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**Sažetci predavanja | Lecture abstracts**

## GENSKO PROFILIRANJE TUMORA I PERSONALIZIRANA ONKOLOGIJA

VRBANEC D.[1]

[1] Sveučilište Jurja Dobrile u Puli
• *Medicinski fakultet u Puli*
dvrbanec197@gmail.com

Napredak temeljnih znanosti u posljednjim desetljećima, osobito u području molekularne biologije, patofiziologije i kliničke medicine doveo je do razvoja novih spoznaja o biološkim značajkama tumora i do uvođenja brojnih novih terapijskih postupaka, koji se često zajednički nazivaju personalizirana onkologija. Danas je poznato da je rak uglavnom genetska bolest koja uključuje genetske i epigenetske promjene ili mutacije koje reguliraju staničnu diobu i invazivnost i koje dovode do pretvorbe normalne stanice u zloćudne. Personalizirana onkologija uključuje primjenu rezultata novih metoda, poput genomike, transkriptomike, metabolomike ili proteomike. Novi postupci analize kao sekvenciranje slijedeće generacije (NGS) sve više zamjenjuje konvencionalne tehnike poput testiranja samo jednog gena, i omogućuju analiziranje stotina gena ili cijelog genoma pomoću malih količina tkiva prikupljenih biopsijom, te cirkulirajuće tumorske DNA dobivene iz krvi (ctDNA), cirkulirajućih tumorskih stanica (CTC) ili egzosoma. Genetsko profiliranje tumora može poboljšati klasifikaciju tumorskih podtipova, identificirati one bolesnike koji će imati najveću korist od sustavnih terapija i analizirati varijante zametne linije koje utječu na nasljedni rizik od raka. Za mnoge vrste tumora, odabir probira, dijagnostičkog testiranja i terapije uključuje genomske podatke o tumoru (somatske promjene), promjene zametne linije u naslijeđenim genima raka (npr. *BRCA1* i *BRCA2*) kao i genetske promjene promjene zametnih linija. Ciljani genski paneli pokazali su značajnu korisnost u mnogim vrstama tumora, posebno u onih za koje bi moglo biti odgovorno više od jedne genetske promjene. Testiranje na tumorske specifične stečene (somatske) genetske promjene danas je praktički postao standard u skrbi za mnoge vrste tumora. Somatske mutacije mogu se podijeliti na one koje su onkogene (eng. *drivers*), te na one koje su biološki inertne (eng. *passengers*). Među tzv. pokretačkim mutacijama postoji podskupina prediktivnih biomarkera za vjerojatni terapijski učinak, takozvane mutacije u kojih očekujemo klinički terapijski odgovor.

Većina mutacija koje ukazuju na klinički učinak terapije ciljevi su djelovanja inhibitora kinaza malih molekula ili protutitijela. Danas su određeni i genetski polimorfizmi za mnoge enzime koji metaboliziraju lijekove i njihove ciljeve (primjerice receptore) i oni vjerojatno doprinose varijabilnosti terapijskog odgovora u bolesnika.

S većim napretkom u poznavanju biomarkera i personalizirane medicine razvijena su klinička ispitivanja temeljena na genomici. Mnoge od ovih kliničkih studija uključene su u podskupinu tzv. "basket" (košara) ili "umbrella" (kišobran) kliničkih studija u okviru glavnih protokola koji se temelje na genomici, odnosno tehnikama kao što je NSG. Postoji mnogo primjera takvih randomiziranih kliničkih studija koje su do sada provedene ili su u tijeku, primjerice francuska klinička studija Shiva, studija MOSCATO 01, studija MyPathway, studija TAPUR i neke novo osmišljene studije poput studije WINTHER, I-PREDICT i mnoge druge.

## TUMOR GENETIC PROFILING AND PERSONALIZED ONCOLOGY

VRBANEC D.[1]

[1] Juraj Dobrila University of Pula
• *School of Medicine*
dvrbanec197@gmail.com

