dijagnosticiran *high-risk* GIST želuca 21x31x28 cm. Učinjena je resekcija te je upućen onkologu. Uveden je imatinib 400 mg, a nakon 7 mjeseci pojavljuju se metastaza jetre i peritoneja. Na imatinib 800 mg pacijent je bez progresije bolesti 15 mjeseci, kada progrediraju jetrene i peritonejske metastaze. Druga linija sunitinibom i treća regorafenibom trajale su 5 i 3 mjeseci, uz mršavljenje i klinički i radiološki porast izraslina trbušne stijenke. U 10/2023. pristiže nalaz SGP-a tumora i mutacija *PDGFRA D842V* sa sugestijom terapije avapritinibom. Putem NPLVSGP-a nabavljen je avapritinib – prva primjena lijeka u RH, a procedura SGP, odobrenja i uvoza potrajala je tri mjeseca. Od veljače 2024. pacijent redovno uzima avapritinib 300 mg do danas (8 ciklusa). Rađene su dvije CT reevaluacije, svaka s parcijalnom regresijom, opće se stanje poboljšava, udebljao se 14 kg. Nuspojave terapije nema, nema alteracija kognitivnog statusa, u EKG-u se otprije prati graničan QTc, koji je tijekom liječenja minimalno produžen na 490ms. Kardiolog smatra da ne postoji realna opasnost od malignih aritmija. U listopadu se planira kontrolna reevaluacija.

Zaključak: Pacijent je idealan za ilustraciju važnosti inicijalne molekularne dijagnostike, jer imatinib i sunitinib na *PDGFRA D842V* mutirani GIST ne djeluju, kao i za uvid u djelotvornost avapritiniba u dugotrajnoj kontroli metastatskog *PDGFRA D842V* mutiranog tumora.

Ključne riječi: gastrointestinalni stromalni tumori, *PDGFRA D842V*, avapritinib, molekularna dijagnostika

AVAPRITINIB IN FOURTH-LINE TREATMENT FOR METASTATIC GASTROINTESTINAL STROMAL TUMORS – A CASE REPORT

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Introduction: GIST is the most common digestive tract mesenchymal tumor, but only 1–2% gastrointestinal cancers are GIST. Probable origin is Cajal's cells of the muscular layer facilitating peristalsis. GIST is driven by activating mutations in *KIT* and *PDGFRA* genes for TK receptors with *KIT* exon11 being the most frequent (60–70%). *PDGFRA D842V* exon18 is present in 10–15% only gastric GISTs. Avapritinib is an oral TKI registered for advanced *PDGFRA D842V* mutated GIST and systemic mastocytosis treatment.

Case Report: In May 2021, a high-risk gastric GIST measuring 21x31x28cm, was diagnosed in a male patient born 1948. It was radically resected, and the patient was referred to an oncologist. After 7 months of adjuvant imatinib 400 mg, liver and peritoneal metastases emerged on CT scan. Disease is stable for 15 months of subsequent imatinib 800 mg, then liver and peritoneal metastases progress. Second line sunitinib and third line regorafenib control the disease for 5 and 3 months, the patient loses weight and registers abdominal wall protuberance growth. CT records peritoneal and subcutaneous progression. In October 2023 tumour molecular profiling resulted in *PDGFRA D842V* mutation finding, with the suggestion of avapritinib treatment. Avapritinib was obtained *via* a special health insurance fund, whilst this medication is not routinely available in Croatia. Therefore, the procedure of genetic testing, granting and acquisition of the first avapritinib in the country, took roughly 3 months. Patient is taking avapritinib 300mg from February 2024, 8 months by now, with two interim CTs, both showing partial regression. Patient's general condition improved, he gained 14 kg of body mass, with no treatment side-effects, no cognitive alterations. There was a borderline QTc in ECG from before, and it has slightly prolonged during treatment to 490 ms. Cardiologist finds no threats of malignant arrhythmias. Next CT scan is in October 2024.

Conclusion: This case is illustrative of the initial molecular profiling importance, because imatinib and sunitinib have no effect on *PDGFRA D842V* mutated GIST. It is also beneficial for the direct insight on this targeted drug's effect in control of metastatic disease.

Keywords: gastrointestinal stromal tumors, *PDGFRA D842V*, avapritinib, molecular diagnostic

SEKCIJA TUMORI DOJKE / BREAST CANCER SESSION

NOVOSTI U LIJEČENJU KARCINOMA DOJKE

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Rak dojke područje je neprestanog razvoja. Svake godine objavljuju se brojna istraživanja koja oblikuju terapijski pristup liječenju raka dojke. Kliničari i pacijenti u potrazi za optimalnim liječenjem traže ravnotežu između eskalacije i deeskalacije liječenja.

Kirurzi prednjače u procesu deeskalacije. Rezultati ispitivanja SENOMAC podržavaju izostavljanje aksilarne disekcije (ALND) u svim subpopulacijama pacijenata s do dva pozitivna sentinel limfna čvora (SLNB), uključujući pacijente s mastektomijom te one s ekstranodalnim širenjem. Jedno retrospektivno (EUBREST-06/OMA) i jedno prospektivno (NEOSENTITURK) ispitivanje pokazalo je da, u pacijenata s inicijalno pozitivnom aksilom, koja se nakon neoadjuvantne kemoterapije (NAKT) konvertirala u negativnu aksilu, SLNB i ciljane aksilarne disekcije (kombinacija SLNB i ekscizija prethodno označenog pozitivnog čvora) imaju slične rezultate u smislu lokoregionalnog recidiva. ALND je i dalje indicirana kod rezidualne bolesti nakon NAKT. ICARO ispitivanje ipak sugerira da je SLNB razuman pristup ako se pronađu samo zaostale izolirane tumorske stanice. U tijeku su ispitivanja koja testiraju može li se ALND zamijeniti zračenjem limfne drenaže (RNI) ako se u konačnom patohistološkom nalazu pronađe više rezidualne bolesti (mikro ili makrometastaza). Čak je i uloga SLNB-a upitna. Ispitivanje SOUND pokazalo je da u bolesnika s luminalnim karcinomom dojke, veličine do 2 cm, s negativnim aksilarnim ultrazvukom, preživljenje bez invazivne bolesti (IDFS) jednako bez obzira napravimo li SLNB ili ne.

Klinički onkolozi ne zaostaju za kirurzima. Ispitivanje NSABP 51 pokazalo je da nema potrebe za zračenjem limfne drenaže u slučaju inicijalno pozitivne aksile, koja se nakon NAKT konvertirala u negativnu aksilu. Potreban je oprez kod subpopulacije pacijenata s mastektomijom kod kojih RNI povećava IDFS za 3%. Prema objavljenim podacima studija LUMINA i PRIME II, izostavljanje radioterapije nakon poštudne operacije dojke (BSC) u bolesnika s T1N0 ne-lobularnim luminalnim tumorima, gradus 1–2, ne utječe na ishode preživljenja, ali povećava stopu lokoregionalnih recidiva na 10 godina s 1 na 10 %. Potrebna je individualna odluka za svakog pacijenta o potrebi za adjuvantnom radioterapijom nakon BSC.

Nažalost, internistički onkolozi ne prate trendove u kirurgiji i radioterapiji. Utjecaj farmaceutske industrije i mnoštvo novih ispitivanja koja predlažu nove terapijske mogućnosti rezultiraju eskalacijom terapije.

Nije bilo većih promjena u liječenju HER 2 (epidermalni faktor rasta dva) pozitivnog karcinoma dojke. U završnoj analizi ispitivanja Katherine, trastuzumab emtanzin (TDM-1), u usporedbi s trastuzumabom, u bolesnica s rezidualnom bolesti nakon NAKT, statistički je značajno poboljšao IDFS za 13,7% (67,1 vs 80%, HR 0.54) kao i ukupno preživljenje (OS) za 4,7% (84,1 vs 89,9%, HR 0.66). Glavna dilema u metastatskoj bolesti je optimalno liječenje nakon progresije na drugolinijsko liječenje trastuzumab derukstekanom (TDx). Dodatak tukatiniba trastuzumab emtanzinu, u HER2CLIMB-02 istraživanju produljilo je preživljenje bez progresije bolesti (PFS) sa 7,4 na 9,5 mjeseci HR 0,76 (p=0,0163). Retrospektivna analiza bolesnica s pneumonitisom uzrokovanim s TDx, pokazala je sigurnost reindukcije terapija s Tdx u slučaju pneumonitisa stupnja 1, uz prijedlog smanjenja doze TDx-a kod reindukcije.

U trostruko negativnom raku dojke (TNBC), dodatak pembrolizumaba NAKT (ispitivanje KEYNOTE 522) značajno je povećao stopu kompletnog patološkog odgovora te stopu bez povrata bolesti. Subanaliza KEYNOTE-522 pokazala je korist pembrolizumaba čak i kod tumora manjeg rizika kao T2N0 TNBC.

U metastatskoj bolesti obećavaju prvolinijski rezultati kombinacije konjugata antitijela i lijeka (ADC) te imunoterapije. datopotamab-derukstekan (Dato-TDx) i durvalumab u primarno ligand programiranoj staničnoj smrti 1 (PD-L1) negativnih pacijenata postigli su visoku stopu objektivnog odgovora od 79% te PFS od 13,8 mjeseci. U malom randomiziranom ispitivanju MORPEHUS-pan BC, u PD-L1 pozitivnih bolesnica, atezolizumab i sacituzimab govitekan produljili su PFS spram atezolizumaba i nab-paklitaksela (12,2 vs 5,9 mjeseci). U tijeku su mnoga randomizirana ispitivanja faze III čije rezultate željno iščekujemo.

Estrogen receptor (ER) pozitivni rak dojke je najčešći rak dojke, te je i većina objavljenih ispitivanja provedena u ovoj subpopulaciji.

Pitanje potrebe za adjuvantnom kemoterapijom jedno je od većih kliničkih dilema. Pojava Oncotype DX multigenetskog testa olakšala je kliničku praksu uz i dalje nerazriješenu dilemu potrebe za kemoterapijom u premenopausalnih žena s pozitivnim limfnim čvorovima. Subanaliza ispitivanja RxPONDER pokazala je da kod žena u pre/perimenopauzi s do tri pozitivna limfna čvora te Oncotype rezultatom < 25, nizak anti-mullerov hormon može razlikovati žene koje neće imati koristi od kemoterapije.

Dvije godine adjuvantne terapije inhibitorom ciklin-ovisnih kinaza 4 i 6 (CDK 4/6) abemaciclib je zlatni standard u visokorizičnih luminalnih tumora (4 ili više pozitivnih limfnih čvorova ili pozitivni čvorovi uz tumor > 5 cm ili tumor gradus 3). Ispitivanje NATALEE, testira tri godine ribocikliba, u dozi 400 mg, na široj populaciji pacijentica. Uključene su sve bolesnice s pozitivnim limfnim čvorovima, kao i bolesnice s negativnim čvorovima uz uvjet tumor gradus 3 ili T3 tumor ili tumor gradus 2 uz KI 67 > 20% ili visoki genomski rizik. Nakon medijana praćenja od 36 mjeseci, ribociklib je statistički značajno poboljšao IDFS (90,7 vs 87,6 %, HR 0,749).

Dva ispitivanja KEYNOTE-756 (pembrolizumab) i CA-209-7FL (nivolumab) testiraju ulogu neoadjuvantno-adjuvantne imunoterapije u luminalnom karcinomu dojke. Sve bolesnice su imale tumor gradus 3, uz pozitivne limfne čvorove ili T3 tumor. Dodatak imunoterapije povećao je stopu kompletnog patološkog odgovora. Učinak imunoterapije bio je veći kod PD-L1-pozitivnih i tumora niske ER ekspresije. Dugoročni rezultati nisu dostupni.

Inhibitori CDK 4/6 prvotinijski su standard u liječenju metastatskog luminalnog raka dojke. Ispitivanje MONARCH 3 pokazalo je da abemaciclib poboljšava OS za 13 mjeseci (66,8 vs 53,7 mjeseci, HR 0,80), ali bez postizanja statističke značajnosti. Među tri CDK 4/6 inhibitora jedino je ribociklib produžio OS.

Dodatak novog inhibitora fosfatidilinozitol 3-kinaze (PI3K) inavolisiba palbociklibu i fulvestrantu u bolesnika s PI3K mutacijom koji su progredirali tijekom ili unutar 12 mjeseci od završetka adjuvantne endokrine terapije udvostručilo je vrijeme do progresije bolesti (15,7 vs 7,3 mj., HR 0,43, P < 0,0001). Inavolisib je očekivano povećao toksičnost karakterističnu za PI3K inhibiciju (mukozitis, hiperglikemija, osip, proljev), ali s niskom stopom prekida (6%). Čekamo podatke o preživljenju.

Nakon što je nekoliko manjih ispitivanja sugeriralo benefit nastavka terapijom CDK 4/6 inhibitorom nakon progresije na iste, ispitivanje NEXTMONARCH, prvo ispitivanje faze III, pokazalo je da za pacijente koji su progredirali na terapiju palbociklib ili ribociklib, nastavak CDK 4/6 inhibitora uz prelazak na abemaciclib produžio PFS za manje od mjesec dana (6,0 naspram 5,3 mj. HR 0,73, p = 0,02).

Kada se razvije endokrina rezistencija, liječenje se najčešće nastavlja s kemoterapijom. Ispitivanje DESTINY BREAST-06 odgovorilo je na dva pitanja: Može li Tdx, nakon neuspjeha endokrine terapije, postati prva opcija u luminalnom karcinomu dojke s niskom ekspresijom HER 2, te možemo li proširiti primjenu Tdx-a na populaciju luminalnih bolesnica s HER 2 ultraniskom ekspresijom (definirano kao HER 2 (0) ekspresija ali s primjetnim bojanjem na HER 2). Tdx je spram kemoterapije produžio PFS i to vrlo slično u pacijenata s niskom HER 2 (13,2 vs 8,1 mj. HR 0,62) kao i HER 2 ultraniskom ekspresijom HER 2 (13,2 vs 8,3 mj., HR 0,83).

Prošla godina u području raka dojke obilježena je daljnjim naporima u deeskalaciji kirurgije i radioterapije. Studije su međutim kreirane bez koordinacije između disciplina te ostaje pitanje možemo li paralelno deeskalirati kirurgiju i radioterapiju. U sustavnom liječenju, potencijalna primjena adjuvantnog ribocikliba, triplet terapija s inavolisibom u bolesnika s endokrinom rezistencijom, te ranija i šira uporaba Tdx-a u luminalnom raku dojke glavne su inovacije, bez većih napredaka u deeskalaciji ili boljoj selekciji pacijenata za sistemno liječenje.

Ključne riječi: rak dojke, imunoterapija, inhibitori o ciklinima ovisnih kinaza 4/6, eskalacija, deeskalacija

YEAR IN REVIEW – BREAST CANCER

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Breast cancer is an ever-evolving field with the publication of numerous trials that shape the breast cancer treatment landscape. Clinicians and patients searching for optimal treatment struggle to find the right balance between treatment escalation and de-escalation.

Surgeons are leading the way in the de-escalation process. The results of the SENOMAC trial further support the omission of axillary dissection (ALND) in all subpopulations of patients with up to two positive sentinel lymph nodes (SLNB), most importantly mastectomy patients and those with extranodal extension. For patients with clinically positive axilla who undergo neoadjuvant chemotherapy (NACT) and convert to negative axilla, SLNB only is a reasonable approach. One retrospective (EUBREST-06/OMA) and one prospective (NEOSENTI-TURK) trial showed that SLNB and Targeted axillary dissection (combination of SLNB and excision of the clipped positive node) have similar results in terms of local recurrence, questioning the need for clipping. ALND is still indicated for residual disease after neoadjuvant treatment. The ICARO trial suggests that SLNB only, is a reasonable approach if only residual isolated tumor cells are found. Many trials are underway to see if ALND can be replaced with nodal irradiation if more residual disease (micro or macrometastases) is found on the final surgical report. Even the role of SLNB is questioned. SOUND trial proved that in patients with luminal breast cancer, up to 2 cm, with a negative axillary ultrasound, invasive disease-free survival (IDFS) is the same whether or not we perform SLNB.

Clinical oncologists are right up there with surgical colleagues. NSABP 51 trial showed no need for nodal irradiation in the case of an initially positive axilla, which converts to a negative axilla after NACT. Caution should be taken for a subpopulation of mastectomy patients for whom nodal irradiation provides a 3 % IDFS benefit. According to LUMINA and PRIME II trials published data, omission of RT after breast-conserving surgery (BSC) in patients with T1N0 non lobular luminal tumors, grade 1–2, does not affect survival outcomes but increases locoregional recurrence in 10 years from 1 to 10%. This results in shared decision-making with every patient about the need for adjuvant radiotherapy.

Unfortunately, medical oncologists are falling behind. The impact of the pharmaceutical industry and a plethora of new trials that suggest new therapeutic options result in therapy escalation.

There were no groundbreaking trials in epidermal growth factor receptor two positive (HER 2+) breast cancer. In the final analysis of Katherine trial, trastuzumab emtansine (TDM-1), compared to trastuzumab, in patients with residual disease after NACT, statistically significantly improved both IDFS by 13.7% (67.1 vs 80 %, HR 0.54) and overall survival (OS) by 4.7% (84.1 vs 89.9 % HR 0.66). The main dilemma in the metastatic setting is optimal treatment after second-line progression on trastuzumab deruxtecan (TDx). The addition of tucatinib to TDM-1 in HER2CLIMB-02 modestly increased progression-free survival (PFS) from 7.4 to 9.5 months HR 0.76 (p=0.0163). According to a retrospective analysis of pneumonitis pattern with TDx, it is safe to rechallenge with TDx in case of pneumonitis grade 1, with a suggestion to reduce the dose of TDx.

In triple-negative breast cancer (TNBC), the addition of pembrolizumab to NACT (KEYNOTE-522 trial) significantly increased complete pathological response and event-free survival. There has been a press release about positive OS results. Subanalysis showed that pembrolizumab is beneficial even in smaller-risk tumors such as T2N0 TNBC. In the metastatic settings, there are promising results for first-line antibody-drug conjugates (ADC) – immunotherapy combinations. datopotamab-deruxtecan (Dato-TDx) and durvalumab in primarily programmed death-ligand 1 (PD-L1) negative patients achieved a high objective response rate of 79% and PFS of 13.8 months. In a small randomized trial MORPEHUS-pan BC trial in PD-L1 positive patients, atezolizumab and sacituzimab govitecan prolonged PFS to atezolizumab and nab-paclitaxel (12.2 vs 5.9 months). Many randomized phase III trials are underway, and we eagerly await the results.

Estrogen receptor positive (ER) breast cancer is the most frequent breast cancer, and most published trials were conducted in this subpopulation.

To give or not to give adjuvant chemotherapy that is the question. With the emergence of Oncotype DX; this question is mainly answered except for premenopausal women with node-positive disease. A subanalysis of the

RxSPONDER trial showed that in pre/perimenopausal women with node-positive disease and Oncotype score of < 25, low anti-Mullerian hormone could differentiate women who will not benefit from chemotherapy.

Two years of adjuvant Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor abemaciclib is an established standard in high-risk luminal tumors (4 or more positive nodes or positive nodes with either tumor > 5 cm or grade 3 tumor). In the NATALEE trial, ribociclib was tested in a broader patient population. All patients with node-positive disease and selected node-negative patients (grade 3 or T3 tumors, or grade 2 tumors with KI 67 > 20% or high genomic risk) were randomized to 3 years of 400 mg daily ribociclib or placebo. At a median follow-up of 36 months, ribociclib statistically significantly increased IDFS 90.7 vs 87.6 %, HR 0.749.

Neoadjuvant-adjuvant immunotherapy is emerging, with two trials, KEYNOTE-756 (pembrolizumab) and CA-209-7FL (nivolumab), reporting an increased pathological response rate with the addition of immunotherapy. Patients had grade 3 disease with either node-positive or T3 tumors. The impact of immunotherapy was higher in PD-L1-positive and ER-low tumors. Long-term results are unavailable.

CDK 4/6 inhibitors are the mainstay treatment for first-line metastatic luminal breast cancer. The MONARCH 3 trial reported that abemaciclib prolonged OS by 13 months (66.8 vs 53.7 months, HR 0.80), but without reaching statistical significance. We conclude that among three CDK 4/6 inhibitors, only ribociclib consistently prolonged OS.

Adding new phosphatidylinositol 3-kinase (PI3K) inhibitor inavolisib to palbociclib and fulvestrant for patients with PI3K mutation who progress during or under 12 months of end-of-adjuvant-endocrine therapy doubled PFS time (15.7 vs 7.3 mo., HR 0.43, $P < 0.0001$). inavolisib expectedly increased toxicities common to PI3K inhibition (mucositis, hyperglycemia, rash, diarrhea) but with a lower-than-expected discontinuation rate (6%). We are waiting for OS data.

After several smaller trials suggested some benefit of CDK 4/6 inhibition beyond progression but only if CDK 4/6 is switched, the NEXTMONARCH trial, first phase III trial, showed that for patients who progressed on mostly palbociclib or ribociclib, continuing CDK 4/6 and switching to abemaciclib prolonged PFS for less than a month (6.0 vs 5.3 mo. HR 0.73, $p = 0.02$).

When endocrine resistance develops, patients are mostly switched to chemotherapy or ADCs. DESTINY BREAST-06 trial answered two questions: Can Tdx in luminal, HER 2 low patients become the preferred therapeutic option after ET failure, and can we broaden the TDx population from HER2 low to HER 2 ultralow patients defined as HER 2 zero, but with some positive staining. TDx prolonged PFS, to a similar degree, over chemotherapy in both HER 2 low (13.2 vs. 8.1 mo. HR 0.62) and HER 2 ultralow patients (13.2 vs. 8.3 mo., HR 0.83).

Last year in breast cancer was marked by further efforts in the de-escalation of surgery and radiotherapy, which is still discipline-specific and needs more coordination between disciplines. In systemic treatment, escalation efforts of adjuvant ribociclib and inavolisib in endocrine resistance metastatic settings and earlier and broader use of TDx in luminal breast cancer have been the most echoing improvements in the oncology community.

Keywords: breast cancer, immunotherapy, cyclin dependent kinase 4/6 inhibitor, escalation, deescalation

HER2 POZITIVAN RANI RAK DOJKE: NOVI STANDARDI U PRISTUPU AKSILI U RANOM RAKU DOJKE

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Uvod: Pojačana izraženost HER2 receptora prisutna je u 15–20 % slučajeva raka dojke koji često pokazuju agresivnije ponašanje u usporedbi s drugim tipovima, predstavljajući dodatne izazove u procesu liječenja. U kontekstu neoadjuvantnog liječenja operabilnih HER2+ tumora, danas se neoadjuvantno liječi većina HER2+ tumora >2 cm i/ili s pozitivnim limfnim čvorovima. Standard u neoadjuvantnom liječenju HER2+ bolesnica uključuje kemoterapiju temeljenu na kombinaciji antraciklina i taksana te dualnu anti-HER2 blokadu pertuzumabom i trastuzumabom. Nakon operativnog zahvata slijedi adjuvantna radioterapija (ovisno o indikaciji), nastavak anti-HER2 terapije (ovisno o stopi odgovora) i endokrina terapija ako se radi o hormonski ovisnim tumorima. Neoadjuvantnim pristupom znatno se povećava broj pošteđenih operacija te se bitno smanjuje broj potrebnih disekcija aksile.

Prikaz slučaja: Bolesnici u dobi od 51 godine dijagnosticiran je luminal B, hormon receptor pozitivan (HR+), HER2+ tumor sa zahvaćanjem pazušnih i infraklavikularnih limfnih čvorova. Provedena je neoadjuvantna kemoterapija po ddAC-wPT protokolu uz blokadu HER2+ receptora. Uslijedila je segmentektomija uz SLNB te disekcija aksile. Prema PHD-u postignut je potpuni patološki odgovor (pCR) primarnog tumora i limfnih čvorova, dok su u jednom limfnom čvoru bili prisutni znakovi deplecije limfocita i fibrozne reakcije. Nakon operacije provedeno je adjuvantno zračenje te je nastavljena aplikacija dvojne anti-HER terapije do ukupno 18. ciklusa. Nastavljena je endokrina terapija tamoksifenom uz LHRH agonist.

Zaključak: Optimalan klinički pristup u aksili nakon neoadjuvantne kemoterapije još uvijek je neizvjestan i aktivno se istražuje. Odluka o izostavljanju disekcije aksile ili SLNB-a, te postavljanje indikacije za zračenje, ovisi o kombinaciji kliničkih, patoloških i terapijskih čimbenika. Multidisciplinarni tim i točna dijagnostika igraju ključnu ulogu u sigurnom i uspješnom provođenju deeskalacije.

Ključne riječi: aksila, rani rak dojke, HER2, disekcija

HER2 POSITIVE EARLY BREAST CANCER: NEW STANDARDS IN TREATMENT OF AXILLA IN EARLY BREAST CANCER

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Introduction: Increased expression of the HER2 receptor is present in 15–20% of breast cancer (BC) cases and often exhibits more aggressive behavior compared to other types, presenting additional challenges in the BC treatment. In the context of neoadjuvant treatment (NACT) for operable HER2+ BC, tumors larger than 2cm

and/or with positive lymph nodes are treated in neoadjuvant setting. The current standard NACT of HER2+ patients includes chemotherapy based on a combination of anthracyclines and taxanes, and dual anti-HER2 blockade with pertuzumab and trastuzumab. This is followed by surgical intervention and adjuvant radiotherapy (if indicated), continuation of anti-HER2 therapy (the choice depends on the response rate), and endocrine therapy in HR+ tumors. The neoadjuvant approach significantly increases the number of breast-conserving surgery and greatly reduces the number of necessary axillary dissections.

Case Report: A 51-year-old patient was diagnosed with a HR+/HER2+ BC with involvement of the axillary and infraclavicular lymph nodes. Neoadjuvant chemotherapy was administered according to the ddAC-wPT protocol with HER2+ receptor blockade. Additionally, a segmentectomy was performed along with SLNB and axillary dissection. According to the pathology findings, a complete pathological response (pCR) was achieved in the primary tumor and lymph nodes, while in one lymph node, there were signs of lymphocyte depletion and fibrous reaction. After the surgery, adjuvant radiation was administered, and the application of dual anti-HER2 therapy was continued for a total of 18 cycles. Endocrine therapy with tamoxifen has been continued along with an LHRH agonist.

Conclusion: The optimal clinical approach of the axilla after NACT is still a matter of ongoing research. The decision to omit axillary dissection or SLNB depends on clinical, pathological, and therapeutic factors. A multidisciplinary approach and accurate diagnosis play a key role in the safe and successful implementation of de-escalation in axillary surgery.