Advances in basic science, especially in the area of the molecular biology, pathophysiology and clinical medicine in the last decades have increasingly elevated our knowledge of tumor biologic features and have led to the introduction of several new therapeutic procedures, which are often collectively referred to as personalized oncology. Today it is known that cancer is mostly genetic disease involving genetic and epigenetic alterations or

mutation that regulates cell division and invasiveness in order to transform normal cell into malignant cell. Personalized oncology includes the application of the results of some new methods such genomics, transcriptomics, metabolomics, or proteomics. New procedures of analysis as next generation sequencing (NGS) have increasingly substituted for conventional techniques such as single-gene testing and allow evaluation of hundreds of genes or the entire genome using small quantities of tissue collected by biopsy, blood-derived circulating tumor DNA (ctDNA), circulating tumor cells (CTC) or exosomes. Tumor genetic profiling can refine cancer subtype classification, identify which patients are most likely to benefit from systemic therapies and screen for germline variants that influence heritable cancer risk. For many types of cancer, the choices of screening, diagnostic testing, and therapy incorporate genomic information about the tumor (somatic changes), germline changes in inherited cancer genes (eg, *BRCA1* and *BRCA2*), and germline changes in genetic modifiers. Targeted gene panels have shown expanded usefulness across many cancer types, especially those for which more than one genetic variant may be responsible. Testing for tumor-specific acquired (somatic) genetic changes is an evolving standard of care across many cancer types. Somatic mutations are subclassified into those that there oncogenic(drivers), versus those that are biologically inert (passengers). Among the driver mutations, there is a subset of predictive biomarkers for drug response so-called clinically actionable mutations

Most mutation that are clinically actionable are targets of small-molecule kinase inhibitors or antibodies. Genetic polymorphisms for many drug metabolizing enzymes and drug targets (eg, receptors) have been identified and probably contribute to interpatient variability in drug response.

With increasing advancements in biomarkers and personalized medicine genomic-guided trials have been developed. Many of this trial are included in the group of basket or umbrella trials under the master protocols framework based on the genomic alterations or technique such as NSG. There are many examples of such randomized studies that have been reported to date, for example French Shiva trial, MOSCATO 01 study, MyPathway study, TAPUR study, and some newly designed studies like WINTHER, I-PREDICT study and many more.

**In extenso rad | In extenso article**

## ONKOLOZI NA VALOVIMA COVID19 PANDEMIJE

BUDISAVLJEVIĆ A.[1], Kelemenić R.[2]

[1] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
[2] Opća bolnica Varaždin
• *Odjel za hematologiju, onkologiju i kliničku imunologiju i alergologiju*
anuska.budisavljevic@gmail.com

**Sažetak**: *Ciljevi:* Liječnici često imaju sindrom sagorijevanja na poslu. Onkolozi imaju visoki rizik sagorijevanja. Covid-19 pandemija dovela je do značajnih promjena, kako u svakodnevnim životima tako i na radnom mjestu liječnika. Ciljevi su ispitati koliko je ova pandemija utjecala na promjene u radu i radnom okruženju onkologa te, je li Covid-19 pandemija imala utjecaj na razvoj sindroma sagorijevanja na poslu. *Metode:* presječno ispitivanje provedeno je tijekom listopada 2021 godine. Istraživanje je provedeno putem elektronske anonimane google form online ankete koja je poslana na 167 e-mail adresa specijalista ili specijalizanta, internističke onkologije ili onkologije i radioterapije. Anketa, koja je bila dostupna za ispunjavanje u periodu od 6. do 24. rujna 2021, sadržavala je pitanja o demografskim podacima i pitanja o utjecaju pandemije Covid-19 na rad onkologa. Sindrom sagorijevanja na poslu evaluiran je izdvojenim pitanjem o osjećaju sagorijevanja na poslu (veća emotivna iscrpljenost i osjećaju otuđenosti) u komparaciji s periodom prije pandemije. *Rezultati:* Ukupno je zabilježeno 73 odgovora. Većina onkologa (84%) imala je tijekom Covid-19 pandemije veći osjećaj sagorijevanja na poslu nego prije pandemije. Hrvatski onkolozi vrlo su se brzo prilagodili novim zahtjevima i novim standardima

u zbrinjavanju onkoloških bolesnika te je 94% onkologa tijekom pandemije koristilo mogućnost telemedicine. Dvije trećine onkologa smatra da je njihova edukacija u ovom periodu nazadovala. *Zaključak:* Tijekom Covid-19 pandemije zabilježena je visoka razina sagorijevanja onkologa. Telemedicina je vrlo brzo usvojena kao novi standard rada. U slučaju nastavka online edukacije, potrebno je bolje promišljanje i organiziranje iste s obzirom na ocjenu onkologa o nazadovanju onkološke edukacije tijekom Covid-19 pandemije.