Keywords: axila, early breast cancer, HER2, dissection

GUŽVA U 16-STERCU, IZAZOVI SEKVENCIRANJA TERAPIJE HORMON RECEPTOR POZITIVNOG RANOG RAKA DOJKE: INHIBITORI O CIKLINIMA OVISNIH KINAZA 4/6, INHIBITORI POLI ADP-RIBOZA POLIMERAZE I INHIBITORI KONTROLNIH TOČKA

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Uvod: Luminalni rak najčešći je podtip te predstavlja oko 70% svih slučajeva raka dojke. Standardno liječenje ranog raka dojke uključuje antihormonalnu, a u određenim slučajevima i kemo- i radioterapiju. Novija istraživanja su također u određenim slučajevima visokog rizika dokazala djelotvornost CDK 4/6 inhibitora, abemacicliba i ribocikliba kao i PARP inhibitora olapariba u *BRCA* mutiranih, u adjuvantnom liječenju luminalnog HER2 negativnog raka dojke. Međutim, ne postoje jasne preporuke odabira i sekvenciranja ovih lijekova u neoadjuvantnom i adjuvantnom liječenju.

Prikaz slučaja: Predmenopausalna bolesnica u dobi od 33 godine započela je obradu zbog palpabilne tvorbe u desnoj dojci. Kliničkim pregledom i radiološkom obradom utvrđena su dva tumora od 3,1 i 1,5 cm, u desnoj dojci te uvećani limfni čvorovi u desnom pazuhu. Biopsijom je potvrđen luminalni B, HER2 negativni invazivni lobularni rak gradusa 3. Napravljen je i citološka punkcija limfnog čvora pazuha koja je bila negativna. Provedena je neoadjuvantna kemoterapija po ddAC-T protokolu, nakon koje je učinjena mastektomija i biopsija limfnog čvora čuvara. Konačni patohistološki nalaz potvrdio je ostatni tumor u dojci veličine 2,1 cm te fibrozu u dva limfna čvora koja najvjerojatnije predstavlja odgovor na neoadjuvantnu terapiju. Zbog pozitivne obiteljske anamneze na rak dojke, provedeno je genetsko testiranje kojim je potvrđen status nositeljice patogene mutacije *BRCA2* gena. Postoperativno je provedena adjuvantna radioterapija. Daljnje liječenje je nastavljeno adjuvantnom antihormonalnom terapijom letrozolom i LHRH agonistom. Bolesnica je kandidat za adjuvantno liječenje abemaciclibom i olaparibom.

Zaključak: Odabir i sekvencioniranje terapije u liječenju bolesnica s ranim hormonski ovisnom rakom dojke su posebno važni obzirom da se radi o izlječivoj bolesti s visokom prevalencijom povrata.

Gljučne riječi: hormon receptor pozitivan, rani rak dojke, inhibitori o ciklinima ovisnih kinaza 4/6, inhibitori poli ADP-riboza polimeraze, imunoterapija

CROWD IN PENALTY AREA, CHALLENGES OF SEQUENCING HORMONE RECEPTOR POSITIVE EARLY BREAST CANCER THERAPY: CYCLIN DEPENDENT KINASE 4/6 INHIBITORS, POLY ADP-RIBOSE POLYMERASE INHIBITORS, AND CHECKPOINT INHIBITORS

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Introduction: Luminal subtype is the most common and represents about 70% of all breast cancers. Standard treatment of early breast cancer includes endocrine therapy and, in certain cases, chemo- and radiotherapy. Recent research has also proven the effectiveness of CDK 4/6 inhibitors, abemaciclib and ribociclib, as well as PARP inhibitor, olaparib in *BRCA* mutated in the adjuvant treatment of luminal HER2-negative high-risk tumors. However, there are still no standard guidelines for selecting and sequencing these drugs in the neoadjuvant and adjuvant treatment.

Case Report: A 33-year-old premenopausal patient started work-up due to a palpable lesion in the right breast. Clinical examination and imaging revealed 2 tumors, 3.1 and 1.5 cm in size, in the right breast and enlarged lymph nodes in the right axilla. The biopsy confirmed luminal B, HER2-negative, grade 3 invasive lobular carcinoma. A cytological puncture of the lymph node was also performed and was negative. Neoadjuvant chemotherapy according to the ddAC-T protocol was administered, and afterward, a mastectomy and sentinel lymph node biopsy were performed. Pathohistological examination showed a residual tumor of 2.1 cm in the right breast and fibrosis in two lymph nodes, which most likely corresponds to a response to neoadjuvant therapy. Due to a family history of breast cancer, genetic testing was performed, which showed that the patient was a carrier of a pathogenic mutation in the *BRCA2* gene. She underwent adjuvant radiotherapy. Further treatment was continued with adjuvant endocrine therapy – letrozole and an LHRH agonist. The patient is a candidate for adjuvant treatment with abemaciclib and olaparib.

Conclusion: Selection and sequencing of treatment in patients with hormone-dependent tumors are extremely important considering that it is a curable disease with a high prevalence of recurrence.

Keywords: Hormone receptor positive, early breast cancer, cyclin dependent kinase 4/6 inhibitors, poly ADP-ribose polymerase inhibitors, immunotherapy

TERAPIJA RANOG TROSTRUKO NEGATIVNOG RAKA DOJKE, ESKALACIJA I DEESKALACIJA, KADA JE MANJE – VIŠE?

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Trostruko negativni rak dojke (TNBC) je heterogen tumor i najagresivniji podtip raka dojke. Mutacije u Breast Cancer gene (*BRCA*) najčešće su prisutne u TNBCte se preporučuje, sukladno kriterijima, odrediti *BRCA* status pri dijagnozi. Unatoč mnoštvu klasifikacija temeljenih na genomici, transkriptomici i epigenomici, njihova klinička primjena zasad nije utvrđena te nisu integrirane u rutinsku kliničku praksu.

Smjernice sugeriraju neoadjuvantnu kemoimunoterapiju za tumore veće od 2 cm ili one s pozitivnom aksilom. Za manje tumore rezervirana je kirurgija uz adjuvantnu sistemsku terapiju ovisno o riziku. Temeljem studije KEYNOTE-522, perioperativna primjena imunoterapije pembrolizumabom u kombinaciji s polikemoterapijom povećala je stopu kompletnog patohistološkog odgovora (pCR), smanjila stopu povrata bolesti i povećala

ukupno preživljenje te predstavlja današnji standard liječenja. Neoadjuvatni pristup je ključan budući su rezultati primjene imunoterapije u adjuvantnom setingu negativni. Translacijska istraživanja su za sada izostala te nemamo prediktivnih biljega za potencijalnu deeskalaciju ovog toksičnog protokola. Trenutno nije jasna sekvenca postneoadjuvantne terapije. Inače, standard je adjuvantni pembrolizumab do godine dana. Inhibitori poli (ADP-riboza) polimeraze se preporučuju kod pacijenata s patogenom gBRCA1/2 mutacijom i rezidualnom bolesti. Za ostale s nepostignutim pCR-om, može se primijeniti kapecitabin, posebno kod nebazalnog fenotipa. Ostaje kontroverza istodobne primjene pembrolizumaba s olaparibom ili kapecitabinom.

Retrospektivne opservacijske studije pokazuju benefit adjuvantne kemoterapije i kod manjih pT1a TNBC-a. Nekoliko retrospektivnih studija ukazuje na mogućnost izbjegavanja kemoterapije u stadiju I kod obilnog prisustva limfocita koji infiltriraju tumor, tzv. TILs. Potrebna su prospektivna randomizirana ispitivanja za dodatne potvrde.

Multimodalna terapija poboljšala je ishode liječenja, ali istovremeno povećala toksičnost. Ispituju se specifični biomarkeri za precizniju identifikaciju kandidata za manje intenzivnu terapiju. Iščekujemo studije OPT-PEMBRO i OPTIMICE-pCR za postneoadjuvantni pembrolizumab. Kod bolesnika s rezidualnom bolesti velika su očekivanja od konjugata antitijelo-lijek. Možda su nam na horizontu i druge strategije liječenja ili nove terapijske opcije drugačijih mehanizama.

Ključne riječi: rani rak dojke, trostruko negativni rak dojke, imunoterapija, geni BRCA1/2

TAILORING THERAPY FOR EARLY TRIPLE NEGATIVE BREAST CANCER, ESCALATION AND DE-ESCALATION, WHEN IS LESS – MORE?

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Triple-negative breast cancer (TNBC) is a heterogeneous tumor and the most aggressive subtype of breast cancer. Mutations in the Breast Cancer gene (*BRCA*) are most commonly found in TNBC, and it is recommended, according to guidelines, to determine *BRCA* status at diagnosis. Despite various genomic, transcriptomic, and epigenomic classifications, their clinical use remains unclear and not part of routine practice.

Guidelines suggest neoadjuvant chemoimmunotherapy for tumors larger than 2 cm or those with positive axillary nodes. For smaller tumors, surgery is combined with adjuvant systemic therapy depending on the risk. The KEYNOTE-522 study shows that perioperative pembrolizumab with chemotherapy improves complete pathological response (pCR), reduces disease recurrence, and enhances overall survival, setting the current standard of care. The neoadjuvant approach is essential since adjuvant immunotherapy has yielded negative results. Currently, there is no translational research or predictive biomarkers for de-escalating this toxic protocol. The sequence of post-neoadjuvant therapy is currently unclear. Adjuvant pembrolizumab is standard for up to a year. PARP inhibitors are recommended for patients with pathogenic g*BRCA1/2* mutations and residual disease, while capecitabine is an option for those without pCR, particularly in non-basal phenotypes. The concurrent use of pembrolizumab with olaparib or capecitabine remains controversial.

Retrospective observational studies show a benefit of adjuvant chemotherapy even for smaller pT1a TNBCs. Several retrospective studies suggest that chemotherapy might be avoidable in stage I with high levels of tumor-infiltrating lymphocytes (TILs). Prospective randomized trials are needed for further confirmation.

Multimodal therapy has improved outcomes but also increased toxicity. Specific biomarkers are being studied to more precisely identify candidates for less intensive therapy. We're awaiting results from the OPT-PEMBRO and OPTIMICE-pCR studies on post-neoadjuvant pembrolizumab. In patients with residual disease, antibody-drug conjugates are highly anticipated. Other treatment strategies or new therapeutic options with different mechanisms may also be on the horizon.

Keywords: early breast cancer, triple negative breast cancer, immunotherapy, BRCA1/2 genes

SEKCIJA UROGENITALNIH TUMORA / UROGENITAL TUMORS SESSION

LIJEČENJE LOKALNOG VISOKORIZIČNOG KARCINOMA PROSTATE

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Uvod: Rak prostate je najčešći zloćudni tumor u muškaraca, a drugi po mortalitetu nakon karcinoma pluća u Hrvatskoj. Rak prostate u većini slučajeva se dijagnosticira u ranom stadiju. Opcije liječenja lokalne bolesti su radikalna prostatektomija ili radikalna radioterapija sa ili bez dodatka androgen deprivacijske terapije i nove generacije anti-androgene terapije u slučaju lokalnog visokorizičnog karcinoma prostate.

Prikaz slučaja: Godine 2013. u 62-godišnjeg bolesnika učinjena je biopsija prostate zbog povišenog prostata specifičnog antigena (PSA) 90 ng/mL, a patohistološki verificiran je adenokarcinom prostate, Gleasonovog zbroja 4+3. Inicijalnom obradom ne nađe se znakova diseminirane bolesti te je učinjena radikalna prostatektomija s limfadenektomijom. Patohistološkom analizom utvrđi se adenokarcinom prostate Gleasonovog zbroja 4+5 sa zahvaćanjem sjemenih mjehurića, pozitivnim regionalnim limfnim čvorovima i pozitivnim resekcijskim rubovima. Vrijednost postoperativnog PSA bila je 27 ng/mL. Započeto je liječenje androgen deprivacijskom terapijom LHRH agonistom i bicalutamidom. Nakon 10 mjeseci liječenja zabilježen je nadir vrijednosti PSA od 0,07 ng/mL. Za vrijeme trajanja terapije prati se diskretan porast PSA, a u studenom 2019. godine PET CTom s kolinom verificiran je povrat bolesti u zdjeličnom limfnom čvoru. Obzirom na razvoj kastracijski rezistentnog karcinoma prostate započeta je terapija enzalutamidom na što se inicijalno prati dobar odgovor. Tijekom razdoblja od 32 mjeseca ponovo se prati blagi porast PSA uz radiološki stabilnu bolest, te je nastavljena ista terapija. U ožujku 2024. godine PET CTom s kolinom verificirana je progresija bolesti u zdjelične i retroperitonealne limfne čvorove te je provedeno stereotaksijsko zračenje (SBRT) navedenih limfnih čvorova.

Zaključak: Liječenje i praćenje bolesnika s lokalnim visokorizičnim karcinomom prostate predstavlja veliki izazov. Multidisciplinarni pristup koji uključuje operativni zahvat, zračenje i sistemsku terapiju smatra se optimalnim načinom liječenja lokalnog visokorizičnog karcinoma prostate s dugoročno najboljim ishodom.

Ključne riječi: rak prostate, metastatski, kastracijski rezistentan, PET CT s kolinom

MANAGEMENT AND TREATMENT OF LOCALISED HIGH-RISK PROSTATE CANCER

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Introduction: Prostate cancer is the most common cancer in men and the second leading cause of cancer-related death after lung cancer in Croatia. The majority of patients are diagnosed in the early stage. Treatment options for localized disease are radical prostatectomy or radical radiotherapy with or without the addition of androgen deprivation therapy (ADT) and the new generation of antiandrogen therapy in high risk localized disease.

Case Report: In 2013, a 62 year-old patient underwent a prostate biopsy due to an elevated prostate-specific antigen (PSA) of 90 ng/mL. The histology report verified prostate adenocarcinoma with Gleason score of 4+3. No distant metastases were found on initial staging. Radical prostatectomy and lymphadenectomy was performed. Pathohistological examination revealed Gleason score 4+5 with positive surgical margins, seminal vesicles involvement and positive regional lymph nodes. The postoperative PSA value was 27 ng/mL and androgen deprivation therapy with LHRH agonist and bicalutamide was initiated. PSA nadir was 0.07 ng/mL after 10

months of therapy. While the therapy was ongoing, PSA started to rise and in November 2019 choline PET detected a recurrent disease in one pelvic lymph node. Therapy with enzalutamide was initiated for castration resistant disease with good biochemical response. During the period of 32 months there was a continuously rising trend of PSA value with radiological stable disease until March 2024 when choline PET confirmed lymph node disease progression. SBRT of PET positive retroperitoneal lymph node was performed.

Conclusion: The management of patients with high-risk, early-stage prostate cancer represents a major challenge. However, multimodal treatment strategies including surgery, radiation therapy, and systemic therapy offer a great potential for improved long-term outcomes for patients with high-risk prostate cancer who may harbor occult metastatic disease.

Keywords: prostate cancer, metastatic, castration-resistant, choline PET CT

KAKO SEKVENCIONIRATI LIJEČENJE U METASTATSKOM KASTRACIJSKI REZISTENTNOM KARCINOMU PROSTATE?

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Uvod: Rak prostate drugi je najučestaliji tumor u muškaraca u svijetu. Iako je udio bolesnika s kastracijski rezistentnom bolešću mali u odnosu na ukupan broj bolesnika (1,2 – 2,1 %), ti bolesnici čine populaciju s visokim morbiditetom, te značajno kraćim preživljenjem.

Prikaz slučaja: Godine 2018. bolesniku u dobi od 67 godina utvrđen je adenokarcinom prostate Gleasonovog zbroja 4+3 u 9/18 cilindara uz inicijalni PSA 20,6 ng/mL te bez udaljenih presadnica u standardnoj obradi. Učinjena je radikalna prostatektomija i zdjelična limfadenektomija. Zbog biokemijskog relapsa nakon 3 mjeseca učinjena je „spasonosna“ radioterapija ležišta prostate. Dva mjeseca nakon radioterapije bilježi se ponovno porast PSA. Na pozitronskoj emisijskoj tomografiji s kolinom verificira se patološko nakupljanje radiofarmaka u limfnom čvoru opturatorne regije lijevo. Započeta ADT uz stereotaksijsku ablativnu radioterapiju (SBRT) zahvaćenog limfnog čvora. Nakon 6 mjeseci bilježi se biokemijski relaps uz kastracijsku razinu testosterona. Kompjuteriziranom tomografijom utvrđi se sklerotična lezija u tijelu kralješka L3 karakteristike presadnice. Započeta terapija enzalutamidom uz zolendronat kao prvolinijsko liječenje metastatskog kastracijski rezistentnog raka prostate uz SBRT presadnice u kralježnici. Nakon 15 mjeseci utvrđena radiološka koštana progresija te se započinje kemoterapija docetakselom. Nakon 6 ciklusa terapija prekinuta zbog nuspojava te daljnjeg porasta PSA. Nastavljeno liječenje kabazitakselom no nakon 3 ciklusa bilježi se porast PSA uz radiološku progresiju koštanih presadnica i novonastale presadnice u retroperitonealnim limfnim čvorovima. Kemoterapija karboplatinom provedena je u 6 ciklusa, nakon čega je verificirana klinička i radiološka progresija s novonastalim jetrenim metastazama. Zbog kliničke deterioracije stanja bolesnika nastavljeno je simptomatsko i palijativno liječenje.

Zaključak: U kastracijski rezistentnoj bolesti na raspolaganju stoje inhibitori androgene signalizacije novije generacije, kemoterapija, radionuklidna terapija, PARP inhibitori te imunoterapija. Bolesnik prikazan u ovom slučaju s obzirom na brzu progresiju na više linija liječenja dobar je kandidat za multigeno testiranje što može pružiti dodatne prognostičke i prediktivne informacije.

Ključne riječi: rak prostate, multimodalna terapija, sekvencioniranje terapije, antiandrogena terapija

HOW TO SEQUENCE TREATMENT IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER ?

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Introduction: Prostate cancer is the second most common cancer in men worldwide. Although the proportion of patients with castration-resistant disease is small (1.2–2.1%), these patients have high complication rates and significantly shorter survival.

Case report: In 2018, a 67-year-old patient was diagnosed with Gleason score 4+3 prostate adenocarcinoma in 9/18 cylinders with an initial PSA of 20.6 ng/mL and no metastases on standard radiological workup. Radical prostatectomy and pelvic lymphadenectomy were performed. Due to a biochemical relapse after three months, salvage radiotherapy of the prostate bed was performed. Two months after radiotherapy, a significant PSA rise was observed. Positron emission tomography with choline verified the left obturator lymph node metastasis. ADT was started, and stereotactic ablative radiotherapy (SBRT) of the affected lymph node was performed. After six months, a biochemical relapse was observed. Computed tomography revealed a metastatic sclerotic lesion in the L3 vertebra. Enzalutamide and zoledronate as first-line treatment of metastatic castration-resistant prostate cancer was initiated, and SBRT of spinal metastasis was performed. After 15 months, radiological bone progression was detected, and docetaxel chemotherapy was started. After six cycles, the therapy was discontinued due to side effects and biochemical progression. Treatment with cabazitaxel continued, but after 3 cycles, an increase in PSA was noted along with the radiological progression of bone metastases and newly formed metastases in the retroperitoneal lymph nodes. Chemotherapy with carboplatin was continued for six cycles, after which clinical and radiological progression with new liver metastases was verified. Due to the clinical deterioration of the patient's condition, palliative treatment was continued.

Conclusion: Next-generation androgen receptor inhibitors, chemotherapy, radionuclide therapy, PARP inhibitors, and immunotherapy are available in castration-resistant disease treatment. This patient was a good candidate for multigene testing, which may have provided additional prognostic and predictive information.

Keywords: prostate cancer, multimodal treatment, treatment sequencing, anti-androgenic therapy

NOVOSTI U LIJEČENJU UROTELNOG KARCINOMA – PRIKAZ SLUČAJA

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Uvod: Urotelni karcinom u uznapredovalom i metastatskom stadiju poznat je kao jedan od onih s najlošijom prognozom, odnosno preživljenjem. Nedavno je kombinacija pembrolizumaba i enfortumab-vedotina (EV) postala najbolja opcija liječenja u prvoj liniji. U Hrvatskoj je trenutno dostupna kemoterapija uz terapiju održavanja avelumabom što je bio donedavni standard prvolinijskog liječenja. Velika nezadovoljena potreba su i opcije drugolinijskog kao i daljnjeg tretmana, iza progresije na liječenje kemoterapijom i inhibitorima kontrolnih točaka. Enfortumab vedotin, konjugat lijeka i protutijela usmjeren na Nektin-4, pokazao se učinkovitim za takvu populaciju progresora, a odnedavno je dostupan i u našoj zemlji.

Prikaz slučaja: Kod 65-godišnjeg bolesnika je u srpnju 2023. godine, nakon verificiranog pT3bN0 urotelnog karcinoma mokraćnog mjehura, učinjen radikalni operativni zahvat. Već kod prvog planiranog ciklusa adjuvantne kemoterapije ddMVAC protokolom, suspektna je proširena bolest, a nakon četiri ciklusa navedenog protokola sigurna progresija bolesti kontrolnom radiološkom obradom, te slijedi liječenje nivolumabom u drugoj liniji. Nakon 16 provedenih ciklusa liječenja utvrđena je daljnja progresija bolesti. Započinje se terapija EV-om u

srpnju 2024. Već nakon prve aplikacije, dolazi do razvoja makuloznog eritematoznog osipa po koži trupa i udova bolesnika (zahvaćajući 30% površine tijela). Uz kortikosteroidnu terapiju regresija osipa, te je uz odgodu i redukciju doze nastavljena terapija. U drugom je ciklusu, s obzirom na ponovno javljanje kožne nuspojave po smanjenju doze kortikosteroida, dodatno reducirana doza. Osim kožnih promjena, bolesnik liječenje dobro podnosi.

Zaključak: Enfortumab vedotin, jedan od novijih konjugata lijeka i antitijela, etablirao se u liječenju urotelnih karcinoma u uznapredovalim fazama. Usmjeren je na Nectin-4, adhezijsku molekulu koja je osim u određenim vrstama karcinoma, visoko izražena u epidermalnim keratinocitima i kožnim adneksama. Dolaskom novijih terapija, konjugata lijeka i antitijela, u kliničkoj se praksi susrećemo s novim profilom nuspojava.

Ključne riječi: urotelni karcinom, enfortumab-vedotin, pembrolizumab, nektin-4

ADVANCES IN THE TREATMENT OF UROTHELIAL CARCINOMA – A CASE REPORT

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Introduction: Advanced and metastatic urothelial carcinoma is known for its poor prognosis and survival rates. Recently, the combination of pembrolizumab and enfortumab vedotin (EV) has emerged as the best first-line treatment option. In Croatia, chemotherapy combined with avelumab maintenance therapy is currently available, which was the previous first-line treatment standard. There remains a significant unmet need for second line and further treatment options following progression after chemotherapy and checkpoint inhibitors. Enfortumab vedotin, a drug-antibody conjugate targeting Nectin-4, has proven effective for this patient population with disease progression and has recently become available in our country.

Case Report: In July 2023, a 65-year-old patient underwent radical surgery following the confirmation of pT3bN0 urothelial carcinoma of the bladder. At the first planned cycle of adjuvant chemotherapy with the ddMVAC protocol, there was suspicion of disease spread. After four cycles of the protocol, radiological evaluation confirmed disease progression, and second-line treatment with nivolumab was initiated. After 16 cycles of treatment, further disease progression was detected. Therapy with EV was initiated in July 2024. After just one application, the patient developed a macular erythematous rash on the skin of the trunk and limbs, covering 30% of the body surface. With corticosteroid therapy, the rash regressed, and treatment continued with delayed administration and dose reduction. In the second cycle, due to the recurrence of skin side effects following the reduction of corticosteroid dose, the EV dose was further reduced. Aside from skin changes, the patient tolerated the treatment well.

Conclusion: Enfortumab vedotin, one of the newer drug-antibody conjugates, has established itself in the treatment of advanced stages of urothelial carcinoma. It targets Nectin-4, an adhesion molecule that is highly expressed not only in certain types of cancer but also in epidermal keratinocytes and skin adnexa. With the advent of newer therapies, including drug-antibody conjugates, clinical practice is encountering a new profile of side effects.

Keywords: urothelial carcinoma, enfortumab vedotin, pembrolizumab, Nectin-4

ADRENOKORTIKALNI KARCINOM – IZAZOVI LIJEČENJA

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Uvod: Kao iznimna rijetka, „orphan” bolest, adrenokortikalni karcinom (ACC) još uvijek predstavlja enigmnu u pogledu adekvatne terapije. S obzirom na nisku incidenciju (<1 slučaj na milijun ljudi u godini) te kratko vrijeme preživljavanja, za sada postoji vrlo mali broj prospektivnih istraživanja, što većinu terapijskih preporuka bazira na retrospektivnim podacima.

Klinička slika i dijagnostika: Ovisno o hormonskoj proizvodnji ACC se dijele u funkcionalne i nefunkcionalne. U skladu s tim, 40–60% pacijenata se inicijalno prezentira simptomima prekomjerne razine hormona, u vidu Cushingovog sindroma, virilizacije, hiperaldosteronizma. Ostali pacijenti se prezentiraju ili nespecifičnim znakovima tumorske bolesti ~30 % (bolovi u trbuhu, konstitucijski znakovi maligniteta) ili slučajno nađenom tumorskom masom pri slikovnoj dijagnostici ~20–30%.

Slikovna dijagnostika (MSCT, MR) je osnova primarnog razlučivanja karaktera žarišne tvorbe nadbubrežne žlijezde, s diferencijalnom dijagnozom koja uključuje adenome, metastatske lezije, feokromocitom, odnosno ACC. Uloga FDG-PET je prvenstveno korisna u isključenju koštanih metastaza. Opći je konsenzus da se ne radi preoperativno perkutano uzorkovanje tkiva, s obzirom na malu količinu materijala koja onemogućuje konkluzivnu potvrdu maligniteta, česte komplikacije procedure te rizik lokalnog širenja („*seeding*”) tumora. Nakon kirurške resekcije, Weiss klasifikacija koja uzima u obzir 9 mikroskopskih karakteristika, je osnova diferenciranja benigne od maligne tvorbe.

Određivanje stadija i prognoza: TNM (tumor, node, metastasis) klasifikacijski sistem je osnova određivanja stadija ACC-a. Od ostalih faktora, Ki-67 proliferacijski indeks se pokazao kao pojedinačno najsnažniji prediktor povrata bolesti nakon resekcije. Većina pacijenata s ACC-om se inicijalno prezentira s uznapredovalom bolesti, gdje su najčešća sjela metastaza jetra, pluća, limfni čvorovi i kosti. Sveukupno 5-godišnje preživljenje pacijenata s ACC-om je <35 %, sa stopom povrata bolesti do 70–80%, s razmjerno manjim postotkom u nižim stadijima bolesti.