## Uvod

Liječnici se po definiciji profesije ne bave sobom već svojim pacijentima. (Najvažnija će mi briga biti zdravlje i dobrobit mojega pacijenta, liječnička prisega).[1] Od onkologa se očekuje i visoka razina suosjećanja, osjetljivosti i empatije za liječenje osoba oboljelih od raka te emocionalna otpornost za pomoć pacijentima u vrlo teškim vremenima.[2]

Poznata je činjenica da liječnici često imaju osjećaj sagorijevanja na poslu, čak i oni koji imaju izraženu psihološku otpornost.[3] Istraživanje o sagorijevanju na poslu hrvatskih liječnika provedeno 2017. godine pokazalo je da 63% ispitivanih liječnika imalo visoku razinu sagorijevanja.[4] Onkolozi imaju značajno veću razinu sagorijevanja na poslu u odnosu na druge liječničke profesije.[5–8] U nedavno provedenom istraživanju o sagorijevanju onkologa u zemljama istočne Europe, prije pandemije Covid-19, čak je 74% ispitanika iz jugoistočne Europe (gdje su bili uključeni hrvatski onkolozi) imalo rizik visokog sagorijevanja.[9]

U Hrvatskoj je tijekom 2020 godine u Klinikama, Kliničkim centrima i Kliničkim bolničkim centrima (KBC) i Općim i županijskim bolnicama (OB) radilo 130 specijalista internističke onkologije ili onkologije i radioterapije, 106 onkologa (84%) u KBC-ovima i 24 onkologa (18%) u OB-ovima. 62 liječnika u tijeku je specijalizacije iz internističke onkologije ili onkologije i radioterapije (77% za KBC i 23% za OB).10 Hrvatski prosjek od 3.1 onkologa/100 000 stanovnika značajno je niži od europskog prosjeka (Italija 7.1; Španjolska 3.9; Ujedinjeno Kraljevstvo 3.8; Njemačka 3.5).[10] Prekomjerno radno opterećenje (koje neizostavno proizlazi iz navedenih brojki), kao i povećan broj radnih sati poznati su faktori rizika za razvoj sagorijevanja na poslu.[11]

Covid-19 pandemija neupitno je dovela do većeg stresa i sagorijevanja kod liječnika.

Nedavno objavljeni rezultati dva internetska istraživanja koje je provela Radna skupina za otpornost Europskog društva za medicinsku onkologiju (ESMO) naglasili su u kojoj je mjeri pandemija COVID-19 utjecala na sagorijevanje. Prvo istraživanje provedeno je od u svibnju 2020., kada je 38% ispitanika izjavilo je da je imalo osjećaj izgaranja. Naknadna anketa provedena u kolovozu 2020. pokazala je da se udio ispitanika koji su prijavili osjećaj izgaranja popeo na 49%.[12,13]

Ciljevi ovog istraživanja su (I) evaluirati utjecaj Covid-19 pandemije na promjene u svakodnevnom radu onkologa, istražiti prevalenciju Covid-19 bolesti među onkolozima, stavove onkologa o cijepljenju protiv Covida-19 te (II) istražiti utjecaj Covid-19 pandemije na razinu sagorijevanja hrvatskih onkologa.

## Metode

Presječno ispitivanje provedeno je tijekom listopada 2021 godine. Istraživanje je provedeno putem elektronske google form online ankete. Anonimna anketa na hrvatskom jeziku ispunjavala se u periodu od 06. do 24. rujna 2021. Anketa je poslana na 167 e-mail adrese internističkih onkologa ili onkologa radioterapeuta (u daljnjem tekstu „onkologa"), u funkciji specijalista ili specijalizanata, koji rade u općim i županijskim bolnicama te klinikama, kliničkim centrima i kliničkim bolničkim centrima. Ukupno je registrirano 73 odgovora, stopa odgovora bila je 43%. Sve „vraćene" ankete imale su 100% odgovora ispunjeno.

Anketa se sastojala od tri djela. U prvom dijelu ankete bili su demografski podaci te podaci o utjecaju Covid-19 pandemije na promjene u svakodnevnom radu onkologa, prevalenciji Covid-19 infekcije među onkolozima i stavovima o cijepljenju protiv Covid-19 infekcije. Drugi dio ankete bio je Olderburški upitnik o sagorijevanju (Oldenburg Burnout Inventory). Treći dio ankete bio je kratka skala o psihološkoj otpornosti (Brief Resilience Scale). Osim Oldenburškog upitnika o sagorijevanju na poslu, sagorijevanje je bilo evaluirano i jednim izoliranim pitanjem jesu li ispitanici osjetili veće sagorijevanje na poslu (veću emotivnu iscrpljenost i otuđenost) tijekom pandemije u odnosu na period prije pandemije. Podaci o centrima u kojima su radili ispitanici nisu sakupljani kako bi se osigurala anonimnost ispitanika s obzirom da u pojedinim centrima rade po jedan ili dva onkologa.