Liječenje: Lokalizirana bolest: Radikalna kirurška resekcija je osnova terapije za bolesnike u I. i II., te za određene u III. stadiju bolesti. Postizanje negativnih rubova resekcije je preduvjet minimiziranja rizika povrata bolesti, što često implicira resekciju ipsilateralnog bubrega, gušterače, slezene te dijela jetre i ošita.

Čak i nakon R0 resekcije, ovisno o stadiju, stopa povrata bolesti se kreće od 40–70 %. U nedostatku randomiziranih studija ne postoje čvrste preporuke za neoadjuvantno liječenje, te većina autora predlaže primarno kiruršku resekciju.

Za sada jedini FDA odobreni adrenokortikalni citotoksični lijek mitotan čini osnovu adjuvantnog liječenja ACC-a. Sistematski pregledni članak Tang Y i sur., koji je analizirao 1249 pacijenata, pokazao je da adjuvantno primijenjeni mitotan značajno smanjuje stopu povrata bolesti i smrtnost nakon resekcije ACC-a kod pacijenata bez metastaza. Recentne studije su pokazale da korist adjuvantno primijenjenog mitotana imaju prvenstveno pacijenti s visokim rizikom povrata bolesti nakon resekcije, što uključuje slučajeve s velikom tumorskom masom, pozitivnim rubovima resekcije, rupturiranom kapsulom tumora te visokim Ki-67 indeksom (>10 %). Navedeno je značajno prvenstveno iz aspekta izbjegavanja potencijalno ozbiljnih nuspojava mitotana kod pacijenata s niskim rizikom povrata bolesti nakon resekcije.

Konkluzivnije informacije o opravdanosti primjene mitotana kod bolesnika s niskim rizikom povrata bolesti, te o kombinaciji mitotana s cisplatinom/etopozidom za bolesnike s vrlo visokim rizikom povrata bolesti, trebali bi dobiti iz trenutno aktivne Adiuvo-2 studije.

S obzirom na činjenicu da adjuvantna radioterapija nema značajnog učinka u sistemnoj kontroli bolesti, pa tako i ukupnom preživljenju, a i ACC se smatra radiorezistentnim tumorom, taj modalitet liječenja nije preporučen u rutinskoj kliničkoj praksi.

Metastatska bolest: S 5-godišnjim preživljenjem od 0–17%, metastatski ACC spada u malignitete s najlošijom prognozom. Trenutno ne postoji kurativna sistemna terapija za takve bolesnike, a u određenim slučajevima s oligometastatskom bolesti (pluća, jetra) u obzir dolazi i kirurška resekcija.

S obzirom da monoterapija mitotanom u metastatskoj bolesti ima vrlo nisku stopu ukupnog odgovora (ORR) od 10–30%, kombinirana terapija koja uključuje i etopozid, doksorubicin te cisplatinu (EDP) je općenito preporučena. U randomiziranoj studiji na 304 bolesnika s proširenim ACC-om (FIRM-ACT) pokazana je značajna razlika i u odgovoru (RR) i preživljenju bez povrata bolesti (PFS) pacijenata na terapiji EDP i mitotanom, u usporedbi s onima koji su primali mitotan i streptozotocin.

Za sada ne postoji konsenzus o drugoj liniji liječenja metastatskog ACC-a. U tom kontekstu postoji veći broj studija o ulozi imunoterapije u liječenju bolesnika s metastatskim ACC-om, čiji rezultati još generalno nisu previše entuzijastični. Navedeno bi se potencijalno moglo objasniti imunosupresivnim djelovanjem lokalno izlučenih glukokortikoida i disreguliranom Wnt/ β - kateninskom signalizacijom.

Najekstenzivnije evaluirani imunoterapijski protokol je monoterapija pembrolizumabom, koji je naveden u NCCN smjernicama kao terapijska opcija u metastatskom ACC-u, uključujući i prvu liniju liječenja. On bi bio izbor liječenja prvenstveno za pacijente koji ne toleriraju EDP kemoterapiju te za one koji su oligosimptomatski i imaju sporiju kinetiku tumora.

Od ostalih terapijskih protokola za spomenuti je primjenu tirozin kinaznog inhibitora (TKI) kabozantiniba kod pacijenata s progresijom bolesti nakon mitotana. U retrospektivnoj studiji na 16 pacijenata postignuta su 3 djelomična odgovora te 5 slučajeva stabilne bolesti 4 mjeseca i duže. Također, u tijeku je klinička studija faze II (CaboACC) s analizom utjecaja kabozantiniba u proširenoj bolesti te studije kombinacije kabozantiniba s različitim imunoterapeutima.

Iako još uvijek u ranim fazama, postoji opravdana nada za etabliranjem ciljne terapije ACC-a. Navedeno se bazira na novim prospektivnim istraživanjima te identifikaciji biomarkera koji bi pouzdano predviđali njihovu učinkovitost uz testiranje nove generacije (NGS) koje bi identificiralo mutacije pogodne za terapijsko djelovanje.

Cljučne riječi: adrenokortikalni karcinom, kemoterapija, imunoterapija, metastatski

ADRENOCORTICAL CARCINOMA – TREATMENT CHALLENGES

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Introduction: As an extremely rare, “orphan” disease, adrenocortical carcinoma (ACC) still represents an enigma in terms of adequate therapy. Considering the low incidence (<1 case per million people per year) and the short survival time, there is currently a very small number of prospective studies, which bases most therapeutic recommendations on retrospective data.

Clinical picture and diagnostics: Depending on hormonal production, ACC is divided into functional and non-functional. Accordingly, 40–60% of patients initially present with symptoms of excessive hormone levels, in the form of Cushing’s syndrome, virilization, hyperaldosteronism. Other patients present either with non-specific signs of tumor disease ~30% (abdominal pain, constitutional signs of malignancy) or with a tumor mass found accidentally during imaging ~20–30%.

Imaging diagnostics (MSCT, MR) is the basis of primary differentiation of the character of focal formation of the adrenal gland, with a differential diagnosis that includes adenomas, metastatic lesions, pheochromocytoma or ACC. The role of FDG-PET is primarily useful in excluding bone metastases. The general consensus is that preoperative percutaneous tissue sampling is not performed, given the small amount of material that prevents conclusive confirmation of malignancy, the frequent complications of the procedure, and the risk of local tumor seeding. After surgical resection, the Weiss classification, which takes into account 9 microscopic characteristics, is the basis for differentiating a benign from a malignant formation.

Staging and prognosis: The TNM (tumor, node, metastasis) classification system is the basis for determining the stage of ACC. Among other factors, the Ki-67 proliferation index was shown to be the single most powerful predictor of disease recurrence after resection. Most patients with ACC are initially presented with advanced disease, where liver, lung, lymph nodes and bone metastases are the most common sites. The overall 5-year survival of patients with ACC is <35%, with a relapse rate of up to 70–80%, with a relatively lower percentage in lower disease stages.

Treatment: Localized disease: Radical surgical resection is the basis of therapy for patients in stage I and II, and for certain stage III patients. Achieving negative resection margins is a prerequisite for minimizing the risk of disease recurrence, which often implies resection of the ipsilateral kidney, pancreas, spleen, and part of the liver and diaphragm.

Even after R0 resection, depending on the stage, the disease recurrence rate ranges from 40–70%. In the absence of randomized studies, there are no solid recommendations for neoadjuvant treatment, and most authors suggest primarily surgical resection.

So far, the only FDA-approved adrenocortical cytotoxic drug mitotane forms the basis of adjuvant treatment of ACC. A systematic review article by Tang Y et al., which analyzed 1249 patients, showed that adjuvant mitotane significantly reduced the rate of disease recurrence and mortality after ACC resection in patients without metastases. Recent studies have shown that the benefit of adjuvantly administered mitotane is primarily for patients with a high risk of disease recurrence after resection, which includes cases with a large tumor mass, positive resection margins, ruptured tumor capsule and a high Ki-67 index (>10%). This is significant primarily from the aspect of avoiding potentially serious side effects of mitotane in patients with a low risk of disease recurrence after resection.

More conclusive information on the justification of the use of mitotane in patients with low risk of disease recurrence, and on the combination of mitotane with cisplatin/etoposide for patients with a very high risk of disease recurrence, should be obtained from the currently active Adiuvo-2 study.

Given the fact that adjuvant radiotherapy does not have a significant effect in systemic disease control, including overall survival, ACC is considered a radioresistant tumor and this modality of treatment is not recommended in routine clinical practice.

Metastatic disease: With a 5-year survival rate of 0–17%, metastatic ACC is among the malignancies with the worst prognosis. Currently, there is no curative systemic therapy for such patients, and in certain cases with oligometastatic disease (lung, liver) surgical resection is also considered.

Given that mitotane monotherapy in metastatic disease has a very low overall response rate (ORR) of 10–30%, combination therapy including etoposide, doxorubicin, and cisplatin (EDP) is generally recommended. A randomized study of 304 patients with advanced ACC (FIRM-ACT) showed a significant difference in both response (RR) and disease-free survival (PFS) of patients treated with EDP and mitotane compared to those treated with mitotane and streptozotocin.

So far, there is no consensus on the second line of treatment for metastatic ACC. In this context, there are a large number of studies on the role of immunotherapy in the treatment of patients with metastatic ACC, whose results are still generally not too enthusiastic. The above could potentially be explained by the immunosuppressive effect of locally secreted glucocorticoids and dysregulated Wnt/ β -catenin signaling.

The most extensively evaluated immunotherapy protocol is pembrolizumab monotherapy, which is listed in NCCN guidelines as a therapeutic option in metastatic ACC, including first-line treatment. It would be the treatment choice primarily for patients who do not tolerate EDP chemotherapy and for those who are oligosymptomatic and have slower tumor kinetics.

Other therapeutic protocols worth mentioning, include the use of the tyrosine kinase inhibitor (TKI) cabozantinib in patients with disease progression after mitotane. In a retrospective study of 16 patients, 3 partial responses and 5 cases of stable disease for 4 months or longer were achieved. Also, a phase II clinical study (CaboACC) is underway with the analysis of the impact of cabozantinib in advanced disease and studies of the combination of cabozantinib with different immunotherapeutic agents.

Although still in early stages, there is reasonable hope for the establishment of a targeted therapy for ACC. The aforementioned is based on new prospective research and the identification of biomarkers that would reliably predict their effectiveness with new generation testing (NGS) that would identify mutations suitable for therapeutic action.

Keywords: adrenocortical carcinoma, chemotherapy, immunotherapy, metastatic

SEKCIJA GINEKOLOŠKIH TUMORA / GYNECOLOGICAL TUMORS SESSION

NOVOSTI U LIJEČENJU LOKALNO UZNAPREDOVALOG KARCINOMA VRATA MATERNICE – INTERLACE STUDIJA

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Prema zadnjim podacima Hrvatskog registra za rak, u 2018. godini su u Hrvatskoj zabilježena 274 nova slučaja karcinoma vrata maternice, što čini 2% od ukupnog broja slučajeva raka u žena. Podatci o mortalitetu pokazuju da je iste godine od karcinoma vrata maternice umrlo 125 žena. Bolest najviše pogađa žene u dobi od 35 do 55 godina.

U posljednjih 10 godina bilježi se trend pada standardizirane stope incidencije karcinoma vrata maternice, dok je mortalitet stabilan, što čini ovu bolest velikim javnozdravstvenim problemom.

U liječenju lokalno uznapredovalog karcinoma vrata maternice bilo je vrlo malo novosti u zadnjih 25 godina, od kada je kao standard brige za pacijentice uvedena primarna kemoradioterapija, (tjedna primjena cisplatine uz radioterapiju vanjskim snopom na područje zdjelice, minimalno 3D konformalnom tehnikom) nakon čega slijedi intrakavitarna/intersticijska brahiterapija (unutar 8 tjedana). Međutim, cijelo vrijeme se poteže pitanje što još možemo učiniti da se preživljenje pacijentica produlji.

Studija INTERLACE je randomizirana studija faze III koja je ispitala učinkovitost uobičajene konkomitantne kemoradioterapije, u odnosu na indukcijsku kemoterapiju (6 tjednih aplikacija karboplatine i paklitaksela) nakon koje slijedi konkomitantna kemoradioterapija. Podatci ukazuju na značajno poboljšanje ukupnog preživljenja i vremena do progresije bolesti u pacijentica koje su primale indukcijsku kemoterapiju prije standardnog liječenja.

Primjena istog kemoterapijskog protokola (karboplatina i paklitaksel) adjuvantno nije pokazala benefit, prema OUTBACK studiji.

Pitanje je trena kada će indukcijska kemoterapija prije kemoradioterapije postati standard brige za pacijentice sa lokalno uznapredovalim karcinomom vrata maternice.

Ključne riječi: karcinom vrata maternice, kemoradioterapija, indukcijska kemoterapija, lokalno uznapredovali

NEWS IN THE TREATMENT FOR LOCALLY ADVANCED CERVICAL CANCER – INTERLACE STUDY

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According to the latest data from the Croatian Cancer Registry, 274 new cases of cervical cancer were registered in Croatia in 2018, which represents 2% of the total number of cancer cases in women. Mortality data show that 125 women died from cervical cancer in the same year. The disease mainly affects women between the ages of 35 and 55.

Over the past 10 years, the standardized incidence rate of cervical cancer has decreased while the mortality rate has remained stable, making this disease a major public health concern.

There have been few innovations in the treatment of locally advanced cervical cancer over the last 25 years since primary chemoradiotherapy was introduced as the standard treatment for patients (weekly application of cisplatin with external beam radiotherapy to the pelvic area, minimally with 3D conformal technique), followed by intracavitary/interstitial brachytherapy (within 8 weeks). However, the question always arises as to what else we can do to prolong patient survival.

The INTERLACE trial is a randomized phase III trial that investigated the efficacy of conventional adjuvant chemoradiotherapy compared to induction chemotherapy (6 weekly doses of carboplatin and paclitaxel) followed by adjuvant chemoradiotherapy. The data indicate a significant improvement in overall survival and progression free survival in patients who received induction chemotherapy prior to standard treatment.

Adjuvant use of the same chemotherapy protocol (carboplatin and paclitaxel) has shown no benefit according to the OUTBACK study.

It is only a matter of time before induction chemotherapy prior to chemoradiotherapy becomes the standard of care for patients with locally advanced cervical cancer.

Keywords: cervical cancer, chemoradiotherapy, induction chemotherapy, locally advanced

NE-EPITELNI KARCINOMI JAJNIKA

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Ne-epitelni karcinomi jajnika (engl. NEOC) su histološki i klinički različiti rijetki tumori. Oni čine približno 10% svih karcinoma jajnika. NEOC uključuju tumore zametnih stanica (engl. GCT), tumore spolnog tračeka i strome (engl. SCST) i karcinome malih stanica jajnika. Početni simptomi su obično subakutna bol u zdjelici, osjećaj pritiska zbog mase u zdjelici i menstrualne nepravilnosti. Oko 10% pacijenata doživi akutni abdomen kao posljedicu torzije, krvarenja ili rupture tumora. Dijagnostička obrada treba uključiti UZ zdjelice, MSCT abdomena i zdjelice, RTG prsnog koša, i PET snimak u odabranim slučajevima. Određivanje tumorskih biljega kao što su serumski beta humani korionski gonadotropin (β -hCG), alfa fetoprotein (α FP), inhibin B, anti-Müllerov hormon (AMH) i laktat dehidrogenaza (LDH), uz kompletnu krvnu sliku, te prikaz funkcije jetre i bubrega, treba preporučiti. Definiranje stadija bolesti preuzeto je od epitelnog karcinoma jajnika kojeg je izvorno definirala Međunarodna federacija ginekologije i opstetricije (FIGO). Kirurški pristup može se provesti otvorenim putem ili, u odabranim slučajevima, minimalno invazivnim pristupima, kako bi se izbjegla ruptura tumora tijekom operacije. Potreban je pažljiv pregled trbušne šupljine. Kirurgija koja čuva plodnost – jednostrana salpingo-ooforektomija uz očuvanje kontralateralnog jajnika i maternice (engl. FSS) i kemoterapija na bazi platine ostaju standard skrbi, pružajući visoku stopu izlječenja u svim fazama. Kod žena u postmenopauzi i bolesnica s uznapredovalim stadijem bolesti ili obostrano zahvaćenim jajnicima preporučuje se abdominalna histerektomija i bilateralna salpingo-ooforektomija.

GCT kod žena čine 2–5% svih malignih tumora jajnika. Dijagnosticiraju se uglavnom u prva tri desetljeća života s najvećom incidencijom u mladih djevojaka u dobi od 15 do 19 godina. GCT nastaje iz primordijalnih zametnih stanica embrionalne gonade. Svjetska zdravstvena organizacija (WHO) histološki je klasificirala GCT jajnika u nekoliko kategorija: disgerminome, embrionalne karcinome, tumore žumanjčane vrećice (engl. YST), negestacijske koriokarcinome, zrele i nezrele teratome i miješane tumore zametnih stanica. Ovisno o histologiji, stadiju i molekularnim značajkama GCT, nakon operacije slijedi aktivno praćenje ili adjuvantna kemoterapija. Postoperativno se nastavljaju pratiti samo disgerminomi ograničeni na jajnik i nezreli teratom stupnja I. Svi bolesnici sa stadijem I YST liječe se adjuvantnom kemoterapijom nakon operacije. Nedavni podaci upućuju na pomno praćenje stadija I YST nakon kompletne kirurške resekcije i urednog postoperativnog α FP, ali ovaj stav nije široko prihvaćen i o odluci treba razgovarati s pacijentima. BEP (bleomicin, etopozid i cisplatin) najpopularniji je protokol, dok se EP protokol (etopozid, cisplatin) može razmotriti u bolesnika koji nisu podobni za bleomicin (poodmakla dob i plućni komorbiditet). Otprilike će 15–20% pacijenata s uznapredovalom bolešću,

većina unutar prve dvije godine primarnog liječenja, doživjet recidiv. Terapija povrata bolesti uključuje operaciju i kemoterapiju. U bolesnika s relapsom osjetljivim na platinu (progresija > 4–6 tjedana nakon završetka kemoterapije) IP/TIP (ifosfamid, platina sa ili bez paklitaksela) treba razmotriti kao drugu liniju liječenja. Drugi kemoterapijski protokoli uključuju: gemcitabin-TIP, TE/TP (paklitaksel, etopozid/paklitaksel, cisplatin), vinblastin, ifosfamid, cisplatin (VeIP) i cisplatin, vinblastin, bleomicin (PVB). Bolesnici rezistentni na terapiju baziranu na platini primaju vinkristin, aktinomycin D, ciklofosfamid (VAC) ili paklitaksel, gemcitabin ili gemcitabin, oksaliplatin. Studija faze III koja je u tijeku, TIGER, definitivno će procijeniti ulogu kemoterapije visokim dozama (engl. HDCT) kod recidiva tumora zametnih stanica kod muškog spola u usporedbi sa standardnom konvencionalnom kemoterapijom. GCT može izraziti KRAS, BRCA1/2 i c-KIT mutacije. Do sada nijedna ciljana terapija nije pokazala klinički značajnu učinkovitost u neseletiranim populacijama pacijenata u nekoliko kliničkih ispitivanja, iako je normalizacija tumorskog biljega ili kratkoročni odgovor na liječenje opisana nakon primjene sunitiniba, imatiniba i brentuksimab vedotina. Uloga inhibitora kontrolnih točaka imunološkog sustava u tumorima zametnih stanica tek treba biti definirana.

Tumori spolnog tračka i strome jajnika uključuju i benigne i maligne tumore koji potječu od spolnog tračka, stromalnih stanica, ili oboje. Prema klasifikaciji WHO, SCST uključuju čiste tumore spolnog tračka (juvenilni i adultni granulozna stanični tumori – GrCTs), čiste stromalne tumore (fibromi, tekomi, fibrosarkomi, tumori Leydigovih stanica, tumori stromalnih stanica i tumori steroidnih stanica) i miješane SCST (Sertoli-Leydigovi tumori – SLCTs). SCST se javljaju u različitim dobnim skupinama, pri čemu se GrCT javljaju uglavnom u žena u peri- ili postmenopauzi, a SLCT u žena u dobi između 20 i 40 godina. Većina njih se javlja u ranoj fazi, uglavnom su jednostrani. SCST su često funkcionalni, luče estrogen i testosteron, što uzrokuje preuranjeni pubertet i virilizaciju. Zbog proizvodnje estrogena, hiperplazija endometrija i karcinom endometrija mogu se vidjeti u do 10% pacijenata. GrCT mogu lučiti inhibin i AMH. Liječenje SCST uključuje operaciju, kemoterapiju i ciljanu terapiju. Za pacijente sa stadijem IA GrCT, sama operacija daje izvrsnu prognozu. Mladim pacijentima koji imaju stadij IA dobro diferenciranog SLCT bez heterolognih elemenata, i u reproduktivnoj su dobi, nudi se FSS. Onima sa slabo diferenciranom malignom bolešću nudi se adjuvantna kemoterapija (BEP). Za GrCT i SLCT stadija većeg od IA, nudi se operacija i adjuvantna kemoterapija bez obzira na diferencijaciju tumora. GOG trenutno provodi randomizirano ispitivanje faze II koje uspoređuje BEP s kombinacijom paklitaksela i karboplatina za pacijentice s novodijagnosticiranim i kemoterapijski naivnim rekurentnim metastatskim SCST jajnika. Alternativne kemoterapijske opcije uključuju: PVB, EP, CAP, VAC i tjedni paklitaksel za pacijente s relapsom. Pokazalo se da hormonska terapija ima ulogu u GrCT-a koji izražavaju steroidne receptore. Ovi tumori odgovaraju na primjenu agonista gonadotropina, tamoksifena, progestina i inhibitora aromataze. Anastrozol je polučio kliničku dobit kod 41 pacijentice s recidivirajućim GrCT u prospektivnom multicentričnom ispitivanju faze II PARAGON. Unatoč ograničenim dostupnim podacima, čini se da je hormonska terapija koristan alternativni tretman za pacijente s uznapredovalim stadijem ili rekurentnim odraslim GrCT. Angiostatski agensi su također ispitivani u bolesnika s rekurentnim adultnim GrCT zbog prekomjerne ekspresije vaskularnog faktora rasta. ALIENOR/ENGOT ov-7/GINECO je randomizirana studija koja je istraživala istovremenu primjenu bevacizumaba i tjednog paklitaksela te terapiju održavanja bevacizumabom naspram tjedne primjene paklitaksela i praćenja u 60 bolesnika s relapsom SCST. Dodatak bevacizumaba tjednom paklitakselu nije polučio kliničku dobit mjerenu 6-mjesečnim PFS-om (71% vs 72%).

Karcinomi jajnika malih stanica – hiperkalcijemičnog tipa (SCCOHT) se javljaju u adolescenata i mladih žena s najvećom incidencijom u trećem desetljeću života. Razine kalcija u serumu mogu poslužiti u procjeni odgovora na liječenje te pomoći u dijagnozi recidiva. Prognoza SCCOHT-a je vrlo loša jer je rizik širenja izvan jajnika visok. Karcinomi jajnika malih stanica – plućnog tipa (SCCOPT) pogađaju pacijentice u peri- ili postmenopauzi. SCCOPT je pretežno jednostran i ima lošu prognozu čak i kad se rano dijagnosticira. U liječenju se preporuča kombinacija više modaliteta koji podrazumijevaju kirurški debulking kojeg slijedi kemoterapija i eventualno radioterapija. Terapija na bazi cisplatina i etopozida općenito se smatra najprikladnijom. Nedavno je predložena HDCT za pacijente koji su postigli R0 nakon operacije i/ili potpuni odgovor nakon kemoterapije. Navedena terapijska opcija koju slijedi autologna transplantacija matičnih stanica povezana je s boljim preživljavanjem. Liječenje relapsa bolesti često je vrlo izazovno budući kemoterapijom postizemo kratku remisiju. Do danas nijedna ciljana terapija nije ispitana u SCCOHT-u. Obećavajući rezultati anti-PD1 antitijela ekstrapolirani su iz studija s karcinomom pluća malih stanica.

Ključne riječi: ne-epitelni rak jajnika, kemoterapija, hormonska terapija, ciljana terapija

NON-EPITHELIAL OVARIAN CANCER

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Non-epithelial ovarian cancers (NEOCs) are histologically and clinically distinct rare tumors. They account for approximately 10% of all ovarian cancers. NEOCs include germ cell tumors (GCTs), sex cord-stromal tumors (SCSTs) and small cell carcinomas of the ovary. The initial symptoms of NEOCs are usually subacute pelvic pain, feeling of pressure due to a pelvic mass and menstrual irregularities. About 10% of patients experience an acute abdomen as a result of a torsion, hemorrhage or tumor rupture. Diagnostic work-up include pelvic ultrasound, an abdomino-pelvic computed tomography scan, chest X-ray and positron emission tomography scan in selected cases. Tumors markers such as serum beta human chorionic gonadotropin (β -hCG), alpha fetoprotein (α FP), inhibin B, anti-Müllerian hormone (AMH) and lactate dehydrogenase (LDH) levels, along with full blood count, liver and renal functions, should be recommended. The staging system for NEOCs is generally adopted from the epithelial ovarian cancer originally defined by the International Federation of Gynecology and Obstetrics (FIGO). A surgical approach can be carried out through an open route or, in selected cases, by minimally invasive approaches, to avoid tumor rupture during surgery. A careful examination of the abdominal cavity is required. Fertility-sparing surgery – unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus (FSS) and platinum-based chemotherapy remains the standard of care, providing a high chance of cure at all stages. In postmenopausal women and in patients with advanced-stage disease or with bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy is recommended.

Female GCTs account for 2–5% of all ovarian malignancies. They are diagnosed principally in the first three decades of life with peak incidence in young girls aged 15 to 19 years old. GCT originates from the primordial germ cell of the embryonic gonad. The World Health Organization (WHO) has classified ovarian GCTs histologically into several categories: dysgerminomas, embryonal carcinomas, yolk sac tumors (YSTs), non-gestational choriocarcinomas, mature and immature teratomas and mixed germ cell tumors. Depending on the histology, staging and molecular features of the GCTs, surgery will be followed by active surveillance or adjuvant chemotherapy. Only dysgerminomas confined to the ovary and grade I immature teratoma are managed with surveillance post-operatively. All patients with stage I YSTs are treated with adjuvant chemotherapy after surgery. Recent data suggest close surveillance for stage I YSTs with complete surgical staging and negative postoperative α FP, but this policy is not widely accepted and needs to be discussed with the patients. BEP (bleomycin, etoposide and cisplatin) is the most popular regimen while EP protocol (etoposide, cisplatin) can be considered in patients ineligible to bleomycin (advanced age and pulmonary comorbidity). Around 15–20% patients with advanced disease, majority within the first two years of primary treatment, will experience relapse. Salvage treatment includes surgery and chemotherapy. In patients with platinum-sensitive relapse (progression > 4–6 weeks after completion of chemotherapy), IP/TIP (ifosfamide, platinum with or without paclitaxel) should be considered as second line treatment. Further chemotherapy regimens include: gemcitabine-TIP, TE/TP (paclitaxel, etoposide/paclitaxel, cisplatin), vinblastine, ifosfamide, cisplatin (VeIP) and cisplatin, vinblastine, bleomycin (PVB). Patients resistant to a platinum-based therapy receive vincristine, actinomycin D, cyclophosphamide (VAC) or paclitaxel, gemcitabine or gemcitabine, oxaliplatin as salvage therapy. Ongoing trial phase 3, TIGER, will definitively assess the role of high dose chemotherapy (HDCT) in relapse male germ cell tumors by comparing with standard conventional-dose chemotherapy. GCT can acquire *KRAS*, *BRCA1/2* and *c-KIT* mutations. So far, no molecularly targeted treatment has shown clinically meaningful activity in unselected patient populations across several clinical trials, though tumor marker stabilization or short-term treatment responses have been described after treatment with sunitinib, imatinib and brentuximab vedotin. The role of immune checkpoint inhibitors in germ cell tumors still needs to be elucidated.

Ovarian sex cord stromal tumors include both benign and malignant cancers which originate from either the sex cord or stromal cells, or both. According to WHO classification, SCSTs include pure sex cord tumors (juvenile and adult granulosa cell tumors – GrCTs), pure stromal tumors (fibromas, thecomas, fibrosarcomas, Leydig

cell tumors, stromal cell tumors and steroid cell tumors) and mixed SCST (Sertoli-Leydig cell tumors – SLCTs). SCSTs occur in different age groups, with GrCTs occurring mainly in peri- or postmenopausal women, and SLCT in women aged between 20 to 40. The majority of these present at an early stage, mostly unilateral. SCSTs are often functional, secreting oestrogen and testosterone, which causes precocious puberty and virilization. Due to oestrogen production, endometrial hyperplasia and endometrial carcinoma can be seen in up to 10% of patients. GrCTs can secrete inhibin and AMH. Treatment of SCST involves surgery, chemotherapy and targeted therapy. For patients with stage IA GrCT, surgery alone provides an excellent prognosis. For young patients who have stage IA well-differentiated SLCT without heterologous elements, and are of reproductive age, FSS is offered. Those with poorly differentiated malignancy are offered adjuvant chemotherapy (BEP). For GrCT and SLCT staging greater than IA, surgery and adjuvant chemotherapy are offered irrespective of tumor differentiation. The GOG is currently conducting a randomized phase II trial which investigates the BEP protocol with the combination of paclitaxel and carboplatin for patients with newly diagnosed and chemotherapy-naïve recurrent metastatic SCSTs of the ovary. Alternative options include: PVB, EP, CAP, VAC and weekly paclitaxel for relapsed patients. Hormone therapy has been shown to have a role in GrCTs which express steroid hormone receptors. Response to gonadotropin-releasing hormone agonists, tamoxifen, progestin and aromatase inhibitors (AIs) has been reported. Anastrozol achieved clinical benefit in 41 patients with recurrent GrCTs in the prospective multicentre phase II PARAGON trial. Despite limited available data, hormone therapy appears to be a useful alternative treatment for patients with advanced-stage or recurrent adult GrCTs. Anti-angiogenic agents have also been investigated in patients with recurrent adult GrCT, due to the overexpression of vascular endothelial growth factor. ALIENOR/ENGOT ov-7/GINECO is a randomized study that investigated the concomitant use of bevacizumab and weekly paclitaxel and maintenance therapy with bevacizumab versus weekly paclitaxel and follow-up in 60 patients with relapsed SCST. Addition of bevacizumab to weekly paclitaxel did not result in clinical benefit as measured by 6-month PFS (71% vs 72%).

Small cell carcinomas of the ovary hypercalcemic type (SCCOHT) occur in adolescents and young women with a peak incidence in the third decade of life. Serum calcium levels may serve as a marker for treatment response and recurrences. The prognosis of SCCOHT is very poor and the risk of extra-ovarian spread is high. Small cell carcinomas of the ovary pulmonary type (SCCOPT) affect peri- or postmenopausal patients. SCCOPT are predominantly unilateral and have dismal prognosis even when diagnosed early. A combination of treatment modalities, consisting of debulking surgery, followed by chemotherapy and possibly radiotherapy is recommended. Cisplatin and etoposide-based therapy is generally considered most appropriate. More recently, HDCT for patients who achieved a complete response after surgery and/or chemotherapy with autologous stem cell transplantation (ASCT) rescue has been proposed and is associated with better survival. The management of relapsed disease is often very challenging, since we achieve short remission with chemotherapy. To date, no targeted therapies have been tested in SCCOHT. The promising results of the anti-PD1 antibodies are extrapolated from trials of the small-cell lung cancers.

Keywords: Non-epithelial ovarian cancer, chemotherapy, hormonal therapy, targeted therapy



ISKUSTVO KLINIČKOG BOLNIČKOG CENTRA ZAGREB S PRIMJENOM SEKVENCIONIRANJA NOVE GENERACIJE U UZNAPREDOVALOM KOLOREKTALNOM KARCINOMU

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Uvod: Kolorektalni karcinom (CRC) predstavlja značajan svjetski javnozdravstveni problem, zauzimajući treće mjesto najčešćeg karcinoma u svijetu. Ukupna petogodišnja stopa preživljenja kod bolesnika s uznapredovalim CRC-om iznosi 5 do 10%. Sekvencioniranje nove generacije (NGS) je metoda ključna za napredak u razumijevanju biologije CRC-a, poboljšanje skrbi bolesnika te razvoj novih terapija.

Metode: Retrospektivno su identificirana 62 bolesnika s uznapredovalim CRC-om kod kojih je proveden NGS u našoj ustanovi u razdoblju od svibnja 2020. do prosinca 2023. Odabir bolesnika kod kojih je proveden NGS je bio prema nahođenju ordinarijusa. NGS analiza je provedena korištenjem FoundationOne®CDx testa koji ispituje četiri primarne klase genomskih promjena u 324 relevantna gena za rak. Također, pruža informacije o opterećenju tumora mutacijama (TMB), mikroalitskoj nestabilnosti (MSI) i gubitku heterozigotnosti.

Rezultati: Od 62 bolesnika, 28 su bili muškarci, a 34 žene. Lijevostrani CRC je imalo 48 bolesnika, a desnostrani 14. Medijan dobi pri dijagnozi je iznosio 52 godine, a 31 pacijent se inicijalno prezentirao s uznapredovalim CRC-om. 55 bolesnika je bilo ECOG PS 0, dok su ostali imali PS 1. U većine bolesnika su dokazane RAS mutacije, 34 bolesnika su imala mutaciju KRAS-a, a najčešće se radilo o G13D (9) te G12V (8). Dodatno, uočene su i 2 NRAS mutacije. 4 bolesnika je imalo BRAF V600E mutaciju, 6 PIK3CA mutaciju, 3 ERBB2 amplifikacije, dok su po 2 imala BRCA i PALB2 mutacije. Što se tiče drugih mutacija, 33 bolesnika je imalo APC mutacije, a 39 TP53 mutacije. Na temelju granice od 10 mut/Mb, 6 bolesnika je imalo visok TMB uz ukupni medijan od 4 mut/Mb, dok je 5 bolesnika imalo MSI tumore.

Zaključak: Iako relativno mala, naša kohorta pokazuje podatke iz stvarnog svijeta koji su u skladu s ostalim studijama. NGS ostaje važna metoda za identifikaciju mutacija i procjenu genomske slike kod CRC-a, individualizaciju terapije te poboljšanje učinkovitosti i ishoda liječenja.

Ključne riječi: sveobuhvatno gensko profiliranje, kolorektalni karcinom, metastatski, ciljana terapija

UNIVERSITY HOSPITAL CENTRE ZAGREB EXPERIENCE WITH NEXT-GENERATION SEQUENCING IN ADVANCED COLORECTAL CANCER

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Introduction: Colorectal cancer (CRC) represents a major global public health issue, ranking as the third most common cancer worldwide, with an overall 5-year survival rate ranging from 5 to 10% in patients with metastatic disease. Next-generation sequencing (NGS) plays a crucial role in advancing the understanding of CRC biology, improving patient care through personalized treatment, and driving the development of innovative therapies.

Methods: Sixty-two patients with advanced CRC who underwent NGS at our institution between May 2020 and December 2023 were retrospectively identified. Patient selection for NGS was at the discretion of the physician. The NGS analysis was conducted using FoundationOne®CDx, which examines four primary classes of genomic alterations in 324 well-known cancer-relevant genes. Additionally, it provides information on tumor mutational burden (TMB), microsatellite instability (MSI), and loss of heterozygosity.

Results: In a cohort of 62 patients, there were 28 males and 34 females. Forty-eight patients had left-sided CRC, while 14 cases were right-sided. The median age at diagnosis was 52 years. Thirty-one patients presented with metastatic disease initially. Most (55) exhibited an ECOG PS of 0, with 7 at PS 1. The majority of patients had *RAS* mutations. Thirty-four patients had *KRAS* mutations, the most common being G13D (9) and G12V (8). Additionally, 2 *NRAS* and 4 *BRAF* V600E mutations were observed. Six patients had *PIK3CA* mutations, 3 had *ERBB2* amplifications, and 2 had *BRCA* and *PALB2* mutations. Regarding currently non-druggable mutations, 33 patients had *APC* mutations, while 39 had *TP53* mutations.

Based on the 10 Mut/Mb cut-off value, 6 patients were TMB-high with a median value of TMB 4 mt/mb. 5 patients had MSI-H tumor

Conclusion: Although relatively small, our cohort shows real-world data which is concordant with other similar studies. NGS is an important method for evaluation of genomic landscape in CRC and improvement of treatment outcomes.

Key words: next-generation sequencing, colorectal cancer, metastatic, cancer therapy

SMANJEN INDEKS MIŠIČNE MASE KOD BOLESNIKA S METASTATSKIM KOLOREKTALNIM KARCINOMOM – PROSPEKTIVNA STUDIJA

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Uvod: Značajan broj bolesnika s metastatskim kolorektalnim karcinomom (mCRC) suočava se s malnutricijom zbog biologije bolesti i nuspojava povezanih s liječenjem. Malnutricija mijenja ukupni metabolizam i tjelesni sastav, što u konačnici dovodi do smanjenja mišićne mase. Te se promjene mogu mjeriti na različite načine, uključujući bioelektričnu impedancijsku analizu (BIA). Indeks skeletne mišićne mase (SMI) izračunava se dijeljenjem skeletne mišićne mase u kilogramima (mjereno pomoću BIA) s kvadratom visine u metrima. Ova je studija imala za cilj utvrditi je li smanjeni indeks skeletne mišićne mase (SMI) prognostički čimbenik za preživljenje bez progresije bolesti (PFS) kod bolesnika s mCRC.

Metode: U istraživanje je uključeno ukupno 112 bolesnika koji su započeli liječenje mCRC-a u Kliničkom bolničkom centru Zagreb između 1. siječnja 2020. i 31. prosinca 2022. Bolesnici su vagani pomoću BIA vage (Tanita PRO Body Composition Analyzer MC-780MA-N, Tanita Corporation, Tokyo, Japan) prije početka kemoterapije kao dio cjelokupnog fizikalnog pregleda. Ishodi su praćeni do 31. prosinca 2023.

Rezultati: Bolesnici su podijeljeni u dvije skupine, mušku i žensku (po 56 u svakoj skupini). Muška skupina imala je prosječan SMI od 8,86 sa standardnom devijacijom (SD) od 1,02. Muški bolesnici sa SMI manjim od 1 SD prosjeka imali su kraći PFS (7,6 mjeseci naspram 13,4 mjeseca, $p=0,010$). Ženska skupina imala je prosječan SMI od 6,95 s SD-om od 0,98. Razlika u preživljenju kod žena sa SMI manjim od 1 SD prosjeka nije bila statistički značajna (8,2 naspram 10,8 mjeseci, $p=0,09$).

Zaključak: Na temelju rezultata našeg istraživanja, SMI se pokazao kao pouzdan prognostički pokazatelj kod muških bolesnika s metastatskim mCRC-om, ali ne i kod žena. Potrebna su daljnja istraživanja kako bi se utvrdila točna granična vrijednost i istražio uzrok te razlike.

Ključne riječi: indeks skeletne mišićne mase, kolorektalni karcinom, preživljenje bez progresije, bioelektrična impedanca

REDUCED MUSCLE MASS INDEX IN PATIENTS WITH METASTATIC COLORECTAL CANCER – PROSPECTIVE SINGLE CENTER STUDY

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Introduction: A significant number of patients with metastatic CRC (mCRC) experience malnutrition due to the disease's biology and treatment-related side effects. Malnutrition alters the overall metabolism and body composition, ultimately leading to a reduction in muscle mass. These changes can be measured in several ways, including bioelectrical impedance analysis (BIA). Skeletal muscle index (SMI) is calculated by dividing the skeletal muscle mass in kilograms (measured using BIA) by the square of height in meters.

This study aimed to determine if reduced skeletal muscle index (SMI) was a prognostic factor for progression-free survival (PFS) in patients with mCRC.

Methods: A total of 112 patients who started treatment for mCRC at University Hospital Center Zagreb between January 1, 2020, and December 31, 2022, were included in the study. Patients were weighed with a BIA scale (Tanita PRO Body Composition Analyzer MC-780MA-N, Tanita Corporation, Tokyo, Japan) before the start of chemotherapy as part of a complete physical examination. Outcomes were monitored until December 31, 2023.

Results: Patients were divided into male and female groups (both 56). The male group had an average SMI of 8.86 with a standard deviation (SD) of 1.02. Male patients with SMI less than 1 SD on average had lower PFS (7.6 months vs 13.4 months, $p=0.010$). The female group had an average SMI of 6.95 with an SD of 0.98. The difference in survival in the female patients with SMI less than 1 SD on average was not statistically significant (8.2 vs 10.8 months, $p=0.09$).

Conclusion: Based on the findings of our study, SMI appears to be a reliable prognostic indicator in male patients with metastatic mCRC, but not in females. Further research is required to determine the exact cut-off value and explore the discrepancy's cause.

Keywords: skeletal muscle index, colorectal cancer, progression free survival, bioelectrical impedance

KLINIČKI POTENCIJAL PRIMJENE ONCOTYPE DX TESTA U LIJEČENJU RANOG RAKA DOJKE U HRVATSKOJ – PROSPEKTIVNA MULTICENTRIČNA STUDIJA

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Uvod: Odluka o propisivanju adjuvantne kemoterapije u luminalnim karcinomima dojke predstavlja klinički problem. Tradicionalnim kliničko-patološkim značajkama nedostaje prediktivna vrijednost. Pojava multigenetskih testova, posebice Oncotype DX, olakšala je donošenje odluka. Prethodne studije pokazale su da upotreba Oncotype-a rezultira smanjenjem potrebe za kemoterapijom u 36% pacijenata (49% deeskalirano, 13% eskalirano na kemoterapiju). Nažalost, Hrvatski zavod za zdravstveno osiguranje ne pokriva troškove Oncotype.

Metode: Provedena je prospektivna multicentrična studija u deset od šesnaest zdravstvenih ustanova u Hrvatskoj s organiziranom onkološkom skrbi. Zabilježene su sve bolesnice s novo dijagnosticiranim ranim luminalnim karcinomom dojke. Bolesnice koje su kliničari procijenili kao kandidate za Oncotype, zasebno su zabilježene s odgovarajućim kliničko-patološkim značajkama. Nadalje, upotrijebljeni su podatci radne skupine za karcinom dojke Hrvatskog društva za patologiju i sudsku medicinu o godišnjoj incidenciji karcinoma dojke kako bi se približno odredila potrebu za Oncotype testom, kao i utjecaj upotrebe Oncotype-a u jednoj godini.

Rezultati: Između travnja i lipnja 2023. zabilježena je 241 novodijagnosticirana bolesnica s luminalnim ranim rakom dojke. Među njima, 62 bolesnice (25%) smatralo se podobnim za testiranje na Oncotype. Deset bolesnica (17%) bilo je izvan kriterija kliničkih studija. Prema radnoj skupini patologa za rak dojke, u 2021., bilo je oko 2140 novodijagnosticiranih lokalnih luminalnih karcinoma dojke. Procjena potrebe za Oncotype testom je 535 testova godišnje za Hrvatsku. U našoj studiji bez rezultata Oncotype, 45 bolesnica (72%) preporučena je kemoterapija. Koristeći objavljene podatke, to sugerira da bi u jednoj godini 188 bolesnica moglo biti pošteđeno kemoterapije, dok bi u 18 bolesnica liječenje bilo eskalirano na kemoterapiju, što bi rezultiralo redukcijom propisivanja adjuvantne kemoterapije u 170 bolesnica u jednoj godini.

Zaključak: Multigenetsko testiranje za donošenje odluka o adjuvantnoj kemoterapiji nužno je uvesti u Hrvatsku. Prema procjeni, za hrvatsku populaciju, godišnje bi trebalo napraviti 535 pretraga, što bi rezultiralo sa 170 bolesnica manje na kemoterapiji. Financijski učinak bit će predmet daljnjih istraživanja.

Ključne riječi: Rak dojke, kemoterapija, adjuvantna, prediktivno genetsko testiranje

POSSIBLE CLINICAL IMPACT OF IMPLEMENTING ONCOTYPE DX TEST IN TREATMENT DECISION MAKING FOR EARLY BREAST CANCER IN CROATIA – A PROSPECTIVE MULTICENTER STUDY

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Introduction: The decision to prescribe adjuvant chemotherapy in luminal breast cancers represents a challenging decision. Traditional clinicopathological features lack a predictive value. The widespread use of multigenetic tests, particularly Oncotype DX, has simplified these decisions. Previous studies showed that the use of Oncotype resulted in a decreased need for chemotherapy use in 36% of patients (49% deescalated, 13% escalated to chemotherapy). Unfortunately, Oncotype is not reimbursed by the Croatian Health Insurance Fund.

Methods: Prospective multicentric study was conducted in ten of the sixteen Croatian institutions with established oncology care. All patients with newly diagnosed luminal early breast cancer were recorded. Subgroup of patients who were according to clinicial judgement evaluated as candidates for Oncotype, were separately recorded with corresponding clinicopathological features. Data from a Croatian Pathologist Breast Cancer Working Group was used to approximate the need and clinical impact of Oncotype use in one year.

Results: Between April and June 2023, 241 newly diagnosed luminal early breast cancer patients were recorded. Among them, 62 (25%) were eligible for Oncotype testing. Ten (17%) were outside clinical trial criteria. According to the Breast Cancer Pathologist Working Group, in 2021, there were 2140 newly diagnosed luminal early breast cancers, what, further on, h means approximately 535 multigenetic tests per year is to be prescribed in Croatia. In our study, without Oncoytpe results, 45 (72%) patients were recommended chemotherapy. Using published data, this suggests that in one year, 188 patients could be spared chemotherapy, and in 18 patients, treatment would be escalated to chemotherapy, resulting in less adjuvant chemotherapy prescription in 170 patients.

Conclusion: Multigenetic testing prior to adjuvant chemotherapy decision-making is an unmet need in Croatia. If multigenetic testing was reimbursed, approximately 540 tests would be sufficient to cover the needs of the Croatian population. Testing should result in, per year, 170 patients less receiving chemotherapy. The financial impact is to be further investigated.

Key words: breast cancer, chemotherapy, adjuvant, predictive genomic testing

ULTRA NISKODOZNA RADIOTERAPIJA KOD PACIJENTICE S MYCOSIS FUNGOIDES KOŽE GLAVE I VRATA: PRIKAZ SLUČAJA

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Uvod: Mycosis fungoides (MF) najčešći je oblik kožnog T-staničnog limfoma (CTCL), vrste ne-Hodgkinovog limfoma koji prvenstveno zahvaća kožu. Radioterapija ultra niskim dozama (ULDR) novi je pristup liječenju MF-a, osobito u slučajevima kada tradicionalno liječenje nije indicirano ili u slučajevima kada su iscrpljene druge opcije liječenja.

Prikaz slučaja: 89-godišnja žena javila se na pregled dermatologa radi eritematoznih promjena i plakova na koži lica i vrata. Učinjena je biopsija lezije na licu. Patohistološka analiza verificirala je infiltraciju epidermisa atipičnim limfocitima, imunohistokemijski pozitivnih za CD3, CD4 i CD5, a negativnih za CD79a, CD8 i CD20. Sistemsko liječenje nije indicirano zbog brojnih komorbiditeta. Tim za radioterapiju limfoma naše Ustanove indicirao je palijativnu iradijaciju lokaliziranih lezija na licu. Klinički ciljni volumen (CTV) uključivao je područje od 8 mm od površine kože. Planirani ciljni volumen (PTV) definiran je kao CTV plus margina od 5 mm. PTV je određen rubom od 3 mm od površine kože. Totalna doza od 8 Gy u 2 frakcije, koje su provedene u istom danu, propisana je na srednju dozu PTV-a te je provedena fotonskim snopom 6 MV. Šest mjeseci nakon završetka iradijacije primijećen je potpuni odgovor kožnih lezija bez akutnih nuspojava primijenjenog zračenja.

Zaključak: ULDR predstavlja obećavajuću opciju liječenja MF-a, osobito kod pacijenata kod kojih su konvencionalne mogućnosti liječenja ograničene. Međutim, odluku o primjeni ULDR treba se donijeti individualno na temelju cjelokupnog stanja pacijenta, stadija bolesti i ciljeva liječenja.

Ključne riječi: Radioterapija ultra niskim dozama, Mycosis fungoides, tumori glave i vrata, prikaz slučaja

ULTRA-LOW DOSE RADIOTHERAPY FOR A PATIENT WITH HEAD AND NECK INVOLVEMENT OF MYCOSIS FUNGOIDES: CASE REPORT

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Introduction: Mycosis Fungoides (MF) is the most common form of cutaneous T-cell lymphoma (CTCL), a type of non-Hodgkin lymphoma that primarily affects the skin. Ultra-low dose radiotherapy (ULDR) is an emerging treatment approach for MF, particularly in cases where traditional treatments may not be suitable or for patients who have exhausted other options.

Case Report: An 89-year-old female presented with erythematous patches and plaques on face and neck. A skin biopsy from a cutaneous face lesion was performed and a histological evaluation of the specimen revealed the infiltration of atypical lymphocytes into the epidermis, which was positive for CD3, CD4, and CD5, and negative for CD79a, CD8, and CD20. Systemic treatments were not performed due to comorbid diseases. The oncology board at our radiation therapy department examined the patient and decided to enroll her in a palliative radiation therapy program for the treatment of localized lesions on the face. The clinical target volume

(CTV) included an 8 mm area ranging from the skin surface. The planning target volume (PTV) was defined as the CTV plus a 5 mm margin. The PTV was cropped by a 3 mm margin from the skin surface. A dose of 8Gy in 2 fractions in the same day was prescribed to the mean dose of the PTV using a 6 MV photon beam. Six months after completion of the radiation therapy, complete response was observed for the cutaneous lesions, and there were no observed adverse events resulting from the administered irradiation.

Conclusion: ULDR represents a promising, low-risk option for managing MF, particularly in patients where conventional treatment options are limited or not ideal. However, the decision to use ULDR should be individualized based on the patient's overall condition, disease stage, and treatment goals.

Key words: ultra low dose radiotherapy, Mycosis fungoides, head and neck cancer, case reports

IZBOR LIJEČENJA NAKON PROGRESIJE NA TERAPIJU INHIBITORIMA O CIKLINIMA OVISNIH KINAZA 4/6

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Uvod: Karcinom dojke jedan je od najčešćih karcinoma u svijetu. Najčešći podtip čine HR⁺/HER2⁻ karcinomi dojke za koje standard liječenja predstavlja primjena CDK4/6 inhibitora uz endokrinu terapiju. Međutim, ne postoje prospektivni podaci o idućoj liniji liječenja nakon progresije. Cilj ove studije bio je usporediti učinkovitost liječenja pacijenata s metastatskim HR⁺/HER2⁻ karcinomom dojke nakon progresije na CDK 4/6 inhibitore.

Metode: Provedena je studija u KBC-u Rijeka na pacijenticama s metastatskim HR⁺/HER2⁻ karcinomom dojke liječenim CDK 4/6 inhibitorima tijekom barem jednog mjeseca od listopada 2018. godine. Uspoređivane su vrijednosti ukupnog preživljenja (OS; vrijeme od početka liječenja idućom linijom terapije do smrti ili gubitka kontakta) i preživljenje do progresije bolesti (PFS; vrijeme od početka liječenja idućom linijom terapije do kliničke ili radiološke progresije) nakon progresije na CDK 4/6 inhibitore.

Rezultati: Od 160 pacijentica uključenih u studiju, tijekom terapije CDK4/6 inhibitorima došlo je do progresije bolesti kod 79 pacijenata od kojih je kod 63,3% (N=50) provedena iduća linija liječenja.

Primijećen je duži PFS u pacijenata čija je iduća linija liječenja bila ciljana terapija u odnosu na hormonsku terapiju (HR 0,33 (95% CI 0,15–0,74) i kemoterapiju (HR 0,45 (95% CI 0,44–0,19–1,00)), dok je ukupan OS iznosio 1,4 godine te nije bilo razlike između primijenjene terapije.

Ukupno je 27 pacijenata koji su zatim liječeni drugom linijom terapije uz PFS od 0,3 godine, a OS 0,8 godina, bez razlike u izboru terapije.

Zaključak: U izboru iduće linije terapije, nakon progresije tijekom liječenja CDK4/6 inhibitorima, ciljana terapija povezana je s dužim PFS-om u odnosu na kemoterapiju i hormonsku terapiju. Vrijednosti OS nisu značajnije varirale ovisno o izboru vrste terapije.

Ključne riječi: rak dojke, inhibitori o ciklinima ovisnih kinaza 4/6, ukupno preživljenje, preživljenje bez progresije bolesti

CHOICE OF TREATMENT AFTER PROGRESSION ON CYCLIN DEPENDENT KINASE 4/6 INHIBITORS

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Introduction: Breast cancer is one of the most common cancers in the world. The most common subtype is HR+/HER2- breast cancer, for which the standard treatment consists of CDK4/6 inhibitors along with endocrine therapy. However, there is no prospective data on the next line of treatment after progression. The aim of this study was to compare the effectiveness of treatment in metastatic patients with HR+/HER2- breast cancer after progression on CDK 4/6 inhibitors.

Methods: A study was conducted at KBC Rijeka on female patients with metastatic HR+/HER2- breast cancer treated with CDK 4/6 inhibitors for at least one month from October 2018. Overall survival (OS; time from initiation of next-line therapy to death or loss of contact) and progression-free survival (PFS; time from initiation of next-line therapy to clinical or radiological progression) were compared in patients who underwent subsequent line of therapy after progression on CDK 4/6 inhibitors.

Results: Of the 160 patients included in the study, disease progression occurred in 79 patients on CDK4/6 inhibitors, of which 63.3% (N=50) underwent a subsequent line of treatment.