Deskriptivna analiza korištena je za karakterizaciju ispitanika te su rezultati prikazani u apsolutnim brojevima i postocima.

## Rezultati

### *Sociodemografske karakteristike*

Od 167 kontaktiranih onkologa, specijalista i specijalizanata, anketu je ispunilo 73 anketirankih, stopa odgovora bila je 43%. Većinu anketa ispunile su žene, 74%. Ukupno je u anketi sudjelovalo 55 (75%) specijalista i 18 (25%) specijalizanata. Najveći broj anketiranih imao je između 11–20 godina radnog iskustva (35%), zatim slijedi 27 % ispitanika do 5 godina iskustva. 14% ispitanika ima više od 20 godina iskustva rada u onkologiji. U KBC-ovima zaposleno je 46 ispitanika (63%), a u OB-ovima 27 (37%)

### *Utjecaj Covid-19 pandemije na svakodnevni rad onkologa*

Tijekom prvog, drugog i trećeg vala pandemije Covid-19, 78% ispitanika radilo je u području s visokom incidencijom Covid-19. Najveći postotak onkologa, tijekom Covid-19 pandemije, nastavio je raditi na svojim radnim mjestima (70%), njih 11% dobrovoljno je promijenilo radno mjesto, dok je 19% premješteno na drugo radno mjesto, ali ne dobrovoljno. Više od polovice onkologa (53%) nije sudjelovalo u zbrinjavanju Covid-19 pozitivnih bolesnika. Ukoliko su radili s Covid-19 pozitivnim bolesnicima, to je bilo najčešće u hitnoj službi – 37%, na Covid-19 odjelu – 27% i u intenzivnoj jedinici – 6,5%. Covid-19 pandemija dovela je do većeg broja radnih sati kod svakog drugog onkologa, više od trećine imalo je veći broj noćnih smjena, a samo se u 4% slučajeva satnica smanjila. Većina onkologa (59%) ocijenila je da je tijekom Covid-19 pandemije njihova edukacija u onkologiji nazadovala, dok za 20% nije bilo značajnog utjecaja pandemije na edukaciju u onkologiji. Gotovo su svi onkolozi (92%) tijekom pandemije koristili mogućnost telemedicine u zbrinjavanju onkoloških bolesnika. Od toga 80% putem A5 uputnice, telefona ili e-mail-a, a 19% putem videokonferencije. Mogućnost rada od kuće koristilo je 10% onkologa. Nošenje protektivne opreme (maska na licu) u 82,3% slučajeva utječe na komunikaciju s bolesnicima. Dvije trećine anketiranih (68%) smatra da ih na ovaj način bolesnici teže razumiju, 59 % smatra da im je na ovaj način otežano pratiti reakcije bolesnika, a 59% smatra da nošenje maski depersonalizira odnos s bolesnikom. Većina onkologa (85%) imala je tijekom Covid-19 pandemije veći osjećaj sagorijevanja na poslu (veća emotivna iscrpljenost i veći osjećaj otuđenosti) nego prije pandemije.

### *Prevalencija Covid-19 i cijepljenje*

Do zaključivanja ankete ukupno je 14 onkologa (19%) bilo je pozitivno na Covid-19 (dokazano PCR brisom nazofaringsa ili brzim antigenskim testom). Niti jedan Covid-19 pozitivan onkolog nije bio hospitaliziran niti je imao teži oblik bolesti. Protiv Covid-19 cijepilo se 66 (90%) onkologa, 4 (5,5%) ih se namjerava cijepiti, a 3 (4.1%) onkologa nije se cijepilo, niti se ne namjerava cijepiti protiv Covid-19. Dvije trećine anketiranih smatra da cijepljenje protiv Covid-19 mora biti obavezno za zdravstvene djelatnike.