Longer PFS was observed in patients receiving targeted therapy compared to hormonal therapy (HR 0.33 (95% CI 0.15-0.74) and chemotherapy (HR 0.45 (95% CI 0.44-1.00)), while OS was 1.4 years regardless of type of therapy.

A total of 27 patients were subsequently treated with second-line therapy, with a PFS of 0.3 years and an OS of 0.8 years, with no difference in the choice of therapy.

Conclusion: In the next line of treatment, after progression on CDK4/6 inhibitors, targeted therapy was associated with longer PFS compared to hormonal therapy and chemotherapy. OS values did not vary significantly in the choice of type of therapy.

Key word: cyclin dependent kinase 4/6 inhibitors, overall survival, progression free survival, breast cancer

RAZLIKA IZMEĐU NUSPOJAVA INHIBITORA O CIKLINIMA OVISNIH KINAZA 4/6: ISKUSTVA I PREPORUKE ZA SVAKODNEVNU KLINIČKU PRAKSU

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Uvod: Inhibitori o ciklinu ovisnih kinaza 4 i 6 (CDK4/6 inhibitori) su lijekovi koji se koriste u liječenju hormonski ovisnog raka dojke. U Republici Hrvatskoj odobrena su tri različita lijeka sa sličnom efikasnošću, no različitim profilom nuspojava. S obzirom da nema dovoljno podataka iz stvarne kliničke prakse mijenjaju li se nuspojave tijekom vremena, cilj ovog istraživanja bio je analizirati razlike u profilu nuspojava nakon 1, 3 i 6 mjeseci praćenja.

Metode: Istraživanje je provedeno u Klinici za tumore KBC Rijeka na skupini od 163 žena liječenih abemaciclibom, palbociclibom i ribociclibom. Nuspojave su istraživane nakon 1, 3 i 6 mjeseci praćenja. Deskriptivna analiza i hi-kvadrat test je učinjen u programu MedCalc (MedCalc Software bvba, Ostend, Belgija).

Rezultati: Najčešće zabilježene nuspojave su neutropenija (57.0%) i leukopenija (42.9%). Nakon prvog su mjeseca praćenja leukopenija i neutropenija bile najmanje zastupljene u pacijentica liječenih abemaciclibom (33,3%)($p=0,0055$; $p=0,002$). U pacijentica liječenih abemaciclibom prati se i najveća incidencija proljeva (33,3%) u odnosu na palbociklib (1.8%) te ribociklib (0%) ($p<0,0001$). Nefrotoksičnost nije zabilježena u skupini liječenih palbociklibom, dok kod abemacicliba iznosi 13,9% te 10,9% kod ribocikliba ($p=0,02$). Nakon tri te šest mjeseci od početka liječenja nema statistički značajne razlike u leukopeniji ($p=0,21$) te nefrotoksičnosti ($p=0,09$) među ispitivanim skupinama, dok je ista ponovo zabilježena u incidenciji proljeva skupine liječene abemaciclibom ($p<0,0001$).

Zaključak: U ranom praćenju, abemaciclib rezultira s najboljim profilom leukograma, no čestim proljevom, radi čega je potreban oprez u pacijenata s ranije poznatim gastrointestinalnim bolestima. Iako se palbociklib povezuje s padom vrijednosti leukograma, rezultira s najmanje nefrotoksičnosti pa bi mogao biti lijek izbora u nefroloških bolesnika. Ribociklib također rezultira padom vrijednosti leukocita i povremenom nefrotoksičnošću, no ne rezultira proljevom. Osim proljeva, razlika u nuspojavama između CDK4/6 inhibitora se smanjila nakon 3 i 6 mjeseci praćenja.

Ključne riječi: inhibitori o ciklinima ovisnih kinaza 4/6, nuspojave; karcinom dojke, metastatski

DIFFERENCE BETWEEN SIDE EFFECTS OF CYCLIN DEPENDENT KINASE 4/6 INHIBITORS: EXPERIENCE AND RECOMMENDATIONS FOR REGULAR CLINICAL USE

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Introduction: Cyclin-dependent kinase inhibitors 4 and 6 (CDK4/6 inhibitors) are hormone-dependent breast cancer treatment drugs. In the Republic of Croatia, three different drugs with similar efficacy but different side effect profiles have been approved. Since there is insufficient data from clinical practice about these side effects over time, this research paper aimed to analyze the incidence of different side effects after 1,3,6-month follow-ups.

Methods: Research was conducted at the Tumor Clinic, University Hospital Center Rijeka, on 163 women treated with abemaciclib, palbociclib, and ribociclib. Side effects were observed after 1, 3, and 6-month follow-ups. Descriptive analysis and Chi-square test were conducted using a computer program called MedCalc (MedCalc Software bvba, Ostend, Belgium).

Results: The most common side effects were neutropenia (57.0%) and leukopenia (42.9%). After the first month, leukopenia and neutropenia were the least present in patients treated with abemaciclib (33.3%)($p=0,0055$; $p=0,002$). The largest incidence of diarrhea was observed in abemaciclib-treated patients (33.3%) in regard to palbociclib (1.8%) and ribociclib (0%)($p>0,0001$). Nephrotoxicity did not occur in the group treated with palbociclib, but it did occur with abemaciclib (13.9%) and ribociclib (10.9%)($p=0,02$). After 3 and 6 months of treatment, there is no statistical significance in leukopenia ($p=0,21$) and nephrotoxicity ($p=0,09$) between groups. At the same time, the difference in diarrhea incidence is still statistically significant in the abemaciclib group ($p<0,0001$).

Conclusion: In the early follow-ups, abemaciclib presented with the best leukogram but with frequent diarrhea. Therefore, caution is needed in patients with gastrointestinal diseases. Palbociclib decreases leukocyte count, yet it is the least nephrotoxic drug, so it could be administered to patients with kidney diseases. Ribociclib also presents with decreased leukocyte count and occasional nephrotoxicity but does not cause diarrhea. Except for diarrhea, the difference in side effects among CDK4/6 inhibitors decreased after 3 and 6-month follow-ups.

Key words: cyclin dependent kinase 4/6 inhibitors; side effects; breast cancer, metastatic

TERAPIJSKI PRISTUP KARCINOMU CRIJEVA KOD PACIJENTA S MIASTENIJOM GRAVIS: PRIKAZ SLUČAJA

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Uvod: Ne postoje smjernice koje evaluiraju kemoterapiju karcinoma crijeva uz miasteniju gravis (MG).

Prikaz slučaja: Bolesniku (67 godina) u kliničkoj slici ileusa učinjena je sigmoidektomija s postavljanjem kolostome u hitnoći u ožujku 2024. Patohistološki je dokazan adenokarcinom sigmoidnog kolona pT4aN1b (KRAS mutacija G12S; NRAS i BRAF bez mutacija) s multiplim jetrenim metastazama. Bolesniku je u studenom 2016. dijagnosticirana MG koja se prezentirala disartrijom i disfagijom uz pozitivna protutijela na acetilkolinске receptore. Do sad je imao nekoliko miasteničnih kriza liječenih kortikosteroidima, ponavljanim plazmaferezama i intarvenskim imunoglobulinima. U trenutku planiranja onkološkog liječenja MG je pod kontrolom uz piridostigmin 240 mg i mikofenolat mofetil 200 mg tablete dnevno. Dodatak mikofenolat mofetila je pridonio stabilizaciji MG, te od tada nije zabilježena ni jedna miastenička kriza. Bolesnik je heterozigotni nositelj alela za reduciranu aktivnost dihidropirimidin dehidrogenaze i UDP-glukuroniltransferaze. Multidisciplinarni tim je odlučio započeti liječenje prema FOLFIRI protokolu, ali primjenjujući 75% uobičajene doze uz bevacizumab. Neutropenija, polineuropatija i mogući kolinergički sindrom povezan s irinotekanom su predstavljali poznati prihvatljiv rizik ove terapije. Nakon tri mjeseca na kontrolnom CT-u prsnog koša, trbuha i zdjelice, zabilježena je 35%-tno smanjenje jetrenih metastaza. Postignut je parcijalni odgovor na terapiju prema RECIST kriterijima. Bolesnik je dosad ukupno primio 9 ciklusa FOLFIRI terapije i bevacizumaba. Nije uočena neutropenija i polineuropatija.

Zaključak: Prezentirani bolesnik je starije životne dobi, i liječen imunoglobulinima što predstavlja rizične čimbenike za pojavu ostalih karcinoma u ljudi s MG. Cilj liječenja je kontrola metastatske, neresektibilne bolesti s prvom linijom terapije. Pretpostavljajući da će prva linija liječenja trajati najduže i uz činjenicu o kumulativnoj toksičnosti preparata platine, započeta je kemoterapija bez platine. Uzimamo u obzir mogućnost liječenja preparatima platine u sljedećoj liniji. Odluka o 75% uobičajene doze je temeljena na farmakogenetičkom profilu bolesnika i nedostatku smjernica što se tiče izbora i doze onkoloških lijekova uz neurološku patologiju opisanog slučaja.

Ključne riječi: karcinom kolona, myasthenia gravis, liječenje, kemoterapija

TREATMENT CHALLENGE OF COLON CANCER AND MYASTHENIA GRAVIS: A CASE REPORT

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Introduction: No guidelines related to the treatment of colon cancer and myasthenia gravis (MG) exist.

Case Report: A sigmoidectomy with colostomy placement in March 2024 was performed in a 76-year-old Caucasian presented with ileus. In November 2016, the patient was diagnosed with MG, which presented with dysarthria and dysphagia with positive antibodies to acetylcholine receptors. So far, he experienced several myasthenic crises treated with corticosteroids, repeated plasmapheresis, and intravenous immunoglobulins. Myasthenia is under control with pyridostigmine 240 mg and mycophenolate mofetil 200 mg tablets daily. Mycophenolate mofetil contributed to the stabilization of MG, and since then no myasthenic crisis has been recorded. The patient is a heterozygous carrier of the allele for reduced activity of dihydropyrimidine dehydrogenase and

UDP-glucuronyltransferase. The multidisciplinary team started treatment according to the FOLFIRI protocol, applying 75% of the usual dose with bevacizumab. Neutropenia, polyneuropathy, and possible cholinergic syndrome associated with irinotecan were known acceptable risks of this therapy. After three months, a control CT scan revealed a 35% reduction in liver metastases representing a partial treatment response according to RECIST criteria. So far, the patient has received a total of 9 cycles of FOLFIRI therapy and bevacizumab. Neutropenia and polyneuropathy were not observed.

Conclusion: The presented patient is elderly and treated with immunoglobulins, which represents risk factors for the occurrence of other cancers in people with MG.^{1,2} The goal of treatment is to control the metastatic, unresectable disease with first-line therapy. Assuming that the first-line treatment would last the longest and with the fact of the cumulative toxicity of platinum preparations, chemotherapy without platinum was started. We consider the possibility of treatment with platinum preparations in the next line. The decision on 75% of the usual dose is based on the patient's pharmacogenetic profile and the lack of guidelines regarding the choice and dose of antineoplastic drugs in addition to the neurological pathology of the described case.

Key words: colon cancer, myasthenia gravis, treatment, chemotherapy

USPOREDBA TRAJANJA I GODINE ODRŽAVANJA KOLEGIJA ONKOLOGIJE UNUTAR STUDIJA MEDICINE NA MEDICINSKIM FAKULTETIMA U JUGOISTOČNOJ EUROPI

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Uvod: Onkologija je grana medicine koja se bavi dijagnostikom i liječenjem malignih bolesti. Važnost učenja onkologije proizlazi iz činjenice da su prema izvješću Svjetske zdravstvene organizacije iz 2020. godine maligne bolesti drugi uzrok smrti u svijetu. Studenti medicine u jugoistočnoj Europi studiraju šest godina, pri čemu je onkologija dio njihovog nastavnog plana i programa. Cilj ovog istraživanja je osvijestiti razliku u trajanju kolegija iz onkologije različitih studija medicine u jugoistočnoj Europi.

Metode: Podatci o planovima i programima medicinskih fakulteta za period 2023/2024 prikupljeni su s internetskih stranica sveučilišta u jugoistočnoj Europi, uključujući Hrvatsku, Bugarsku, Albaniju, Srbiju, Bosnu i Hercegovinu, Crnu Goru i Sjevernu Makedoniju.

Rezultati: Postoji velika razlika u trajanju i godini održavanja kolegija iz onkologije unutar studija medicine na medicinskim fakultetima diljem jugoistočne Europe, kako unutar pojedinih zemalja, tako i između njih. Od 16 fakulteta čiji su podatci prikupljeni, onkologija nije obavezan kolegij studija medicine na njih dva koji nude onkologiju samo kao izborni predmet. U zemljama gdje je onkologija obavezna, trajanje turnusa može varirati od samo 7 dana do cijelog semestra. Druga razlika između medicinskih studija je godina održavanja kolegija iz onkologije. Kolegij se na četiri fakulteta održava na četvrtoj godini, na sedam fakulteta na petoj te na pet fakulteta na šestoj godini studija.

Zaključak: Ova usporedba programa medicinskih studija fakulteta medicine jugoistočne Europe ukazala je na razlike u trajanju i godini održavanja kolegija iz onkologije. Daljnja istraživanja bila bi korisna kako bi se procijenio učinak različitog trajanja i godine održavanja kolegija iz onkologije na ishode učenja studenata te na njihov budući odabir specijalizacije iz onkologije.

Ključne riječi: onkologija, nastavni plan i program, Jugoistočna Europa, medicinski fakultet

COMPARISON OF THE DURATION AND TIMING OF CLINICAL ROTATION IN ONCOLOGY IN MEDICAL SCHOOLS IN SOUTHEASTERN EUROPE

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Introduction: Oncology is the branch of medicine focused on the diagnosis and treatment of malignant tumors. The importance of learning oncology lies in the fact that cancer is the second cause of death according to a 2020 World Health Organization report. Medical students in Southeastern Europe study for six years with oncology forming part of their curriculum. The purpose of this research is to point out the difference in the duration and timing of clinical rotation in oncology in medical schools in Southeastern Europe.

Methods: Data on medical school curriculums for the year 2023/2024 was collected from websites of universities in the southeastern region including Croatia, Bulgaria, Albania, Serbia, Bosnia and Herzegovina, Montenegro and North Macedonia.

Results: There is a wide variation in duration and timing of clinical rotation in oncology in medical studies in medical schools across Southeastern Europe, both within and between countries. Out of 16 medical schools from which data was collected, oncology is not a compulsory clinical rotation in two of them which only offer oncology as an optional rotation. In other countries where oncology is obligatory the duration of the rotation can range from as short as 7 days to as long as the whole semester. The other difference between medical studies is their timing of the oncology rotation. Medical studies of four medical schools place oncology in the fourth year, seven of them place oncology in the fifth year and five of them in the sixth year of the curriculum.

Conclusion: This report has shown variation in duration and timing of clinical rotation in oncology in medical studies in medical schools in Southeastern Europe. Further research would be useful to evaluate the effect of differing duration and timing of rotation on students' oncology learning outcomes and on their future choice to train in this specialty.

Keywords: oncology, curriculum, Southeastern Europe, medical school

UTJECAJ PORASTA MASE NA DJELOTVORNOST IMUNOTERAPIJE

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Uvod: Veliki broj istraživanja ukazuje kako pretilost može imati značajan utjecaj na učinkovitost imunoterapije. Pretilost se može smatrati kroničnim upalnim stanjem koje proizlazi iz povećane produkcije proupalnih citokina u adipocitima. Može dovesti do smanjene sposobnost imunološkog sustava da prepozna i uništi tumorske stanice. Druge studije sugeriraju kako pretilost može paradoksalno pojačati odgovor na imunoterapiju. Povećana količina leptina i inzulina u pretilih bolesnika može potaknuti imunosne mehanizme.

Metode: U presječnoj studiji smo retrospektivno obradili podatke bolesnika koji su bili na imunoterapiji nivolumabom. Uključeni su bolesnici liječeni u KBCO u razdoblju od 2019. do 2024. godine. Proučavane kategorije su dob, spol, trajanje imunoterapije, tjelesna masa i BMI na početku te na kraju liječenja, uz primarno sjelo (karcinomi glave i vrata, kože, pluća, bubrega i mokraćnog mjehura).

Rezultati: Analizirani su podaci 83 bolesnika, 60 (72,29%) muškaraca i 23 (27,71%) žene. Prosječna masa na početku liječenja bila je 74,76 kg (36; 111) i BMI 25,08 kg/m² (13,2; 39,8) dok je prosječna masa na kraju liječenja bila 73,58 kg (33; 110) i BMI 24,65 kg/m² (12,1; 37,8). Prosječno trajanje liječenja za sve regije karcinoma liječenim nivolumabom je bilo 171 dan (15; 91; 746), odnosno 24,42 tjedna. 17 bolesnika imalo je porast tjelesne mase, a njih 25 je izgubilo na masi. 41 (49,36%) bolesnik je gubio na masi te primio mali broj ciklusa terapije. S druge strane, 15 (18,07%) bolesnika je tijekom terapije dobilo na masi ili bilo stacionarno te je primilo veći broj ciklusa. Može se zaključiti kako je 56 (67,47%) bolesnika u skupini studija koje sugeriraju da promjene tjelesne mase mogu mijenjati odgovor na imunoterapiju.

Zaključak: Iz rezultata možemo uočiti kako naši podaci prate hipoteze da porast mase pozitivno utječe na trajanje imunoterapije. Bolesnici s dobitkom na masi ili stacionarnom masom tijekom imunoterapije, imaju duže bolest pod kontrolom.

Ključne riječi: tjelesna masa, indeks tjelesne mase, nivolumab, ishodi liječenja

IMPACT OF WEIGHT GAIN ON IMMUNOTHERAPY

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Introduction: A significant number of studies suggests that obesity can have a substantial impact on the effectiveness of immunotherapy. Obesity can be considered a chronic inflammatory condition resulting from increased production of pro-inflammatory cytokines in adipocytes. It may lead to a reduced ability of the immune system to recognize and destroy tumor cells. Other studies suggest that obesity might paradoxically enhance the response to immunotherapy. Increased levels of leptin and insulin in obese patients may stimulate immune mechanisms.

Methods: In a cross-sectional study, we retrospectively analyzed data from patients undergoing nivolumab. The study included patients treated at KBCO between 2019 and 2024. The categories studied included age, sex, duration of immunotherapy, body weight, and BMI at the beginning and end of treatment period, along with cancer regions (head and neck, skin, lung, kidney, and bladder).

Results: Data from 83 patients were analyzed, including 60 (72.29%) men and 23 (27.71%) women. The average weight at the start of treatment was 74.76 kg (range: 36–111) and BMI was 25.08 kg/m² (13.2–39.8), while the average weight at the end of treatment was 73.58 kg (33–110) and BMI was 24.65 kg/m² (12.1–37.8). The average duration of treatment for all cancer regions treated with nivolumab was 171 days (15-91-746). 17 patients experienced weight gain, while 25 lost weight. 41 (49.36%) patients lost weight and received a small number of therapy cycles. 15 (18.07%) patients gained weight or remained stable and received a greater number of cycles. It can be concluded that 56 (67.47%) patients fall into the study group suggesting that changes in body weight may alter the response to immunotherapy.

Conclusion: The results indicate that our data support the hypothesis that weight gain positively influences the duration of immunotherapy. Patients who gained or maintained weight during immunotherapy had longer disease control.

Keywords: weight, body mass index, nivolumab, treatment outcomes

POJAVNOST NESANIRANIH ZUBA KOD BOLESNIKA KOJI ŽIVE U RURALNOM PODRUČJU, A BOLUJU OD METASTATSKOG KASTRACIJSKI REZISTENTNOG RAKA PROSTATE, U ODNOSU NA ONE KOJI ŽIVE U URBANOM SREDIŠTU – ISKUSTVO JEDNOG CENTRA

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Uvod: Metastatski rak prostate otporan na kastraciju (mKRRP) oblik je uznapredovalog raka prostate koji progredira unatoč androgen deprivacijskoj terapiji. Bolesnicima s metastazama u kostima se zbog rizika od klinički značajnih koštanih neželjenih događaja preporučuju bisfosfonati ili denosumab. Preduvjet za primjenu ovih lijekova je dobro stanje zuba.

Metode: U ovoj retrospektivnoj opservacijskoj studiji, provedenoj na Službi za internu medicinu opće bolnice Šibensko-kninske županije, pretražili smo evidenciju bolesnika s mKRRP-om koristeći lokalno vođeni registar. Pacijenti su liječeni u našoj bolnici od siječnja 2022. do prosinca 2023. godine. Stanje njihovih zuba, kao i cjelokupno oralno zdravlje, ispitivali su onkolog i/ili stomatolozi.

Rezultati: U ovu studiju uključeno je ukupno 26 bolesnika s mKRRP-om, u dobnom rasponu od 49–88 godina. Velika većina njih imala je metastaze u ili također u kostima (88%), dok je manjina (12%) imala isključivo nekoštane metastaze.

Među pacijentima koji su imali metastaze u kostima, njih 19 primilo je medikamentoznu anti-resorptivnu terapiju, i to: bisfosfonate (74%), denosumab (16%), a (10%) bolesnika je u početku liječeno bisfosfonatima, ali je zbog razvoja bubrežne insuficijencije anti-resorptivna terapija promijenjena u denosumab.

Samo u 3 bolesnika s mKRRP-om i koštanim metastazama nije propisana medikamentozna anti-resorptivna terapija, jer je zaključeno kako ih prisutnost metastaza u kostima ne ugrožava.

Zbog nezadovoljavajućeg stanja zuba u 4 bolesnika medikamentozna anti-resorptivna terapija nije propisana. Dvoje od ova 4 bolesnika žive u urbanom središtu, a dvoje dolaze iz ruralnih sredina.

Zaključak: Podaci dobiveni u našem istraživanju pokazuju kako u 15% bolesnika, zbog nezadovoljavajućeg stanja zuba, nije propisana medikamentozna anti-resorptivna terapija. Nezadovoljavajuće stanje zuba jednakom učestalošću se pojavljivalo neovisno žive li osobe u urbanom središtu ili ruralnim područjima. Potrebne su daljnje studije kako bi se potvrdili rezultati ove studije, koja je provedena u jednom centru.

Ključne riječi: rak prostate; stanje zuba, anti-resorptivno liječenje, ruralno, urbano

THE COMPARISON OF FREQUENCY OF POOR DENTAL STATUS IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATIC CANCER LIVING IN RURAL AREAS VERSUS THE ONES WHO ARE LIVING IN URBAN CENTER – SINGLE CENTER EXPERIENCE

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Introduction: Metastatic castration-resistant prostate cancer (mCRPC) is advanced prostate cancer that continues to progress despite androgen deprivation therapy. In these patients who are at risk for clinically significant

skeletal-related events (SREs), bisphosphonates or denosumab are recommended. Prerequisite for administration of these agents is good dental status.

Methods: In the present retrospective observational study, conducted at the Department of Internal Medicine at the General Hospital od Šibenik-Knin county, we examined the records of patients with mCRPC using a locally maintained registry. The patients were treated in our hospital from January 2022. to December 2023. Their dental status, as well as overall oral health, was examined by oncologists and/ or dentists.

Results: A total of 26 patients with mCRPC, in the age range of 49–88 years, were included in this study. The vast majority of them had metastases in or also in the bones (88%), while a minority (12%) had exclusively extra osseous metastases.

Among the patients who had bone metastases, 19 of them have received medical antiresorptive therapy: bisphosphonates (74%), denosumab (16%), and (10%) of patients has been treated at the beginning with bisphosphonates, but later with denosumab.

Only in 3 patients with mCRPC, and bone metastases, this therapy was not prescribed because it did not endanger them.

Due to unsatisfactory dental status in 4 of patients with mCRPC, and bone metastases, treatment with anti-resorptive therapy was not indicated. Regarding their place of living two of these patients came from urban centers, two are living in rural areas.

Conclusion: The data obtained in our study indicate that there was no difference among 15% of patients with mCRPC and bone metastases, who did not receive bone antiresorptive agents, whether the patients are living in urban centers or rural areas. Further studies are necessary to confirm the results of our single-center study.

Keywords: prostate cancer; dental status, antiresorptive therapy, rural, urban

KALCIFILAKSIJA U BOLESNICE NA TERAPIJI PEMIGATINIBOM – PRIKAZ SLUČAJA

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Uvod: Pemigatinib je inhibitor receptora fibroblastnog faktora rasta (FGFR). Koristi se u liječenju metastatskog kolangiokarcinoma s dokazanom *FGFR2* fuzijom ili preraspodjelom. Dermatotoksičnost je poznata, ali se u literaturi opisuje i kalcifilaksija – ishemija kože uzrokovana kalcifikacijom kapilara. Uzroci i liječenje nisu jasno definirani.

Prikaz slučaja: Bolesnici staroj 41 godinu, bez komorbiditeta, je 2021. dijagnosticiran intrahepatalni kolangiokarcinom. Liječena je transarterijskom kemoembolizacijom (TACE), stereotaksijskom radioterapijom (SBRT) i desnostranom hepatektomijom i metastazektomijom VII segmenta, pa kemoimunoterapijom. U listopadu 2023. započela liječenje pemigatinibom. Nakon 7 mjeseci terapije se na koži ispod desne dojke javila eritematозна promjena s bulom koja je brzo progredirala u dermalnu nekrozu. Patohistološki nalaz je govorio u prilog nekrozi s ovapnjenjima. U srpnju 2024. se javila u našu hitnu službu u kliničkoj slici sepse s multiplim nekrotičnim promjenama kože dubine i do 2 cm s ekspaniranim dubokim tkivima. U nalazima je imala visoke upalne parametre, hiperfosfatemiju i hipoalbuminemiju. U mikrobiološkim uzorcima iz rana izolirani su brojne gram pozitivne i gram negativne bakterije. Liječena je antibioticima, analgeticima, parenteralnom hidracijom, 20% albuminima, uz redovite prevoje rana i prekid terapije pemigatinibom. Naknadno su se na natkoljenici javile dvije bulozne promjene koje su bioptirane. Pregledana je od strane dermatologa i imunologa te je postavljena sumnja da se radi o neželjenom učinku lijeka – kalcifilaksija. Ubrzo nakon, unatoč primijenjenim mjerama liječenja bolesnica umire u kliničkoj slici sepse i terminalne maligne bolesti. Nakon smrti pristizje i dermatohistopatološki nalaz koji može odgovarati kalcifilaksiji.

Zaključak: Kalcifilaksija je moguć neželjeni učinak lijeka pemigatiniba premda se opisuje i s drugim lijekovima ili bolestima, poput bubrežnog zatajenja ili hiperparatireoze. Poveznica bi sa terapijom pemigatinibom mogla biti i hiperfosfatemija, koja je poznata nuspojava. Smrtnost je razmjerno visoka, pogotovo kod otvorenih ulceracija. Potrebno je redovito nadzirati bolesnike i pravovremeno prekinuti terapiju. Biti će potrebna dodatna istraživanja kako bi se jasno definiralo zbrinjavanje.

Ključne riječi: pemigatinib, kalcifilaksija, neželjeni učinci, kolangiocelularni karcinom

CALCIPHYLAXIS IN A PATIENT TREATED WITH PEMIGATINIB – A CASE REPORT

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Introduction: Pemigatinib is a fibroblast growth factor receptor (FGFR) inhibitor. It is used in treatment of metastatic cholangiocarcinoma with *FGFR* fusion or rearrangements. Dermatotoxicity is common, but also calciphylaxis – skin necrosis caused by vascular calcification, has been described as a very rare side effect. Mechanism and treatment is not defined.

Case Report: 41-year-old female patient, previously healthy, was diagnosed with intrahepatic cholangiocarcinoma in 2021. She was treated with transarterial chemoembolization (TACE), stereotaxic radiotherapy (SBRT) and right-sided hepatectomy and metastasectomy of the VII segment, and then with chemoimmunotherapy. Treatment with pemigatinib was started in October 2023. After 7 months of therapy, an erythematous skin lesion appeared under the right breast with a bulla that quickly progressed into dermal necrosis. Biopsy reported necrosis with calcifications. In July 2024, she presented to our department with multiple necrotic skin changes, up to 2 cm deep with exposed deep tissue. Laboratory findings showed high CRP, hyperphosphatemia, and hypoalbuminemia. Multiple gram-positive and gram-negative bacteria were isolated from the wounds. Pemigatinib was discontinued. She was treated with antibiotics, analgesics, parenteral hydration, 20% albumin. Wounds were regularly dressed. Later, two new bullous changes appeared on the thigh that were biopsied. She was examined by a dermatologist and an immunologist and calciphylaxis was suspected. Soon after, despite treatment measures, the patient died due to sepsis and terminal malignant disease. Dermatohistopathological exam reported calcium deposits that could correspond with calciphylaxis.

Conclusion: Calciphylaxis could be a side effect of pemigatinib, although it has been described with some other drugs and conditions, such as renal failure or hyperparathyroidism. Hyperphosphatemia, a known side effect of pemigatinib, could be related to calciphylaxis. Mortality is relatively high, especially in advanced stages. Patients must be monitored closely for dermatotoxicity, but further research is needed to better define treatment.

Keywords: pemigatinib, calciphylaxis, side effects, cholangiocarcinoma

KIRURŠKO LIJEČENJE SARKOMA DOJKE U MUŠKARCA

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Uvod: Cilj ovog prikaza slučaja je prikazati rijedak slučaj upalnog nediferenciranog pleomorfog sarkoma u muškoj dojci.

Prikaz slučaja: 64-godišnji muškarac napipao je bezbolni čvor na lijevoj dojci. Širokoiglena biopsija nije pokazala konačnu dijagnozu jer je klasificirana kao B3 pa je učinjena ekscizijska biopsija tkiva koja je pokazala je nediferencirani pleomorfni sarkom promjera 4,5 cm, infiltriran upalnim stanicama. Nakon što smo potvrdili dijagnozu, indicirana je terapija. Učinjena je Stewartova incizija i mastektomija. Patohistološka analiza potvrdila je negativne rubove kirurške resekcije. Nakon mjesec dana PET CT skeniranje pokazalo je plućne metastaze i pacijent je prošao 6 ciklusa kemoterapije doxorubicinom s dobrim odgovorom i postignutom remisijom plućnih metastaza. Tri godine kasnije, tumor je recidivirao i infiltrirao torakalni zid. Pacijent je ponovno podvrgnut kirurškom zahvatu. Učinili smo ekstirpaciju tumora, resekciju torakalne stijenke s velikim prsnim mišićem te resekciju petog, šestog i sedmog rebra i torakoplastiku uz upotrebu core matriks i biološkom mrežicom za rekonstrukciju defekta. Prema patohistološkom nalazu distalni rub resekcije bio je infiltriran tumorskim stanicama pa je učinjena radioterapija. Veća torakalna resekcija nije bila moguća jer bi utjecala na mehaniku disanja. Postoperativni tijek bio je normalan, bez paradoksalnog disanja. Bolesnik je četiri godine nakon liječenja bio u remisiji prema PET-CT pregledu.

Zaključak: Prikazan je rijedak slučaj nediferenciranog pleomorfog sarkoma dojke, njegova mogućnost recidiva i udaljenih metastaza, mogućnosti liječenja, važnost i ograničenja operativnog liječenja kao i dobiti onkoloških zahvata i nepredvidiv klinički tijek bolesti.

Ključne riječi: sarkom dojke; recidiv sarkoma dojke; resekcija toraksa; torakoplastika

SURGICAL TREATMENT OF BREAST SARCOMA IN A MALE PATIENT

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Introduction: The objective of this case report is to present a rare case of inflammatory undifferentiated pleomorphic sarcoma in a male breast.

Case Report: A 64-year-old man palpated a painless nodule on the left breast. Core needle biopsy did not reveal the final diagnosis as it was classified as B3 so an excisional biopsy of the tissue was performed, which revealed an undifferentiated pleomorphic sarcoma with a diameter of 4.5 cm, infiltrated with inflammatory cells. After we confirmed the sarcoma operation therapy was indicated. Stewart incision was performed and mastectomy was done. Pathohistological analysis confirmed negative surgical resection margins. After one month PET CT scan revealed lung metastases and the patient underwent 6 chemotherapy cycles of doxorubicin with good response and contribution of lung metastases remission. Three years later, the tumor recurred and infiltrated the thoracic wall. The patient underwent a surgical procedure again. We did the extirpation of tumor, resection of thoracic wall with large pectoral muscle and within fifth, sixth and seventh ribs resection and thoracoplasty with core matrix and bio-net was performed for reconstruction of the defect. On pathohistology findings distal resection margin was infiltrated by tumor cells so radiotherapy was performed. Larger thoracic resection was not possible as it would affect breathing mechanics. The postoperative course was normal, without paradoxical breathing. The patient has been in remission according to PET-CT examination for four years after the treatment.

Conclusion: We have presented a rare case of undifferentiated pleomorphic sarcoma in the breast, its potential for recurrence and distant metastases, the possibilities of treatment, the importance and limitations of operative treatment as well as the benefit of oncological procedures and unpredictable clinical course of disease.

Keywords: Breast sarcoma, recurrence of breast sarcoma, thoracic wall resection, thoracoplastica

USPJEŠNOST LIJEČENJA INHIBITORIMA O CIKLINIMA OVISNIH KINAZA 4/6 OVISNO O METASTATSKOM SIJELU KARCINOMA DOJKE

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Uvod: Inhibitori kinaza ovisnih o ciklinu 4/6 (CDK 4/6) se koriste u liječenju hormon ovisnih, HER-2 negativnih metastatskih karcinoma dojke. U Republici Hrvatskoj su odobrena tri različita CDK 4/6 inhibitora, no nema dovoljno podataka iz stvarne kliničke prakse ima li određeni lijek prednost pred drugima. U našem smo istraživanju usporedili učinkovitost CDK 4/6 inhibitora ovisno o anatomske lokalizaciji metastaza.

Metode: Istraživanje je provedeno na Klinici za tumore Kliničkog bolničkog centra Rijeka na pacijenticama oboljelima od metastatskog karcinoma dojke koje su barem jedan mjesec bile u liječenju CDK 4/6 inhibitorima. Između formiranih skupina su se uspoređivali ukupno preživljenje (OS) te preživljenje bez progresije bolesti (PFS) s obzirom na prisutnost određenih metastaza također uz međusobnu usporedbu i pojedinih CDK 4/6 inhibitora. Za istraživanje se koristila Kaplan-Meier metoda i log-rank test.

Rezultati: Rezultati ukazuju da pacijentice s jetrenim metastazama imaju kraći PFS (1,5 vs 3 godine, $p=0.001$) i OS (2,8 vs 5,9 godina, $p=0.0001$) u odnosu na pacijentice bez jetrenih metastaza. Rezultati se nisu razlikovali ovisno o prisutnosti drugih metastatskih sjela. Što se tiče izbora lijeka, pokazali smo da pacijentice s metastazama kosti imaju dulji PFS ako su liječene s ribociklibom nego palbociklibom (3,31 vs 1,46 godina, $p=0,03$) te pacijentice s metastazama jetre imaju dulji PFS ako su liječene s abemaciclinom nego palbociklibom (2,3 vs 0,72 godine, $p=0,02$).

Zaključak: Postojanje jetrenih metastaza jedino je metastatsko sjelo koje je utjecalo na preživljenje, a dokazali smo i da je liječenje abemaciclibom povezano s duljim PFS-om od palbocikliba u navedenom settingu. S druge strane, ribociklib je povezan s duljim PFS-om od palbocikliba u pacijentica s koštanim metastazama.

Gljučne riječi: inhibitori o ciklinima ovisnih kinaza 4/6, metastaze jetre, rak dojke, ishodi liječenja

EFFECTIVENESS OF CYCLIN DEPENDENT KINASE 4/6 INHIBITOR TREATMENT DEPENDING ON THE BREAST CANCER METASTATIC SITE

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Introduction: Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors are used in hormone dependent, HER-2 negative metastatic breast cancer treatment. Three different CDK 4/6 inhibitors are approved in the Republic of Croatia but there is not enough data from clinical practice regarding the advance of one CDK 4/6 inhibitor to another. We have compared the effectiveness of CDK 4/6 inhibitors depending on the metastatic site of breast cancer.

Methods: The research has been conducted in The Cancer Clinic of The Clinical Hospital Center Rijeka on breast cancer patients that were on the CDK 4/6 inhibitor therapy for at least a month. Overall survival (OS) and

progression free survival (PFS) were compared between groups that were formed depending on the presence of the specific metastatic site. Same factors were compared between different CDK 4/6 inhibitors, depending on the metastatic site also comparing different CDK 4/6 inhibitors. Kaplan-Meier method and log-rank test were used for the statistical analysis.

Results: Results show that patients with liver metastasis have shorter PFS (1.5 vs 3 years, $p=0.001$) and OS (2.8 vs 5.9 years, $p=0.0001$) in comparison to liver metastasis free patients. Results have not differed depending on the presence of other metastatic sites. Regarding the CDK 4/6 inhibitor selection, results show that bone metastasis patients have a longer PFS if treated with ribociclib than palbociclib (3.31 vs 1.46 years, $p=0.03$) and liver metastasis patients have a longer PFS if treated with abemaciclib than palbociclib (2.3 vs 0.72 years, $p=0.02$).

Conclusion: Liver metastasis presence is the only metastatic site that influenced the survival, and our research also proved that abemaciclib treatment is correlated with a longer PFS than palbociclib in the mentioned setting. On the other hand, ribociclib is correlated with a longer PFS than palbociclib in skeletal metastasis patients.

Keywords: cyclin dependent kinase 4/6 inhibitors, liver metastasis, breast cancer, treatment outcomes

MIJEŠANI NEUROENDOKRINI I NE-NEUROENDOKRINI TUMOR JEDNJAKA S IZOLIRANIM MOŽDANIM METASTAZAMA

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Uvod: MiNEN (miješani neuroendokrini i ne-neuroendokrini tumor) je rijetka novotvorina koja se najčešće sastoji od neuroendokrinog karcinoma (NEC) i adenokarcinoma, barem 30% svakog histološkog podtipa.

Prikaz slučaja: 53-godišnji pacijent se javio u hitnu službu zbog neuroloških simptoma u svibnju 2022. godine, te su mu na CT-u mozga opisane dvije metastaze. Iste su resecirane, patohistološki se radilo o metastazi velikostaničnog neuroendokrinog karcinoma s Ki67 do 90%. Daljnjom obradom je na PET-CT-u opisana metabolički aktivna lezija jednjaka. Histološki, radilo se o MiNEN-u koji se sastoji od neuroendokrinog karcinoma i adenokarcinoma, PDL1 CPS je bio 25. Započeta je kemoradioterapija primarnog tumora uz konsolidacijsku kemoterapiju (6 ciklusa cisplatine i 5-fluorouracila) te je provedena radioterapija mozga. Na kontrolnom PET CT-u nije bilo metabolički aktivne bolesti. U srpnju 2023. godine su otkrivene nove moždane metastaze koje su tretirane gama nožem u srpnju i studenom 2023. godine. Zbog rasta primarnog tumora je u siječnju 2024. započeta kemoterapija po CAPTEM protokolu. U međuvremenu je uzorak primarnog tumora poslan na NGS (Next Generation Sequencing) FMI CDx. Ukupno je primio 6 ciklusa po CAPTEM protokolu. Unatoč tome se vidjela progresija intrakranijski te je liječen ponovno radiokirurgijom u svibnju i lipnju 2024. godine, no uz daljnju progresiju intrakranijski. Budući da je NGS utvrdio visoko mutacijsko opterećenje (TMB 13 mut/Mb) te dvosmislen mikrosatelitski status, započeta je kemoimunoterapija pembrolizumabom i CapOx-om.

Zaključak: Imunoterapija se nije pokazala učinkovitom u liječenju neselektiranih NEC-ova i MiNEN-a. Međutim, visoko tumorsko mutacijsko opterećenje i mikrosatelitska stabilnost su prediktori dobrog odgovora na imunoterapiju, te odobreni prema FDA-u bez obzira na vrstu solidnih tumora. Kod ovog pacijenta smo se odlučili na kemoimunoterapiju koja objedinjuje rezultate molekularne analize te prve linije liječenja metastatskog adenokarcinoma jednjaka.

Budući da su MiNEN-i vrlo rijetki tumori bez puno podataka o liječenju, pogotovo nakon prve linije, smatramo da bi molekularna analiza mogla doprinijeti ishodima bolesnika.

Ključne riječi: miješani neuroendokrini i ne-neuroendokrini tumor; kemoterapija; imunoterapija, metastaze u središnji živčani sustav

ESOPHAGEAL MIXED NEUROENDOCRINE NON-NEUROENDOCRINE NEOPLASMS WITH ISOLATED BRAIN METASTASES TREATED ACCORDING TO COMPREHENSIVE GENOMIC PROFILING

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Introduction: Mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) are rare tumors composed of two histologically different parts, at least 30% each, usually neuroendocrine carcinoma (NEC) and adenocarcinoma, but different histology types might be present.

Case Report: A 53-year-old patient was referred to the emergency department in May 2022 with neurological symptoms. A brain CT revealed two metastases, which were surgically removed. Pathology reported the tumor as a large cell neuroendocrine carcinoma with a Ki67 index of 90%. Following oncologist consultation, a PET-CT scan detected a metabolically active area in the esophagus, diagnosed from endoscopy samples as MiNEN (neuroendocrine carcinoma and adenocarcinoma), with PDL1 CPS 25. He underwent chemoradiation of the primary tumor with consolidation chemotherapy (cisplatin and 5FU) and whole-brain radiation. A PET-CT reevaluation showed no active disease, but new brain metastases appeared in July 2023, treated with Gamma Knife. Due to primary tumor growth, the CAPTEM protocol was initiated in January 2024, alongside Next Generation Sequencing (NGS) of tumor tissue (FMI CDx). Despite 6 CAPTEM cycles, brain metastases progressed, leading to additional Gamma Knife treatments in May and June 2024, which were ineffective. NGS revealed high tumor mutation burden (TMB) – 13 mut/Mb and equivocal microsatellite status. Considering progressive disease in the brain with possible rapid clinical deterioration it was decided to start CapOx chemotherapy with the addition of check-point inhibitor (CPI) pembrolizumab.

Conclusion: Single-agent CPI has been ineffective in biomarker-unselected NECs or MiNEN. However, tumor MSI-H/dMMR status and high TMB (≥ 10 mut/Mb) are predictive biomarkers for response to CPI, leading to FDA approval for tissue-agnostic use in progressive solid tumors. Therefore, we have chosen chemoinmunotherapy based both on molecular profiling and as a standard therapeutic option used for metastatic adenocarcinoma. MiNENs are rare neoplasms with scarce data for treatment, especially after the first line, so molecular profiling could improve patient outcomes.

Keywords: Mixed neuroendocrine non-neuroendocrine neoplasms; chemotherapy, immunotherapy, central nervous system metastases

PREDIKTIVNA VRIJEDNOST RADIOLOŠKE OBRADU U PROCJENI STATUSA LIMFNIH ČVOROVA PAZUHA U BOLESNICA S RANIM RAKOM DOJKE

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Uvod: U bolesnica s ranim rakom dojke, odluka o primarnom onkološkom liječenju – operativni zahvat ili neoadjuvantna terapija – ovisi o biologiji bolesti i stadiju definiranom klinički i radiološki koristeći mamografiju (MMG), ultrazvuk (UZV) i magnetsku rezonancu (MR) dojki. Status limfnih čvorova pazuha može promijeniti pristup liječenju. Cilj ovog rada bio je procijeniti pouzdanost radiološke procjene zahvaćenosti pazušnih limfnih čvorova tumorom.

Metode: Provedena je retrospektivna analiza bolesnica s ranim rakom dojke u kojih je, od 1.1.2023. do 31.12.2023., multidisciplinarni tim za tumore dojke KBC Zagreb, na temelju rezultata provedene obrade, indicirao započinjanje onkološkog liječenja operativnim zahvatom. Status limfnih čvorova pazuha procijenjen je radi-

ološki koristeći UZV i MR. Statistički su određene specifičnost i senzitivnost detekcije metastaza u limfnim čvorovima pazuha radiološkim metodama, kao i koeficijent varijacije između radiološkog i patohistološkog stadija tumora.

Rezultati: Prikupljeni su i analizirani podaci ukupno 148 bolesnica s ranim rakom dojke. U 10,8% (16/148) bolesnica radiološki je postavljena sumnja postojanja pozitivnih limfnih čvorova u pazuhu, od toga je konačni patohistološki nalaz iste potvrdio u njih 43,8% (7/16). U 6,8% (10/148) bolesnica opisani su reaktivni limfni čvorovi bez potrebe za dodatnom obradom, od čega su u njih 20% (2/10) patohistološki dokazane metastaze. U preostalih 82,4% (122/148) bolesnica, limfni čvorovi pazuha radiološki su imponirali negativno, no u njih 17,2% (21/122) patohistološki su dokazane metastaze. Osjetljivost radiološke procjene limfnih čvorova pazuha iznosila je 33,3%, dok je specifičnost bila 78,8%. Pozitivna prediktivna vrijednost radiološkog stadija pazuha iznosila je 28,6%, dok je negativna prediktivna vrijednost bila 82,3%. Koeficijent varijacije između radiološkog i konačnog patohistološkog stadija iznosio je 27,2.

Zaključak: Iako je ova analiza pokazala korist radiološke obrade u procjeni statusa limfnih čvorova pazuha, u ispitivanoj skupini nije se pokazala dovoljno osjetljivom za pouzdani dijagnostički alat.

Ključne riječi: rani rak dojke, radiološka obrada, limfni čvorovi pazuha, patohistologija

PREDICTIVE VALUE OF RADIOLOGICAL EVALUATION IN ASSESSING AXILLARY LYMPH NODE STATUS IN PATIENTS WITH EARLY BREAST CANCER

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Introduction: In early breast cancer, decisions on primary oncological treatment—surgery or neoadjuvant therapy – are based on the disease's biology and staging, determined clinically and radiologically using mammography (MMG), ultrasound (US), and magnetic resonance imaging (MRI). Axillary lymph node status can influence treatment approaches. This study aimed to determine the sensitivity and specificity of radiological assessment of axillary involvement.

Methods: A retrospective analysis was conducted on early breast cancer patients for whom the Multidisciplinary Breast Tumor Team at University Hospital Centre Zagreb between January 1, 2023, and December 31, 2023 recommended surgical treatment based on previous evaluations results. Axillary lymph node status was assessed using US and MRI. The study statistically determined the sensitivity, specificity, and coefficient of variation between radiological and pathological tumor staging.

Results: Data from 148 early breast cancer patients were analyzed. Pathological lymph nodes were identified radiologically in 10.8% (16/148) of the patients and confirmed histopathologically in 43.8% (7/16). 6.8% (10/148) of patients had reactive lymph nodes that did not require further assessment, of which 20% (2/10) had histopathological confirmation of metastases. In the remaining 82.4% (122/148) of cases, the axillary lymph nodes were radiologically negative, but in 17.2% (21/122) of them, metastases were proven by pathohistological analysis. The sensitivity of radiological assessment was 33.3%, specificity was 78.8%, with a positive predictive value of 28.6% and a negative predictive value of 82.3%. The coefficient of variation between radiological and pathological staging was 27.2.

Conclusion: While radiological evaluation was useful in assessing axillary lymph node status, it was not sufficiently sensitive as a reliable diagnostic tool in the studied group.

Keywords: early breast cancer, radiological evaluation, axillary lymph nodes, histopathology

ANALIZA ŽIVOTNE DOBI BOLESNIKA S METASTATSKIM RAKOM PROSTATE REZISTENTNIM NA KASTRACIJU I METASTAZAMA U KOSTIMA KOJI SU PRIMALI ANTIRESORPTIVNU TERAPIJU I ONIH KOJI NISU MOGLI ZBOG NESANIRANIH ZUBA – ISKUSTVO JEDNOG CENTRA

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Uvod: Bolesnici s metastatskim rakom prostate rezistentnim na kastraciju (mKRRP), i koštanim metastazama, imaju povećani rizik nastanka neželjenih događaja na kostima. U tih bolesnika preporuča se medikamentozna antiresorptivna terapija, bisfosfonati ili denosumab, ukoliko su zubi sanirani.

Metode: U ovoj retrospektivnoj opservacijskoj studiji, provedenoj na Službi za internu medicinu opće bolnice Šibensko-kninske županije, pretražili smo evidenciju bolesnika s mKRRP-om koristeći lokalno vođeni registar. Pacijenti su liječeni u našoj bolnici od siječnja 2022. do prosinca 2023. godine. Stanje njihovih zuba, kao i cjelokupno oralno zdravlje, ispitivali su onkolog i/ili stomatolozi.

Rezultati: U ovu studiju bilo je uključeno ukupno 26 bolesnika s mKRRP-om. Većina bolesnika imala je metastaze u kostima (88%). Među pacijentima koji su imali metastaze u kostima, njih 19 primilo je medikamentoznu antiresorptivnu terapiju, bisfosfonate ili denosumab. Dobni raspon bolesnika u studiji, koji su primali navedenu terapiju je bio između 49–82 godina (medijan 74 godine). Zbog nezadovoljavajućeg stanja zuba u 4 bolesnika s mKRRP-om, i metastazama u kostima, liječenje medikamentoznom antiresorptivnom terapijom nije bilo indicirano. Dobni raspon bolesnika koji nisu primali istu terapiju bio je između 67–88 godina (medijan 81 godina). Samo u 3 bolesnika s mKRRP-om i koštanim metastazama nije propisana medikamentozna antiresorptivna terapija, jer ih presadnice nisu ugrožavale od pojave neželjenih koštanih događaja.

Zaključak: Podaci dobiveni u našem istraživanju pokazuju kako većina bolesnika s mKRRP-om i metastazama u kostima su bili stariji ljudi, bez obzira jesu li primali medikamentoznu antiresorptivnu terapiju ili ne. Međutim, pacijenti koji zbog nesaniranih zuba nisu mogli primiti navedenu terapiju su bili nešto stariji od onih koji su je primili. Potrebne su daljnje studije kako bi se potvrdili rezultati ove studije provedene u jednom centru.

Ključne riječi: rak prostate, stanje zuba, metastatski, koštane metastaze

AGE ANALYSIS IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATIC CANCER AND BONE METASTASES WHO HAVE RECEIVED BONE ANTIRESORPTIVE AGENTS AND THOSE WHO COULD NOT BECAUSE OF POOR DENTAL STATUS – SINGLE CENTER EXPERIENCE

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Introduction: Patients with metastatic castration resistant prostatic cancer (mCRPC), and bone metastases, have a higher risk for clinically significant skeletal-related events. In these patients bone antiresorptive agents are recommended, if their dental status is good.

Methods: In the present retrospective observational study, conducted at the Department of Internal Medicine at the General Hospital of Šibenik-Knin county, we examined the records of patients with mCRPC using a locally maintained registry. The patients were treated in our hospital from January 2022 – December 2023. Their dental status, as well as overall oral health, was examined by oncologists and/or dentists.

Results: A total of 26 patients with mCRPC were included in this study. The majority of patients had metastases in the bones (88%). Among the patients who had bone metastases, 19 of them have received medical anti-resorptive therapy, bisphosphonates or denosumab. The age range of patients in the study, who have received it, was between 49–82 years (median 74 years). Due to unsatisfactory dental status in 4 of patients with mCRPC and bone metastases, treatment with anti-resorptive therapy was not indicated. The age range of patients in the study, who have not received medical anti-resorptive therapy, was between 67–88 years (median 81 years). Only in 3 patients with mCRPC and bone metastases medical anti-resorptive therapy was not prescribed because it did not endanger them for possible development of significant unwanted SREs.

Conclusion: The data obtained in our study indicate that the majority of patients with mCRPC and skeletal metastases were older people, whether they have received medical anti-resorptive therapy or not. However patients who could not receive anti-resorptive therapy, because of poor dental status, were somewhat older than the ones who have received it. Further studies are necessary to confirm the results of this single center study.

Keywords: prostate cancer; dental status, metastatic, bone metastases

WILMSOV TUMOR U ODRASLOJ DOBI: PRIKAZ SLUČAJA

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Uvod: Wilmsov tumor (WT) čini 5% dječjih zloćudnih novotvorina i najčešće se dijagnosticira kod djece mlađe od 5 godina, dok je u odrasloj populaciji zabilježen u samo 3% slučajeva. U 10 do 15% slučajeva javlja se kao dio višestrukih malformacijskih sindroma. Wilmsov tumor kod odraslih obično se dijagnosticira nakon nefrektomije. Liječenje je adjuvantno i temelji se na modificiranom SIOP 2016 UMBRELLA protokolu. Prognoza WT u odrasloj dobi lošija je nego u djece, unatoč identičnoj patohistološkoj prezentaciji.

Prikaz slučaja: Dvadesetčetverogodišnja žena prezentirala se akutnom boli u donjem desnom abdominalnom kvadrantu, a CT-om je opisana Bosniak IV cista promjera 15 cm u donjem polu desnog bubrega. Učinjena je radikalna nefrektomija, a patohistološki se opiše tumor koji se sastoji od 20% blastemske i 80% epitelne komponente, sa žarištima nekroze, ograničen na bubreg, bez znakova invazije perirenalne masti i renalnog sinusa, bez zahvaćanja regionalnih limfnih čvorova i negativnih resekcijskih rubova. Imunohistokemijski tumor je bio pozitivan na CD57, BRAF i WT-1 s Ki67 od 50% te je postavljena dijagnoza Wilmsovog tumora, stadij I, s ne-anaplastičnom histologijom i umjerenim rizikom. Postoperativno učinjenom obradom ne nađe se znakova diseminacije bolesti. Učinjeno je i genetsko testiranje, a nakon krioprezervacije jajnih stanica započeta je adjuvantna kemoterapija. Protokol se sastojao od primjene vinkristina i aktinomicina D uz LHRH agonist. Tijekom liječenja nije bilo potrebe za redukcijom doze obzirom da je bolesnica imala blage nuspojave u vidu mučnine, umora i hemoroidalnog krvarenja. Nakon dva mjeseca od početka terapije učinjena je reevaluacija kojom se ne nađe znakova bolesti.