## Zaključak

Čak se 85% onkologa izjasnilo da je tijekom pandemije Covid-19 imalo veći osjećaj sagorijevanja na poslu (emotivna iscrpljenost i osjećaj otuđenosti) u odnosu na period prije pandemije. Nedavno provedeno istraživanje o sagorijevanju onkologa, prije pandemije Covid-19, pokazalo je visoku razinu sindroma sagorijevanja kod 74% onkologa.6 Može se pretpostaviti da je pandemija Covid-19 utjecala na ovaj porast sindroma sagorijevanja onkologa. Hrvatski onkolozi vrlo su se brzo prilagodili novim zahtjevima i novim standardima u zbrinjavanju onkoloških bolesnika te je velika većina onkologa tijekom pandemije koristila mogućnost telemedicine. S druge strane, tijekom pandemije brojna su edukativna predavanja bila dostupna online, putem videokonferencija, no usprkos ovoj činjenici, gotovo dvije trećine onkologa smatra da je njihova edukacija u ovom periodu nazadovala. Iako je tradicionalno glavna liječnička briga ona o bolesnicima, potrebno je sustavno raditi na rasterećenju i poboljšanju uvjeta rada onkologa kao i brinuti za njihovo mentalno zdravlje. Poznato je da manje sagorijevanje na poslu dovodi do bolje produktivnosti liječnika, većeg zadovoljstva njihovih bolesnika i boljih ishoda liječenja bolesnika.[11,14]

## LITERATURA

1. *Hrvatska liječnička komora.* Liječnička prisega. [pristupljeno 2021 Sep 16]. Dostupno na: https://www.hlk.hr/EasyEdit/UserFiles/pdf-ovi-za-vijesti-web/2020/lijecnicka-prisega.pdf
2. *National Health Service.* Entry requirements, skills and interests (clinical oncology). [pristupljeno 2021 Sep 16]. Dostupno na: https://www.healthcareers.nhs.uk/explore-roles/doctors/roles-doctors/clinical-oncology/entry-requirements-skills-and-interests

3. *West CP, Dyrbye LN, Sinsky C i sur.* Resilience and Burnout Among Physicians and the General US Working Population. JAMA Netw Open. 2020 Jul 1;3(7):e209385. doi: 10.1001/jamanetworkopen.2020.9385.
4. *Pintarić Japec V, Vučemilo, L, Kust, D i sur.* Burnout among Croatian physicians: a cross sectional national survey. Croat. Med J, 2019 60(3), 255–264.
5. *Eelen S, Bauwens S, Baillon C, Distelmans W, Jacobs E, Verzelen A.* The prevalence of burnout among oncology professionals: oncologists are at risk of developing burnout. Psychooncology. 2014 Dec;23(12):1415–22. doi: 10.1002/pon.3579. Epub 2014 May 21. PMID: 24846818.
6. *Hlubocky FJ, Rose M, Epstein RM.* Mastering Resilience in Oncology: Learn to Thrive in the Face of Burnout. Am Soc Clin Oncol Educ Book. 2017;37:771–781.
7. *Arrogante O, Aparicio-Zaldivar E.* Burnout and health among critical care professionals: The mediational role of resilience. Intensive Crit Care Nurs. 2017;42:110–115.
8. *Murali K, Makker V, Lynch J, Banerjee S.* From Burnout to Resilience: An Update for Oncologists. Am Soc Clin Oncol Educ Book. 2018 May 23;38:862–872.
9. *Kust D, Murgic J, Vukovic P i sur.* Oncologist Burnout Syndrome in Eastern Europe: Results of the Multinational Survey. JCO Oncol Pract. 2020 Apr;16(4):e366–e376.
10. *Kelemenić-Dražin R, Budisavljević A.* Organisation of oncology care in Croatia. Comparison with surrounding countries. Ann Oncol. 2020. Suppl. Volume 31, S968
11. *Kumar S.* Burnout and Doctors: Prevalence, Prevention and Intervention. Healthcare (Basel). 2016 Jun 30;4(3):37.
12. *Burki TK.* Burnout among cancer professionals during COVID-19. Lancet Oncol. 2020 Nov;21(11):1402. doi: 10.1016/S1470-2045(20)30584-2. Epub 2020 Sep 24.
13. *Omar Abeid M A, Ramadan Marwa M, Khamis Yomna, Ismail Abdelsalam A.* The impact of COVID-19 on the occupational health of oncologists: a descriptive analysis of occupational safety, perceived burnout and social support among practicing oncologists in Alexandria, Egypt. ecancer 2021; 5 1273
14. *Delgadillo J, Saxon D, Barkham M.* Associations between therapists' occupational burnout and their patients' depression and anxiety treatment outcomes. Depress Anxiety. 2018; 35(9):844–850.

## RIDING THE WAVES OF THE COVID-19 PANDEMIC, HOW DO ONCOLOGIST COPE?

BUDISAVLJEVIĆ A.[1], Kelemenić R.[2]

[1] General Hospital Pula
• *Department of Medical Oncology and Hematology*
[2] General Hospital Varaždin
• *Department of Medical Oncology and Hematology, Clinical Imunology and Alergology*
anuska.budisavljevic@gmail.com

**Objectives**: Medical doctors often suffer from a burnout syndrome. Oncologists have a high risk of burnout. The Covid-19 pandemic has led to significant changes in daily, as well as work routines of physicians and has contributed to the development of stress in physicians. This survey explores to which extent has pandemic affected changes in the work and work environment of oncologists and whether the Covid-19 pandemic has had an impact on the burnout syndrome.