Zaključak: Wilmsov tumor se rijetko dijagnosticira u odrasloj populaciji i ovo je prvi slučaj u KBC-u Zagreb. Obzirom na rijetkost ovog tumora u odrasloj dobi, važno je prikazati ovakve slučajeve kako bi pridonijeli što većem broju podataka u svrhu boljeg liječenja i praćenja ovih bolesnika.

Ključne riječi: Wilmsov tumor, odrasli, SIOP 2016 UMBRELLA protokol, multipli malformacijski sindromi

ADULT WILMS TUMOR: CASE REPORT

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Introduction: Wilms' tumor (WT) accounts for 5% of childhood cancers, mostly diagnosed in children younger than five years, with only 3% of cases reported in adults. Ten to fifteen percent of cases occur as a part of multiple malformation syndrome. Adult Wilms' tumors are usually diagnosed following nephrectomy for presumed renal cell carcinoma. Modified SIOP 2016 UMBRELLA protocol is used in adjuvant settings. Even though there is no difference in histopathological presentation, prognosis of adult WT is poorer than in the pediatric population.

Case Report: A 24-year-old female has presented with acute pain in the right lower abdominal quadrant. CT-scan showed Bosniak IV cystic lesion of the right kidney lower pole, measuring 15 cm in diameter. After radical nephrectomy, histologically the tumor comprised of 20% blastemal and 80% epithelial elements, with no perirenal fat tissue and renal sinus invasion, clean surgical margins and negative regional lymph nodes. The immunohistochemistry study was positive for CD57, BRAF and WT-1 with Ki67 50%. Wilms tumor, stage I, with non-anaplastic histology and intermediate risk was diagnosed. No distant metastasis were found on initial staging and multiple malformation syndrome genetic testing was performed. The patient underwent oocyte preservation and adjuvant chemotherapy was started. The treatment consisted of vincristine and actinomycin D along with ovarian suppression. During the therapy grade 1 nausea, fatigue, and hemorrhoidal bleeding occurred without the need for dose reduction. After two months of therapy, radiological reevaluation showed no evidence of disease.

Conclusion: Adult Wilms' tumor is a rare disease and this is the first case in UHC Zagreb. Due to its rarity, it is important to register such patients to international databases, in order to assist in research and development of future management guidelines for this tumor.

Keywords: adults, Wilms' tumor, SIOP 2016 UMBRELLA protocol, multiple malformation syndromes

AVELUMAB KAO TERAPIJA ODRŽAVANJA U UZNAPREDOVALOM UROTELNOM KARCINOMU – AŽURIRANA HRVATSKA ISKUSTVA

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Uvod: Terapija održavanja avelumabom u bolesnika koji nisu progredirali na kemoterapiju baziranu na platinu čini standardnu prvu liniju liječenja uznapređovalog urotelnog karcinoma (uUK). Cilj ovog istraživanja bio je opisati kliničke osobine bolesnika i ishode liječenja avelumabom u terapiji održavanja uUK u hrvatskoj onkološkoj praksi.

Metode: Proveli smo retrospektivno kohortno istraživanje u koje smo uključili 10 hrvatskih onkoloških ustanova u kojima se liječe bolesnici s uUK. Anonimizirani podaci su skupno analizirani.

Rezultati: Ukupno 115 bolesnika s uUK liječeno je avelumabom u terapiji održavanja od srpnja 2022. do kolovoza 2024. Medijan dobi bolesnika kod početka terapije bio je 69 godina, 19% bolesnika je imalo tumor gornjeg urotela, 73% bolesnika primilo je cisplatinu (gemcitabin/cisplatin 62%, ddMVAC 11%), 19% je imalo jetrene metastaze. 67% je bilo ECOG PS 0. Za 104 bolesnika (90%) je učinjena analiza učinkovitosti terapije. Stopa ukupnog odgovora na avelumabu bila je 20% (kompletni odgovor 4%, parcijalni odgovor 16%), stabilna bolest 38%, a progresija bolesti kao najbolji odgovor 36%. Nakon medijana praćenja od 13 mjeseci, 50 bolesnika (44%) je doživjelo progresiju na avelumab. 54 bolesnika (47%) je još na tretmanu avelumabom. Medijan do progresije bolesti je 14 mjeseci, dok medijan ukupnog preživljenja nije dosegnut. Ukupna stopa ozbiljnih nuspojava vezanih za imunoterapiju bila je 21% za gr 2, 6% za gr 3 te 2% za gr 4. Osam bolesnika moralo je trajno prekinuti terapiju zbog nuspojava. Šestnaest bolesnika koji su progredirali na terapiju avelumabom dobili su daljnju aktivnu terapiju.

Zaključak: Osveženi podaci praćenja učinkovitosti avelumaba u hrvatskoj onkološkoj praksi u terapiji održavanja u UK ukazuju na visoku prevalenciju cisplatinških protokola, visoku stopu odgovora na avelumab te nižu stopu imunoterapijom uvjetovanih nuspojava.

Ključne riječi: urotelni karcinom, avelumab, terapija održavanja, platinski spoj

AVELUMAB AS MAINTENANCE AFTER PLATINUM-BASED CHEMOTHERAPY IN ADVANCED UROTHELIAL CANCER – UPDATED CROATIAN EXPERIENCE

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Introduction: Platinum-based chemotherapy followed by avelumab switch maintenance in non-progressors is the standard of care first line treatment for advanced urothelial cancer (aUC). Aim of this study was to assess clinical characteristics and outcomes in a ‘real-world’ cohort of patients treated with avelumab maintenance for aUC within Croatian Uro-Oncology Collaborative Group (CUOCCG).

Methods: This retrospective cohort study assessed patients from 10 CUOCCG-affiliated institutions who received maintenance avelumab. Anonymized data were pooled and centrally analyzed. Herein, updated toxicity, overall response rate, progression-free survival are reported.

Results: Total of 115 patients with aUC who received avelumab maintenance from July 2022 to August 2024 were identified within the CUOCCG network. Median age at avelumab initiation was 69 years (range 41–83 years), 19% had upper tract primary tumor, 73% received prior cisplatin-based chemotherapy (gemcitabine/cisplatin 62%, ddMVAC 11%), 19% had liver metastasis and 67% were ECOG PS 0. 104 patients (90%) were available for

response assessment. The overall response rate with avelumab maintenance was 20% (complete response [CR] for 4%, partial response [PR] for 16%), stable disease (SD) 38%; progression as the best response was noted in 36% of patients, respectively. After a median follow-up time of 13 months (95%CI 8–30 months), 50 patients (44%) experienced disease progression. Fifty-four patients (47%) are still on treatment. Median progression-free survival was 14 months (95%CI 8–20), while median overall survival was not reached. The observed rate of immunotherapy-related side-effects was 21% for grade 2, 6% for grade 3, and 2% for grade 4, respectively. Eight patients (7%) required therapy termination due to serious immunotherapy-related side-effects. Sixteen patients (32% of progressing patients) received active treatment post avelumab progression.

Conclusion: Updated real-world outcomes of patients receiving avelumab maintenance in Croatia continue to show high prevalence of cisplatin-based chemotherapy, high overall response rate and lower incidence of immunotherapy-related side-effects compared to registration trial.

Keywords: urothelial cancer, avelumab, maintenance therapy, platinum compound

PREVALENCIJA SARKOPENIČNE PRETILOSTI U BOLESNICA S GINEKOLOŠKIM TUMORIMA

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Uvod: Sarkopenična pretilost kliničko je stanje karakterizirano sarkopenijom odnosno gubitkom mišićne mase i funkcije te pretilošću odnosno povećanjem udjela masnog tkiva. Prevalencija sarkopenije i pretilosti globalno je u značajnom porastu, kako u općoj populaciji tako i među onkološkim bolesnicima. Sarkopenična pretilost povezana je s lošijim ishodima liječenja, dužim boravkom u bolnici i kraćim preživljenjem kod više vrsta raka. Isto tako smatra se da ovo stanje značajno pospješuje karcinogenezu putem poremećaja metaboličke, hormonalne i citokinske ravnoteže odnosno putem oksidativnog stresa, lipotoksičnosti i sistemske kronične upale. Iako zanimanje za sarkopeničnu pretilost postaje sve veće, dosadašnje su studije inkonzistentne s obzirom na nedostatne definicije ovih stanja i varijabilnosti dijagnostičkih kriterija koji se koriste za procjenu prevalencije sarkopenije i pretilosti.

Metode: Retrospektivna studija koja uključuje 53 bolesnice s ginekološkim tumorima (jajnik, jajovod, endometrij i cerviks) koje su bile hospitalizirane na Klinici za Tumore, KBCSM, tijekom 2024. godine. Pretraživan je Bolnički informatički sustav. Sarkopenija je procijenjena pomoću SARC-F upitnika koje su bolesnice ispunjavale prvi dan hospitalizacije te je izračunat BMI. U obzir su uzete vrijednosti isključivo na prvom ciklusu terapije.

Rezultati: Među 53 bolesnice s ginekološkim tumorima njih 49% bilo je pretilo (BMI \geq 30) dok je kod 32% prema SARC F upitniku procijenjena sarkopenija (SARC F \geq 4) prilikom aplikacije prvog ciklusa terapije. Sarkopeničnu pretilost je prema ovim dijagnostičkim kriterijima imalo 17% bolesnica. Prema ovim rezultatima sarkopenična pretilost nije imala značajnijeg utjecaja na karakteristike tumora.

Zaključak: S obzirom na dokazan utjecaj sarkopenične pretilosti na karcinogenezu te na ishode liječenja onkoloških bolesnika kao i na porast prevalencije ovog kliničkog stanja bitno je i u svakodnevnoj kliničkoj praksi mjeriti i evidentirati ove parametre. Ključan korak je definiranje jasnih dijagnostičkih kriterija te izbor najefikasnijih dijagnostičkih metoda koje su prihvatljive u svakodnevnom radu onkologa.

Ključne riječi: sarkopenija, pretilost, ginekološki tumori, prevalencija

PREVALENCE OF SARCOPENIC OBESITY IN PATIENTS WITH GYNECOLOGIC CANCERS

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Introduction: Sarcopenic obesity is a clinical condition characterized by sarcopenia, i.e. loss of muscle mass and function, and obesity, i.e. an increase in the proportion of adipose tissue. The prevalence of sarcopenia and obesity is significantly increasing globally. Sarcopenic obesity is associated with worse treatment outcomes, longer hospital stay and shorter survival in several types of cancer. It is also believed that this condition significantly promotes carcinogenesis through disturbances in metabolic, hormonal and cytokinetic balance.

Although interest in sarcopenic obesity is increasing, studies to date are inconclusive due to insufficient definitions of these conditions and the variability of diagnostic criteria.

Methods: A retrospective study including 53 patients with gynecologic cancers who were hospitalized at the Clinic for Tumors, CHCSM, during the year 2024. The hospital information system was searched. Sarcopenia was assessed using the SARC-F questionnaire, which the patients filled out on the first day of hospitalization, and BMI was calculated. Only values from the first cycle of therapy were taken into account.

Results: Among 53 patients with gynecologic cancer, 49% were obese (BMI ≥ 30), while 32% were assessed for sarcopenia (SARC F ≥ 4) during the first cycle of therapy according to the SARC F questionnaire. According to these diagnostic criteria, 17% of patients had sarcopenic obesity. According to these results, sarcopenic obesity had no significant impact on tumor characteristics.

Conclusion: Considering the proven influence of sarcopenic obesity on carcinogenesis and the outcomes of treatment of oncology patients, as well as the increase in the prevalence of this clinical condition, it is important to measure and record these parameters in everyday clinical practice. The key step is defining clear diagnostic criteria and choosing the most effective diagnostic methods that are acceptable in the everyday work of an oncologist.

Keywords: sarcopenia, obesity, gynecologic cancers,

LIJEČENJE TRIFLURIDIN-TIPERACIOM U TREĆOJ LINIJI METASTATSKOG KOLOREKTALNOG KARCINOMA – ISKUSTVA U KLINIČKOJ PRAKSI

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Uvodi: Trifluridin-tipiracil je odobren i indiciran za liječenje metastatskog kolorektalnog karcinoma (mCRC) u trećoj liniji. Prema rezultatima studije RECURSE pokazan je jasni benefit u ukupnom preživljenju (engl. *overall survival*) u odnosu na placebo. U studiji SUNLIGHT opisan je jasni benefit dodatka bevacizumaba u ukupnom preživljenju od 3 mjeseca u odnosu na monoterapiju te više nego dvostruko produljenje preživljena bez progresije (engl. *progression-free survival*). U Hrvatskoj je lijek odobren za primjenu od 2021. godine za liječenje mCRC i želučanog karcinoma u trećoj liniji.

Metode: Korištena je deskriptivna analiza podataka iz bolničkog informatičkog sustava (BIS) o pacijentima s dijagnozom metastatskog kolorektalnog karcinoma liječenima u Klinici za tumore trifluridinom-tipiracilom u periodu od početka odobrenja 2021. godine do prosinca 2023. godine.

Rezultati: U analizu je uključeno 29 pacijenata koji su započeli liječenje trifluridinom-tipiracilom zbog proširenog mCRC, od kojih je 12 primalo bevacizumab. Najčešći razlog prekida liječenja je bila progresija bolesti, a nakon nje pogoršanje kliničkog stanja zbog kojega je sustavno liječenje bilo kontraindicirano. Medijan broja ciklusa bez progresije bolesti je bio 3, što označava 12 tjedana. Prosječno trajanje trećelinijskog liječenja kod pacijenata koji su primali bevacizumab je 3,5 mjeseca, dok kod onih bez bevacizumaba je trajanje liječenja bilo

4,1 mjeseca. Kod pacijenata koji su postigli trajanje trećelinjskog liječenja dulje od medijana, prijašnje prvolinijsko i drugolinijsko liječenje je prosječno trajalo 23,2 mjeseca, dok je kod onih ispod medijana prethodno liječenje u prosjeku trajalo 27 mjeseci.

Zaključak: Kod pacijenata liječenih trifluridinom-tipiracilom prema dostupnim podacima u našoj ustanovi trajanje prethodnih linija liječenja povezano je s lošijim ishodima u trećelinjskom liječenju. Dodatak bevacizumaba nije bio povezan s duljim trajanjem trećelinjskog liječenja. Premda je trajanje liječenja trifluridin-tipiracilom relativno kratko u odnosu na prethodne linije liječenja, lijek se pokazuje kao dobra opcija kod pacijenata koji su imali bržu progresiju na liječenju baziranom na fluoropirimidinima, irinotekanu i oksaliplatinu.

Ključne riječi: trifluridin-tipiracil, metastatski kolorektalni karcinom, bevacizumab, pretretirani bolesnici

TRIFLURIDINE/TIPERACIL TREATMENT IN THIRD LINE FOR METASTATIC COLORECTAL CANCER – CLINICAL PRACTICE EXPERIENCE

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Introduction: Trifluridine/tipiracil is approved as the third-line treatment for metastatic colorectal cancer (mCRC). RECURSE study results proved significant benefit in overall survival (OS) when compared to placebo. SUNLIGHT study proved benefit of bevacizumab addition in OS of 3 months compared to trifluridine/tipiracil monotherapy and more than double progression-free survival (PFS) benefit. In 2021 in Croatia the drug was approved for use as a third-line treatment in mCRC and metastatic gastric cancer.

Methods: Descriptive analysis of data from hospital information system (BIS) was used. Data about patients treated with trifluridine/tipiracil from the beginning of 2021 until December of 2023 were analyzed.

Results: 29 patients who started trifluridine/tipiracil treatment in mCRC were analyzed. Bevacizumab was added to the therapy regimen in 12 patients. The most common reason for treatment discontinuation was disease progression, with worsening of clinical state that did not allow systemic treatment the second most common reason. Number of cycles median without disease progression was 3, or 12 weeks. Overall treatment duration in patients who received bevacizumab was 3.5 months, while those who didn't receive bevacizumab had overall treatment duration of 4.1 months. In patients who were treated longer than median number of cycles, prior first and second-line treatment lasted 23.2 months overall, while in those below median number of cycles prior treatment lasted 27 months.

Conclusion: In patients treated with trifluridine/tipiracil longer prior first and second-line treatment was associated with worse outcomes in third-line treatment, according to our data. Bevacizumab addition was not associated with longer treatment duration. Despite its relatively short treatment duration, trifluridine/tipiracil proved a useful treatment option in patients who progressed quickly on treatment based on fluoropyrimidines, irinotecan and oxaliplatin.

Keywords: trifluridine-tipiracil, metastatic colorectal cancer, bevacizumab, heavily pretreated patients

“SENTINEL UMA” – PROJEKT ZA ZAŠTITU MENTALNOG ZDRAVLJA LIJEČNIKA I DRUGIH ZDRAVSTVENIH DJELATNIKA

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Uvod: Projekt “Sentinel Uma,” pokrenut je od strane Sekcije mladih onkologa HDIO uz podršku Sekcije mladih psihijatara HPD-a s ciljem destigmatizacije i zaštite mentalnog zdravlja liječnika i svih zdravstvenih djelatnika. Zdravstveni su djelatnici izloženi visokim razinama stresa što često dovodi do sindroma sagorijevanja. Djelatnici koji zbrinjavaju onkološke bolesnike redovito su izloženi traumatičnim situacijama, bilo da se radi o teško bolesnim pacijentima, smrti ili emocionalno zahtjevnom komunikacijom o lošim vijestima. Administrativna opterećenja, manjak resursa i sustavna ograničenja mogu dovesti do bespomoćnosti, moralnog distresa i moralne ozljede. Moralni distres nastaje kada zdravstveni djelatnici znaju što je ispravno, ali su spriječeni djelovati u skladu s moralnim uvjerenjima zbog vanjskih ograničenja, a moralna ozljeda odnosi se na psihološke posljedice koje proizlaze iz osjećaja krivnje zbog izdaje etičkih uvjerenja ili postupaka koje su poduzeli.

Metode i rezultati: U sklopu projekta “Sentinel Uma” provodi se istraživanje o moralnom distresu i moralnoj ozljedi, te njihovoj povezanosti sa stresom, anksioznošću i depresijom. U istraživanju je dosad sudjelovalo 169 zdravstvenih djelatnika, koji su prijavili umjerene razine anksioznosti, depresije i moralne ozljede, te visoke razine stresa i moralnog distresa. Liječnici u neurologiji, kardiologiji, infektologiji i internističkoj onkologiji izloženi su najvišim razinama moralnog distresa i moralne ozljede prvenstveno zbog suočavanja s terminalnim pacijentima, donošenja odluka o prekidu terapije i ograničenja u resursima.

Zaključak: Ovi pilot rezultati ukazuju na potrebu za sustavnim intervencijama koje uključuju psihološku podršku zdravstvenih djelatnika, osobito u visokorizičnim specijalizacijama kao što je internistička onkologija, uz pružanje etičkih savjeta i obuke za suočavanje s izazovima. Uzimajući u obzir dobivene rezultate, u daljnjim koracima ovog projekta, ciljevi će biti podići svijest o važnosti kontinuirane skrbi o mentalnom zdravlju kroz psihoedukaciju zdravstvenih djelatnika i šire javnosti o izazovima mentalnog zdravlja te predložiti konkretne korake za pomoć u izazovima s kojima se zdravstveni djelatnici svakodnevno suočavaju.

Ključne riječi: internistička onkologija, mentalno zdravlje, sindrom sagorijevanja, moralni distres, moralna ozljeda

SENTINEL OF THE MIND: MENTAL HEALTH PROTECTION CAMPAIGN FOR PHYSICIANS AND HEALTH CARE WORKERS

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Introduction: The “Sentinel of the Mind” project was initiated by the Young Oncologist Section of the Croatian Society for Medical Oncology, with the support of the Young Psychiatrists Section of the Croatian Psychiatric Society. Its core mission is to de-stigmatize and protect the mental health of healthcare workers. Healthcare professionals frequently endure intense stress, often leading to burnout. Those who care for cancer patients are particularly vulnerable, facing traumatic situations such as life-threatening illnesses, death, and emotionally

charged conversations on a daily basis. Additional burdens such as administrative overload, resource shortages, and systemic limitations contribute to feelings of helplessness, moral distress, and moral injury. Moral distress arises when healthcare professionals know the right course of action but are obstructed by external factors. Moral injury refers to the psychological impact of ethical violations, particularly when healthcare workers feel guilt from betraying their ethical beliefs.

Methods and results: As part of the “Sentinel of the Mind” initiative, a study was conducted to explore the links between moral distress, moral injury, and levels of stress, anxiety, and depression among healthcare workers. Thus far, 169 healthcare workers have participated in the study, with findings indicating moderate levels of anxiety, depression, and moral injury, but high levels of stress and moral distress. Physicians working in specialties such as neurology, cardiology, infectious diseases, and medical oncology reported the highest levels of moral distress and injury. These elevated levels are likely due to their exposure to terminal illness, the difficult decision-making process around ending treatment, and the general scarcity of resources.

Conclusion: This pilot study underscores the urgent need for systemic interventions that offer psychological support, particularly in fields with the highest risk of burnout, such as medical oncology. It also highlights the importance of providing ethical guidance and training to help healthcare workers navigate the challenges they face. Given these findings, the next steps for the “Sentinel of the Mind” campaign will focus on raising awareness of the importance of continuous mental health care for medical professionals and offering additional educational programs that address the everyday challenges healthcare workers encounter. This will ensure a sustained focus on mental health protection within the healthcare system, promoting resilience and reducing the risk of burnout.

Keywords: oncology, mental health, burnout, moral distress, moral injury

MJERENJE RAZINE PSIHOLOŠKOG DISTRESA U NEOADJUVANTNO LIJEČENIH BOLESNICA S KARCINOMOM DOJKE

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Uvod: Dijagnoza raka dojke može utjecati na žene i fizički i psihički. Zabilježeno je da 50% bolesnica s karcinomom dojke doživi neku vrstu psihološkog distresa zbog svoje bolesti. To može biti osobito izraženo za bolesnice tijekom neoadjuvantnog liječenja. Ovaj pristup nudi višestruke dobro poznate benefite, no postoji i specifična psihološka nelagoda koju mnoge bolesnice doživljavaju, naročito zbog činjenice da im prije operacije slijedi višemjesečno sustavno liječenje.

Cilj našeg istraživanja bio je procijeniti razinu psihološkog distresa kod žena koje prolaze neoadjuvantno liječenje te moguću korelaciju između demografskih i socioekonomskih karakteristike i razine distresa.

Metode: U istraživanje su bile uključene 53 bolesnice s rakom dojke u različitim ciklusima neoadjuvantnog liječenja. Koristili smo upitnik DASS-21 – validirani i otvoreni alat za probir stresa, anksioznosti i depresije. Demografske i socioekonomske karakteristike uključivale su dob, razinu obrazovanja, status zaposlenja, prihode te bračni status.

Rezultati: Prosječna dob bolesnica bila je 53,34 godine i sve su bile žene. 28,3% od svih uključenih bile su mlađe od 45 godina. Većina bolesnica imala je blagu depresiju (11,3%), anksioznost (15,1%) i stres (11,3%). Tešku depresiju imalo je 5,6 % žena, dok je 3,7 % imalo tešku anksioznost. Izrazito tešku depresiju prijavilo je 3,7% žena, dok je izrazito tešku anksioznost i stres imalo 5,6% odnosno 1,9%. Pokazalo se da je mlađa dob (<45 godina) povezana sa sve tri podskupine tegoba.

Zaključak: Važno je napomenuti da je više od polovice bolesnica u našem istraživanju prijavilo određenu razinu psihološkog distresa, dok je 13,2% ocijenjeno kao teški ili izrazito teški distres. Korištenjem ovakvih instrumenata u našoj praksi možemo identificirati bolesnike koji su u većem riziku od razvoja značajnih psiholoških poteškoća te im na vrijeme pružiti psihološku pomoć koja im je potrebna kako bi uspješno završili liječenje.

Ključne riječi: karcinom dojke, distres, neoadjuvantno liječenje, probir

SCREENING FOR PSYCHOLOGICAL DISTRESS IN NEOADJUVANTLY TREATED BREAST CANCER PATIENTS

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Introduction: Breast cancer diagnosis can affect women both physically and psychologically. It has been reported that 50% of BC patients experience some psychological distress because of their disease. This can be especially true for patients during neoadjuvant treatment. While this approach offers multiple well-known benefits, there is also a specific psychological distress and discomfort that many patients experience, specifically because they will have to endure several months of therapy before surgery.

Our research aimed to evaluate the levels of psychological distress in women receiving neoadjuvant treatment and possible correlation between demographic and socioeconomic characteristics and stress levels.

Methods: 53 breast cancer patients were included in this research at various cycles of their neoadjuvant treatment. We used the DASS-21 questionnaire – a validated and open-access tool used for screening of stress, anxiety, and depression. Demographic and socioeconomic characteristics included age, education level, employment status, income, and marital status.

Results: The mean age was 53.34 years and all of them were women. 28.3% of them were younger than 45 years. Most of the patients had mild depression (11.3%), anxiety (15.1%) and stress (11.3%). Severe depression was found in 5.6% of women while 3.7% had severe anxiety. Extremely severe depression was reported by 3.7% of women while extremely severe anxiety and stress had 5.6% and 1.9% respectively. Younger age (<45 years) has been shown to correlate with all three distress subgroups.

Conclusion: It is important to note that more than half the patients in our research reported at least mild distress while 13.2% scored for severe or extremely severe distress. Using these instruments in our practice can help identify patients that are at a higher risk of developing significant psychological difficulties and provide them in time with the psychological help they need in order to successfully complete their treatment.

Keywords: breast cancer, psychological distress, neoadjuvant therapy, screening

ANGIOSARKOM DOJKE UZROKOVAN RADIOTERAPIJOM

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Uvod: Poštedni kirurški zahvat potom radioterapija dojke je standard u liječenju ranog karcinoma dojke. Angiosarkom nastao nakon provedene radioterapije je iznimno rijetka maligna bolest koja ima agresivan tijek i loš ishod. Čini svega 0.05%–0.3% svih malignih tumora dojke. Javlja se više godina nakon zračenja, najčešće 5–7.