**Methods**: a cross-sectional study was conducted during October 2021. The research was conducted through an electronic anonymous google form online survey, completed in the period from 6th to 24th September 2021. The survey was sent by an e-mail to 167 registrars or specialists in medical oncology or oncology and radiotherapy. The survey included questions about demographic data, the impact of the Covid-19 pandemic on the work of oncologists. Burnout was evaluated by a separate question about the feeling of burnout at work (greater emotional exhaustion and sense of depersonalisation) compared to the period before the pandemic.

**Results**: Majority of oncologists (84%) had a greater sense of burnout at work during the Covid-19 pandemic compared to the period before the pandemic. Croatian oncologists adapted very well to the new requirements and new standards of oncology care and 94% of oncologists used the possibility of telemedicine during the pandemic. Two-thirds of oncologists believe that their education in oncology has declined during this period.

**Conclusion**: During the Covid-19 pandemic, high levels of burnout were recorded by oncologists. Telemedicine was very quickly adopted as a standard of work. If online education is to be continued, one should have in mind the assessment of oncologists on the decline of oncology education during the Covid-19 pandemic.

# SEKCIJA TUMORI GLAVE I VRATA / HEAD & NECK SESSION

## IMUNOTERAPIJA U LIJEČENJU TUMORA GLAVE I VRATA

RAKUŠIĆ Z.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
zrakusic@kbc-zagreb.hr

Prema podacima TCGA (The Cancer Genome Atlas) tumori glave i vrata su imunološki najaktivnije tumorsko tkivo nakon adenokarcinoma pluća i karcinoma bubrežnih stanica. Pojava i progresija tumora glave i vrata povezana je s ozbiljnim imunološkim deficitom uključujući disfunkciju imunoloških stanica, smanjeno izlučivanje citokina i poremećaj u prezentaciji antigena.

Prvi rezultati primjene inhibitora kontrolnih točaka u liječenje rekurentnih i metastatskih (R/M) tumora glave i vrata vezani su za „basket" studiju KEYNOTE-012 i primjenu PD-1 inhibitora pembrolizumaba. Stopa odgovora iznosila je 18%. Ova studija je utjecala na daljnje ispitivanje i proučavanje pembrolizumaba u liječenju tumora glave i vrata. CheckMate-141 je bila prva klinička studija faze III s PD-1 inhibitorom nivolumabom u tumorima glave i vrata. Uspoređena je učinkovitost nivolumaba sa stadardnom kemoterapijom u R/M tumorima glave i vrata. Rezultati su pokazali da je nivolumab značajno bolji od tradicionalne kemoterapije s većim medijanom preživljavanja od 2,4 mjeseca (7,5 mjeseci vs. 5,1 mjeseci), 20% višim jednogodišnjim preživljavanjem (36% vs. 16%), uz značajno smanjen rizik od teških nuspojava.

Randomizirana studija faze III KEYNOTE-048, provedena je na 882 bolesnika, imala je tri grane i usporedila je učinkovitost monoterapije s pembrolizumabom, kombinaciju pembrizumaba, spojeva platine i 5-flurouracila s do tada standardnom terapijom za R/M tumore glave i vrata po protokolu EXTREME (spojevi platine+5-fluorouracil + cetuksimab). Uključeni su bili bolesnici s R/M tumorima orofarinksa, usne šupljine, larinksa i hipofarinksa, inkurabilni za liječenje lokalnom terapijom. Randomizacija je provedena u omjeru 1:1:1, a stratifikacija prema PD-L1 ekspresiji, p16 ekspresiji i ECOG statusu. Rezultati pokazuju da je kod bolesnika sa PD-L1 ekspresijom CPS (combined positive score) ≥20, medijan preživljenja značajno bolji u skupini koja je liječena monoterapijom pembrolizumabom u odnosu na EXTREME protokol, 14,9 : 10,7 mjeseci (HR 0.61; p=0.0007), dok su ORR (overall response rate) i PFS bez statistički značajne razlike. Nadalje pembrolizumab + kemoterapija sa solima platine i 5-fluorouracilom ima bolji medijan preživljenja u cijelokupnoj populacili, bez obzira na CPS ekspresiju, od kombinacije po EXTREME protokolu, 13,0 : 10,7 mjeseci (HR 0.77; p=0.0034). Temeljem navedenih rezultata monoterapija pemrolizumabom je u relevantnim kliničkim smjernicama terapija izbora u 1. liniji liječenja R/M tumora glave i vrata kod bolesnika s visokom ekspresijom PD-L1, a kombinacija pembrolizumaba i kemoterapije sa spojevima platine za istu indikaciju bez obzira na razinu PD-L1 ekspresije.

Na temelju pozitivnih rezultata primjene PD-1 inhibitora u R/M tumorima glave i vrata u studijama faze III Checkmate-141 i KEYNOTE-048 slijedila su brojna istraživanja, od kojih su većina u tijeku, primjene kombinacija PD-1, PD-L1 i CTLA-4 inhibitora, kombinacije inhibitora kontrolnih točaka s SBRT-om (stereotactic body radiation therapy), primjene imunoterapije u lokalno uznapredovaloj bolesti.

Randomizirana studija faze III EAGLE provedena je na 736 bolesnika s R/M karcinomima glave i vrata. Imala je tri grane terapije, monoterapija PD-L1 inhibitorom durvalumab, kombinacija durvalumaba i CTLA-4 inhibitora tremelimumaba i standardnu terapiju (cetuksimab, taksani, metotreksat, fluoropirimidini). Randomizacija je provedena u omjeru 1:1:1. Primarni cilj studije bilo je ukupno preživljenje (OS). Nisu primijećena statistički značajna poboljšanja OS-a za durvalumab u odnosu na standardnu terapiju (HR 0.88) ili durvalumab plus tremelimumab u odnosu na standardnu terapiju (HR 1.04). Stope preživljavanja od 12 mjeseci bile su 37,0% za durvalumab, 30,4% za durvalumab plus tremelimumab i 30,5% za standardnu terapiju. Kombinacija durvalumaba i tremelimumaba nije pokazala veću učinkovitost. Ipak nešto više stope preživljavanja od 12 do 24 mjeseca i stope odgovora ukazuju na kliničku aktivnost durvalumaba.

Za sada jedina, randomizirana studija faze II na 62 bolesnika s metastatskim karcinomima glave i vrata nije utvrdila razliku učinkovitosti u bolesnika koji su liječeni s nivolumabom i SBRT-om u odnosu na one koji su

liječeni samo nivolumabom. Temeljem rezultata studije, autori su zaključili, da dodatak SBTR-a nivolumabu nije utjecao na sigurnosni profil, ali nije ni poboljšao ORR, PFS i OS. Nije uočen niti apskopalni efekt u bolesnika liječenih s nivolumabom i SBRT-om.

Velika očekivanja su bila od studije faze III, JAVELIN H&N 100, provedenoj na 907 bolesnika s lokalno uznapredovalim tumorima orofarinksa, usne šupljine, larinksa i hipofarinksa. Uspoređena je standardna terapija ove bolesti, konkomitantna kemoterapija (trotjedna cisplatina u dozi 100 mg/m$^2$ + IMRT 70Gy/7 tjedana) i placebo s istom konkomitantnom kemoradioterapijom i PD-L1 inhibitorom avelumabom u dozi 10 mg/kg jedan tjedan prije početka kemoradioterapije, za vrijeme kemoradioterapijre i kao terapija održavanja u dvotjednim razmacima u trajanju do 12 mjeseci. Prosječno praćenje za preživljavanje bez progresije bilo je 14,6 mjeseci u skupini koja je primala avelumab i 14,8 mjeseci u skupini koja je primala placebo. Srednje preživljenje bez progresije nije dosegnuto (95% CI 16,9 mjeseci-nije procjenjivo) u skupini koja je primala avelumab, a nije dosegnuto (23,0 mjeseci-nije procjenjivo) ni ti u skupini koja je primala placebo (HR 1.21; p = 0,92). Ozbiljni nuspojave povezane s liječenjem registrirane su u 124 (36%) bolesnika u skupini koja je primala avelumab i u 109 (32%) bolesnika u skupini koja je primala placebo. Primarni cilj produljenja preživljavanja bez progresije s avelumabom uz kemoradioterapiju, nakon čega je uslijedilo održavanje avelumaba u bolesnika s lokalno uznapredovalim karcinomom pločastih stanica glave i vrata, nije ispunjen.