Prikaz slučaja: Bolesnica u dobi od 82 godine dolazi na kontrolu. Prije 6 godina učinjena joj je kvadrantektomija s biopsijom limfnog čvora „čuvara”. Patohistološki nalaz potvrdio je da se radi o invanzivnom karcinomu, pT1N0, tumor 1,3x1,1 cm, l.č. 0/2, ER 100%, PR neg., HER 2 neg., Ki67 7%, imunofenotip: luminal B. Provedena je adjuvantna radioterapija i hormonska terapija (TD 4256cGy/16 frakcija te „boost” 12Gy/4 frakcije te je kroz 5 godina uzimala letrozol). Klinički dojka zadebljane kože, modra, kvrgava – posumnja se na angiosarkom. Ultrazvuk dojke opiše desno zadebljalu kožu sa supkutanim hematomom, BI-RADS 3. Magnetska rezonanca- nema suspektnih tvorbi niti zona patološkog nakupljanja. MSCT toraksa, abdomena i zdjelice ne opiše diseminacije bolesti. Učini se biopsija dojke koja potvrdi da se radi o angiosarkomu nakon provedene radioterapije. Imunohi-

stokemijski više od 80% stanica je jako c-MYC pozitivno. FISH analizom je nađen povećan broj crvenih signala (prosječno 10,6 signala po stanici) što upućuje na amplifikaciju MYC gena. Učini se mastektomija desne dojke te je definitivni patohistološki nalaz u izradi.

Zaključak: Angiosarkom uzrokovan radioterapijom ima lošu prognozu te stopu 5-godišnjeg preživljenja od 10–54%. Iako ne postoje jasne smjernice za liječenje, radikalni kirurški zahvat je terapija izbora. Stope povrata bolesti su visoke i kod bolesnika s R0 resekcijom, 54–92%, ali bolesnici s R1 i R2 resekcijom imaju još lošiju prognozu. Uloga adjuvantne kemoterapije također je dvojbena. Kod žena koje su zračene prije više godina s odgovarajućom kliničkom slikom svakako treba razmišljati i o ovom entitetu.

Ključne riječi: angiosarkom, postradioterapijski, rak dojke, patologija

RADIATION INDUCED ANGIOSARCOMA OF THE BREAST

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Introduction: Breast-conserving surgery followed by radiotherapy is the standard treatment for early breast cancer. Radiation induced angiosarcoma is an extremely rare malignancy with a poor prognosis. It represents only 0.05% to 0.3% of all malignant breast tumors. It usually appears several years after radiation (most commonly 5–7 years).

Case Report: An 82-year-old female patient presented for follow-up. Six years ago, she underwent a quadrantectomy with sentinel lymph node biopsy. The pathohistological examination confirmed invasive carcinoma, pT1N0, tumor size 1.3x1.1 cm, lymph nodes 0/2, ER 100%, PR negative, HER2 negative, Ki67 7%, with a luminal B immunophenotype. The patient received adjuvant radiotherapy (TD 4256 cGy/16 fractions with a boost of 12 Gy/4 fractions) and hormonal therapy (letrozole) for five years. On clinical examination, the breast appeared with thickened skin, a bluish discoloration, and nodularity, raising suspicion of angiosarcoma. Breast ultrasound revealed thickened skin with a subcutaneous hematoma, BI-RADS 3. Magnetic resonance imaging (MRI) showed no suspicious masses or areas of pathological enhancement. Thoracic, abdominal, and pelvic MSCT scans showed no evidence of disease dissemination. A biopsy confirmed radiation induced angiosarcoma. Immunohistochemical analysis demonstrated that over 80% of the cells were strongly positive for c-MYC. FISH analysis revealed an increased number of red signals (an average of 10.6 per cell), indicating MYC gene amplification. A mastectomy of the right breast was performed, and the final pathological report is awaited.

Conclusion: Angiosarcoma has a poor prognosis, with a 5-year survival rate between 10% and 54%. Although there are no clear guidelines, surgery is the treatment of choice. Recurrence rates remain high, even in patients who achieve R0 resection, ranging from 54% to 92%. Patients with R1 or R2 resections have an even worse prognosis. For women with a history of radiotherapy and appropriate clinical symptoms, angiosarcoma should be considered as a potential diagnosis.

Keywords: radiation, angiosarcoma, breast cancer, pathology

KAKO SE PONAŠA ADENOKARCINOM KOLONA S KOMPONENTOM SVIJETLIH STANICA?

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Uvod: Karcinom svijetlih stanica debelog crijeva (CCACC) je podtip kolorektalnog karcinoma kojeg su prvi opisali Hellstrom i Fisher 1964.godine. Tumor je iznimno rijedak i prema PubMed database do sada je opisano 25 slučajeva.

Prikaz slučaja: 65-godišnji pacijent javio se u hitnu službu KB „Sveti Duh zbog mase u lijevom hemiabdomenu, povraćanja i nadutosti unazad mjesec dana. U laboratorijskim nalazima bio je snižen hemoglobin (115 g/l) i povišen CRP (49 mg/l). Učinjeni MSCT abdomena je ukazao na infiltrativni proces sigmoidnoig debelog crijeva s metastazama u jetri. Tijekom pripreme za kolonoskopiju pacijent je razvio kliničke i radiološke znakove za intestinalnu opstrukciju te je premješten na Kirurški odjel. Učinjena je medijalna laparotomija na kojoj je nađen dilatiran transverzalni kolon i cekum te u području sigmoidnog dijela tumor u dužini do 10 cm. Učinjena je subtotalna kolektomija s apendektomijom te terminalna ileostomija. Histološki nalaz pokazao je da se radi o mucinoznom adenokarcinomu s komponentom svijetlih stanica koji infiltrira okolno subserozno masno tkivo bez znakova limfovaskularne i neuralne invazije. Metastaze su nađene u 8 od 9 izoliranih limfnih čvorova. Imunohistokemijska analiza pokazala je da su tumorske stanice svijetle komponente imaju slijedeće karakteristike: CK20+, CD10–, CDX2+, CK7–, CEA+, MUC2–, AFP– i PAS–.

Zaključak: Etiologija svijetlih stanica u clear cell adenokarcinomu debelog crijeva je još uvijek nejasna, ali može biti povezana s akumulacijom glikogena, mucina i lipida. U kliničkoj praksi teško je teško razlikovati metastatski karcinom, na primjer, metastatski karcinom svijetlih stanica i primarni CCACC ako je komponenta svijetlih stanica dominantna. Iz tog razloga neophodna je potvrda kolorektalnog podrijetla tumorskih stanica imunohistokemijskom analizom. Dodatno, potrebno je osvijestiti patologe o važnosti CCACC-a jer se ovaj podtip vjerojatno ponaša zloćudnije od drugih podtipova kolorektalnog karcinoma.

Ključne riječi: Karcinom svijetlih stanica debelog crijeva, kolorektalni karcinom, imunohistokemijska analiza, diferencijalna dijagnoza

HOW DOES ADENOCARCINOMA OF THE COLON WITH A COMPONENT OF CLEAR CELLS BEHAVE?

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Introduction: Colon clear cell carcinoma (CCACC) is a subtype of colorectal cancer (CCA) first described by Hellstrom and Fisher in 1964. The tumor is extremely rare and according to the PubMed database, 25 cases have been described so far.

Case Report: A 65-year-old patient reported to the Emergency Department Clinical Hospital Sveti Duh because of a mass in the left hemiabdomen, vomiting and bloating for the past month. In laboratory findings, hemoglobin was decreased (115 g/l) and CRP was elevated (49 mg/l). The performed MSCT of the abdomen showed the infiltrative process of the sigmoid colon with metastases in the liver. During the preparation for the colonoscopy, the patient developed clinical and radiological signs of intestinal obstruction and was transferred to the Surgical Department. A medial laparotomy was performed, where a dilated transverse colon and cecum with a tumor up to 10 cm in length were found in the sigmoid region. Subtotal colectomy with appendectomy and terminal ileostomy were performed. The histological findings showed that it was a mucinous adenocarcinoma with a clear cell component infiltrating the surrounding subserosal fatty tissue without signs of lymphovascular and neural invasion. Immunohistochemical analysis showed that the tumor clear cell components have the following characteristics: CK20+, CD10-, CDX2+, CK7-, CEA+, MUC2-, AFP- and PAS-.

Conclusion: In clinical practice it is difficult to differentiate between metastatic carcinoma, for example, metastatic clear cell carcinoma and primary CCACC if the clear cell component is dominant. For this reason, it is necessary to confirm the colorectal origin of tumor cells by immunohistochemical analysis. Additionally, pathologists need to be made aware of the importance of CCACC as this subtype is likely to behave more malignantly than other CCA subtypes.

Keywords: colorectal clear cell carcinoma, colorectal carcinoma, immunohistochemical analysis, differential diagnosis

SVEOBUHVAATNO GENSKO PROFILIRANJE U BOLESNIKA S UZNAPREDOVALIM UROTELNIM KARCINOMOM: PRVI REZULTATI HRVATSKE URO-ONKOLOŠKE MREŽE

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Uvod: Mnogi bolesnici s uznapredovalim urotelnim karcinomom imaju somatske patogene genske alteracije. S ciljem poboljšanja ishoda liječenja postoji potreba za uključivanjem novih kliničkih genskih testova u rutinsku upotrebu u bolesnika s uznapredovalim urotelnim karcinomom. Cilj ovog istraživanja bio je ustanoviti prihvaćanje i primjenu sveobuhvatnog genskog profiliranja (SGP) u svakodnevnoj kliničkoj praksi u bolesnika s uznapredovalim urotelnim karcinomom.

Metode: Podaci iz šest centara, članova hrvatske uro-onkološke mreže, retrospektivno su analizirani vezano za korištenje SGP-a tijekom standardnog liječenja bolesnika s uznapredovalim urotelnim karcinomom. Primarni cilj bilo je utvrditi izvedivost SGP-a u svakodnevnoj kliničkoj praksi za ovu izazovnu skupinu bolesnika, korištenjem testa FoundationOne.

Rezultati: Od 2020. do 2024. za 81 bolesnika učinjeno je SGP. Bolesnici su primili imunoterapiju (N=71; 87%) kao prvu liniju (68%) ili drugu liniju liječenja (32%). Srednja dob bila je 68 godina, 67% muškaraca, 79% s primarnim tumorom mokraćnog mjehura, 18% s metastazama u jetri, 74% ECOG PS 1. Uzorak za SGP bio je primarno tumorsko tkivo, metastaze i krv u 84%, 13% i 2% bolesnika. U 11 bolesnika (13%) analiza nije uspjela zbog nedovoljne količine tumorskog tkiva. Prosječno vrijeme do pristizanja izvješća bilo je 1 mjesec. Ukupno 229 genomskih promjena identificirano je u 61 genu, medijan od 3 po bolesniku. 8 najčešćih mutacija su: TERT (25, 30%), TP53 (20, 24%), MTAP (15, 18%), FGFR3 (14, 16%), PIK3CA (9, 10%), ERBB2/ HER2 (8,9%), CDKN2A (7,8%) i ARID1A (7,8%). Potencijalno targetabilna promjena pronađena je u 39 (47%) bolesnika. Sedam bolesnika (8%) primilo je ciljanu terapiju što je rezultiralo u 3 slučaja parcijalnim odgovorom, 3 stabilna bolest i 1 progresija bolesti. Bolesnici s TMB>10 mut/Mb (N=24) imali su numerički veće stope odgovora i ukupnog preživljenja na imunoterapiju.

Zaključak: Integracija SGP-a u liječenju bolesnika s uznapredovalim karcinomom urotela izvediva je i donosi nove terapijske mogućnosti dijelu bolesnika s inače ograničenim mogućnostima liječenja.

Ključne riječi: molekularno profiliranje, urotelni karcinom, ciljana terapija, sveobuhvatno gensko profiliranje

COMPREHENSIVE GENOMIC PROFILING IN PATIENTS WITH ADVANCED UROTHELIAL CANCER: FIRST RESULTS FROM CROATIAN URO-ONCOLOGY NETWORK

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Introduction: Many patients with advanced urothelial cancer (aUC) harbor somatic pathogenic genomic alterations. There is an unmet need to incorporate novel clinical genomic assays into routine care of patients with aUC to improve the benefit of cancer therapy. The aim of this study was to assess uptake and implementation of comprehensive genomic profiling (CGP) in everyday clinical practice of patients with aUC.

Methods: Data from six Croatian Uro-Oncology Network-associated centers were retrospectively analyzed for utilization of CGP during the standard-of-care treatment of patients with aUC. The primary endpoint was feasibility of CGP in real-world settings for this challenging patient population, using FoundationOne platform.

Results: From 2020 to 2024, 81 patients underwent CGP. Patients received ICI (N=71; 87%) as the first line (68%) or second line (32%). Median age was 68 years, 67% male, 79% with bladder primary, 18% with liver metastasis, 74% ECOG PS 1. Specimen for CGP was primary tumor tissue, metastasis and blood in 84%, 13%, and 2% of cases, respectively. In 11 patients (13%) analysis failed due to insufficient amount of tumor tissue. The median turnover time was 1 month. A total of 229 genomic alterations were identified in 61 genes, median of 3 per patient. The 8 most often altered genes were: TERT (25, 30%), TP53 (20, 24%), MTAP (15, 18%), FGFR3 (14, 16%), PIK3CA (9, 10%), ERBB2/HER2 (8, 9%), CDKN2A (7, 8%), and ARID1A (7, 8%). Potentially actionable alteration was found in 39 (47%) patients. Seven patients (8%) received targeted therapy resulting in 3 cases of partial response, 3 stable disease, and 1 progressive disease. Patients with TMB>10 mut/Mb (N=24) had numerically higher response rates and overall survival on ICI.

Conclusion: Integration of CGP in management of patients with aUC is feasible and yields new therapeutic options in a discernible proportion of patients with otherwise limited treatment options.

Keywords: molecular profiling, urothelial cancer, targeted therapy, comprehensive genomic profiling

LJEKARNIČKA SKRB ZA PACIJENTICE S RAKOM DOJKE U FARMAKOTERAPIJSKOM SAVJETOVALIŠTU DOMA ZDRAVLJA ZAGREB CENTAR

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Uvod: Zdravstvena skrb žena s rakom dojke zahtjeva integrirani pristup koji uključuje i pružanje ljekarničke skrbi od strane farmaceuta što potencijalno može doprinijeti smanjenju simptoma nuspojava terapije te poboljšati kvalitetu života i adherenciju. Svrha ovog istraživanja bila je odrediti vrstu i učestalost provedenih intervencija za rješavanje identificiranih terapijskih problema (TP) te njihovu prihvaćenosti kod pacijentica s dijagnosticiranim rakom dojke kojima je u Farmakoterapijskom savjetovalištu Doma zdravlja Zagreb Centar (DZZC) pružena usluga upravljanja farmakoterapijom.

Metode: Provedeno je prospektivno intervencijsko istraživanje u Farmakoterapijskom savjetovalištu DZZC-a u razdoblju od studenog 2022. do svibnja 2024. godine u koje su bile uključene pacijentice starije od 18 godina s postavljenom dijagnozom raka dojke te s najmanje jednom konzultacijom. Na inicijalnoj konzultaciji, uz prikupljanje podataka, određeni su TP i predložene su intervencije za njihovo rješavanje, dok je na kontrolnim konzultacijama utvrđen stupanj njihove prihvaćenosti.

Rezultati: U provedeno istraživanje bila je uključena 81 pacijentica prosječne dobi 58 (33–100) godina koje su u prosjeku bolovale od 10 (1–5) komorbiditeta te koristile 7 (1–20) lijekova i 4 (1–22) dodatka prehrani. Na prve dvije konzultacije identificirano je ukupno 416 TP ($5,0 \pm 3,7$), dok su najčešće intervencije za njihovo rješavanje uključivale „Uvođenje dodatka prehrani/dermatokozmetike/biljnog pripravka“ (24,5 %), „Uvođenje nove terapije“ (16,1 %), i „Edukacija pacijenta“ (12,9 %). Najčešći dodaci prehrani koji su bili predloženi za uvođenje bili su vitamini B kompleksa (9,29%), beta glukani (6,56%), vaginalete za vlaženje rodnice (6,01%), magnezij (4,92%) i vitamin C (4,92%). Od ukupno 243 intervencije predložene pacijenticama, njih 90,0 % je bilo prihvaćeno, dok je od strane liječnika prihvaćena 71 intervencija (87,1 %).

Zaključak: Visok stupanj prihvaćenosti intervencija od strane pacijentica i liječnika ukazuje na spremnost prihvaćanja suradnje i uključivanja farmaceuta u skrb onkoloških pacijentica s ciljem prevencije terapijskih problema.

Ključne riječi: rak dojke, upravljanje farmakoterapijom, ljekarnička skrb, dodaci prehrani

PHARMACEUTICAL CARE FOR BREAST CANCER PATIENTS AT THE PHARMACOTHERAPY COUNSELING CENTER OF THE HEALTH CARE CENTER ZAGREB-CENTER

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Introduction: Health care for women with breast cancer requires an integrated approach, including pharmaceutical care provided by pharmacists that can potentially reduce the symptoms of side effects, improve quality of life, and enhance adherence. This study aimed to determine the type and frequency of proposed interventions for the resolution of identified drug therapy problems (DTPs), as well as their acceptance in patients with breast cancer who were provided with Comprehensive Medication Management services at the Pharmacotherapy Counseling Center of the Health Care Center Zagreb-Centar (HCCZC).

Methods: A prospective interventional study was conducted at the Pharmacotherapy Counseling Center of HCCZC from November 2022 to May 2024, involving patients over 18 years old diagnosed with breast cancer who attended at least one consultation. During the initial consultation, data was collected, DTPs were identified,

and interventions to address them were proposed. During follow-up consultations, the acceptance of proposed interventions was assessed.

Results: The study included 81 patients with an average age of 58 (33–100) years, who had an average of 10 (1–5) comorbidities, used 7 (1–20) medications, and 4 (1–22) dietary supplements. A total of 416 TPs were identified (5.0 ± 3.7) during the initial consultation. At the same time, the most common interventions for their resolution were “Introduction of dietary supplement/dermocosmetics/herbal product” (24.5%), “Introduction of new therapy” (16.1%), and “Patient education” (12.9%). The most recommended dietary supplements were vitamin B complex (9.29%), beta-glucans (6.56%), vaginal moisturizing tablets (6.01%), magnesium (4.92%), and vitamin C (4.92%). Out of 243 interventions proposed to the patients, 90.0% were accepted by them, while physicians accepted 71 interventions (87.1%).

Conclusion: The high acceptance rate of interventions by patients and physicians indicates the readiness to collaborate with and include pharmacists in the care of oncology patients to prevent DTPs.

Keywords: breast cancer, Comprehensive Medication Management services, pharmaceutical care, food supplement

LINIJE LIJEČENJA I ISHODI METASTATSKIH BILIJARNIH KARCINOMA NA KLINICI ZA ONKOLOGIJU I RADIOTERAPIJU KLINIČKOG BOLNIČKOG CENTRA SPLIT U PERIOD OD 2019. DO 2022. GODINE

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Uvod: Bilijarni karcinomi se većinom dijagnosticiraju u uznapredovalom ili metastatskom stadiju (M1) kada su terapijske opcije skromne.

Metode: Proveli smo retrospektivnu analizu medicinskih povijesti pacijenata s dijagnosticiranim bilijarnim karcinomima prezentiranih na multidisciplinarnom timu (MDT) Klinike za onkologiju i radioterapiju KBC Split, u periodu 2019–2022. Podaci su analizirani deskriptivnim statističkim metodama, uz korištenje Microsoft Excela.

Rezultati: Identificirali smo ukupno 58 pacijenata s M1 karcinomima bilijarnog sustava. Od ukupne kohorte, samo 75,4% ($n=43$) je liječeno prvom linijom sistemske terapije, sa srednjim PFS 93 dana. Preostalih 24,9% je zbog lošeg općeg stanja primalo simptomatsko suportivnu terapiju. Drugu liniju je primilo ukupno 23 pacijenta (55,8%) sa srednjim PFS 60 dana. Treću liniju je primilo 9 pacijenata (20,9%) sa srednjim PFS 67 dana. Ukupno 4 pacijenta (9,5%) je primilo četvrtu liniju terapije sa srednjim PFS 26,5 dana. Samo 1 pacijent je primio petu liniju (medijan PFS 12 dana) i šestu liniju (medijan PFS 40 dana). Gensko profiliranje je provedeno kod 8 pacijenata, od kojih je kod 3 pacijenta dokazana neka od mutacija za koju postoji terapijska opcija, te su liječeni ciljanom terapijom u nekoj od linija sistemskog liječenja. Srednje preživljenje M1 pacijenata u našoj analizi je iznosilo 22 mjeseca.

Zaključak: Rezultati naše retrospektivne analize su pokazali značajan pad u broju pacijenata u kasnijim linijama sistemskog liječenja. Srednje preživljenje pacijenata s M1 stadijem bilijarnih malignih tumora iznosi 22 mjeseca, a oko trećina pacijenata koja zbog općeg stanja nisu mogla primiti nijednu liniju sistemske terapije ukazuju na potrebu za unaprjeđenjem strategija liječenja malignoma bilijarnog sustava. Vrijednost upotrebe ciljane terapije bazirane na preciznoj onkologiji bi se trebala dalje istraživati, te biti potencijalno dostupna svim pacijentima s M1 stadijem.

Ključne riječi: bilijarni karcinomi, metastatski, liječenje, sveobuhvatno gensko profiliranje

TREATMENT PATTERNS AND THE OUTCOMES OF METASTATIC BILIARY TRACT CANCERS (BTC) AT THE DEPARTMENT OF ONCOLOGY AND RADIOTHERAPY, UNIVERSITY HOSPITAL SPLIT DURING 2019–2022

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Introduction: BTC are a group of tumors that are in most cases diagnosed in the advanced and metastatic phase of the disease when therapeutic options and results are modest.

Methods: A retrospective analysis of patients presented on our MDT over 4 years (1/19 – 12/22) was conducted. The data were analyzed using descriptive statistics methods, with the use of Microsoft Excel tools.

Results: We identified a total of 58 patients with metastatic (M1) BTC. Among those, only 75.4% of patients (n=43) received the first line of systemic therapy, with a median PFS of 93 days. The remaining 24.9% had only the best supportive care (BSC), due to their poor performance status. A total of 23 patients (55.8%) received second-line treatment, with median PFS of 60 days. A total of 9 patients (20.9%) received third line of therapy, with median PFS of 67 days. 4 patients (9.5%) received the fourth line of therapy, with median PFS of 26.5 days. Only 1 patient received fifth line (5L) with median PFS of 12 days and sixth line of therapy with median PFS of 40 days. Comprehensive Genomic Profiling (CGP) was performed in 8 patients, out of whom 3 patients had actionable mutations and were treated with targeted therapy. The median OS in our subset of patients with M1 BTC was 22 months.

Conclusion: The results of our retrospective analysis showed a significant decrease in the number of patients in later lines of treatment. The median overall survival of 22 months and about a third of patients not receiving anti-cancer therapy define the unmet need in this patient population. The value of the use of targeted therapy based on precision medicine should be further investigated and potentially available to all patients with actionable mutations.

Keywords: biliary tract cancer, metastatic, comprehensive genetic profiling, cancer treatment

KARCINOM BILIJARNOG SUSTAVA – RETROSPEKTIVNA ANALIZA KLINIKE ZA ONKOLOGIJU I RADIOTERAPIJU KLINIČKOG BOLNIČKOG CENTRA SPLIT U PERIOD OD SIJEČNJA 2019. DO PROSINCA 2022. GODINE, USPOREDBA EPIDEMIOLOŠKIH PODATAKA

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Uvod: Karcinomi bilijarnog sustava su grupa rijetkih malignoma koja se razvija iz žučnog mjehura i/ili žučnih vodova. Zbog inicijalno asimptomatskog razvoja, te agresivne prirode bolesti se tipično dijagnosticiraju u lokalno uznapređovalom ili metastatskom stadiju.

Metode: retrospektivna analiza povijesti bolesti pacijenata s malignim tumorima bilijarnog sustava prezentiranih na multidisciplinarnom timu Klinike za Onkologiju i radioterapiju, u periodu od 101.19–12.22. Korištene su deskriptivne statističke metode i Microsoft Excel.

Rezultati: identificirano je ukupno 85 pacijenata s malignim tumorima bilijarnog sustava. Srednja dob u vrijeme dijagnoze je bila 70 godina (31–90), te je najčešći patohistološki podtip bio adenokarcinom (94,1%). Distribucija po spolu je bila 60% muškaraca i 40% žena. 47,1% pacijenata je imalo inicijalno metastatsku bolest (M1). Operacija s kurativnom namjerom je učinjena kod 34 pacijenta koji nisu imali dokaza metastatske bolesti (M0), od kojih je 50% primalo adjuvantnu kemoterapiju, a kod ostalih je provedeno kliničko praćenje. Dio pacijenata je razvio M1 bolest tijekom naše analize, pa smo finalno imali 58 pacijenata s M1 stadijem. Gotovo trećina M1 (24,9%) nije primila nijednu liniju sistemske terapije zbog lošeg općeg stanja, a prvu liniju sistemske terapije je primilo 75,1% pacijenata.

Zaključak: Analizom smo potvrdili da je većina malignih tumora bilijarnog sustava na Klinici za onkologiju i radioterapiju KBC Split u promatranom periodu dijagnosticirana u uznapredovalom stadiju, kod pacijenata starije životne dobi i često su lošeg općeg stanja.

Ključne riječi: bilijarni karcinomi, epidemiologija, kemoterapija, adenokarcinom

BILIARY TRACT CANCERS – SINGLE INSTITUTION RETROSPECTIVE ANALYSIS (2019–2022), THE CROSS-SECTION OF EPIDEMIOLOGICAL DATA

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Introduction: BTC comprises a rare group of malignancies that involve the gallbladder and biliary tree. Due to their aggressive nature and initially asymptomatic course, they are typically diagnosed in the locally advanced and metastatic phase.

Methods: A retrospective analysis of patients presented on our multidisciplinary team (MDT) over the course of 4 years (1/19 – 12/22) was conducted. The data were analyzed using descriptive statistics methods, with the use of Microsoft Excel tools.

Results: We identified a total of 85 patients with diagnosed BTC. The median age at the time of diagnosis was 70 years (range 31–90) and the most common pathohistological subtype was adenocarcinoma (94.1%). The distribution by gender was 60% male and 40% female. 47.1% of patients were initially metastatic (M1). Curative intent surgery was performed in 34 patients, out of whom 50% were treated with adjuvant chemotherapy and the remaining 50% were in close follow up. Some of those patients developed metastatic disease in later stages of our analysis so we had a total of 58 patients with M1 disease. Among those, 75.1% were treated with systemic therapy and 24.9% had only the best supportive care (BSC), due to their poor performance status.

Conclusion: It is confirmed that in our institution the tumors of the biliary system are diagnosed in an advanced stage, in people of older age and often with low performance status.

Keywords: biliary tract cancer, epidemiology, chemotherapy, adenocarcinoma

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