Postoje već izvješća o neoadjuvantnoj primjeni imunoterapije u tumorima glave i vrata. U studiji CheckMate 358 faze I/II provedenoj na 52 bolesnika s karcinoma glave i vrata povezanih s virusom, procijenjen je neoadjuvantni nivolumab u prethodno neliječenih, resektabilnim HPV-pozitivnim ili HPV-negativnim tumorima. Nivolumab je primjenjen u dozi 240 mg iv 1. i 15. dan, uz operaciju planiranu do 29. dana. Sigurnost/podnošljivost (primarni ishod studije) je procijenjena praćenjem nuspojava (AE) i odgodom operacije. Mjeren je radiološki odgovor prije operacije pomoću RECIST 1.1 kriterija. Nuspojave gradusa 3–4 su se registrirane u pet (19,2%) HPV pozitivnih bolesnika i tri HPV negativna bolesnika (11,5%). 38 bolesnika podvrgnuto je kirurškoj resekciji, 10 ih je imalo post-nivolumab biopsiju umjesto operacije, a 4 nisu pristupili operaciji ili biopsiji, uključujući 2 s progresijom tumora. Stope radiološkog odgovora u 49 ispitanih bolesnika bile su 12,0% u HPV pozitivnih i 8,3% u HPV negativnih tumora. Od 17 centralno procijenjenih HPV-pozitivnih tumora, kod jednog (5,9%) je postiglnut je kompletan patološki odgovor, a u tri (17,6%) djelomični patološki odgovor. Neoadjuvantni nivolumab je općenito bio siguran i doveo do patološke regresije kod HPV-pozitivnih (23,5%) i HPV-negativnih (5,9%) tumora.

Većina kliničkih ispitivanja imunoterapije uključuje vrlo heterogenu populaciju bolesnika s tumorima glave i vrata. Temeljem virusne etiologije mogu se uključiti samo karcinomi orofarinksa i epifarinksa. Budući se radi o ograničenom broju bolesnika, direkne usporedbe rezultata liječenja s imunoterapijom karcinoma virusne i nevirusne etiologije nisu sasvim pouzdane. S obzirom na imunosupresiju u malignim bolestima povezanu s virusom, liječenje usmjereno na imunološki sustav razumna je opcija za klinički uspjeh, ali može biti izazovno. Glavnina kliničkih studija s imunoterapijom u tumorima glave i vrata virusne etiologije provodena je na metastatskoj bolesti, a rezultati su ohrabrujući. Postoje podskupine bolesnika koji jako dobro reagiraju, dok drugi nemaju nikakav odgovor. Nedostatak odgovora vjerojatno je multifaktorijalan, vrlo moguće i zbog izbjegavanja imunološkog odgovora tumora s virusnim genomom.

Primjena imunoterapije znatno je promjenila liječenje R/M karcinoma glave i vrata. Unatoč tome, imunoterapija za liječenje R/M tumora glave i vrata još uvijek nije na listi HZZO-a. Na žalost, rezultati do sada provedenih i objavljenih studija nisu dale pozitivne rezultate kombinacije dva različita inhibitora kontrolnih točaka u R/M tumorima, kombinacije PD-1 inhibitora i SBRT-a u metastatskoj bolesti kao i primjene imunoterapije u lokalno uznapredovalim karcinomima glave i vrata.

# IMMUNOTHERAPY IN THE TREATMENT OF HEAD AND NECK CANCERS

RAKUŠIĆ Z.[1]

[1] University Hospital Centre Zagreb

• *Department of Oncology*

zrakusic@kbc-zagreb.hr

According to TCGA (The Cancer Genome Atlas), head and neck cancers are the most immunologically active tumor tissue after lung adenocarcinoma and renal cell carcinoma. The occurrence and progression of head and neck tumors have been associated with severe immune deficiency including immune cell dysfunction, decreased cytokine secretion, and disturbance in antigen presentation.

The first results of the use of checkpoint inhibitors in the treatment of recurrent and metastatic (R/M) tumors of the head and neck are related to the "basket" study KEYNOTE-012 and the use of PD-1 inhibitor pembrolizumab. The response rate was 18%. This study influenced the further investigation and study of pembrolizumab in the treatment of head and neck tumors.

CheckMate-141 was the first phase III clinical trial with the PD-1 inhibitor nivolumab in head and neck cancers. The efficacy of nivolumab and standard chemotherapy in R/M head and neck tumors was compared. The results showed that nivolumab was significantly better than traditional chemotherapy with a longer median survival of 2.4 months (7.5 months vs. 5.1 months), a 20% higher one-year survival (36% vs. 16%), with a significantly reduced risk of severe side effects.

A randomized phase III study of KEYNOTE-048, conducted on 882 patients, had three arms and compared the efficacy of monotherapy with pembrolizumab, a combination of pembrolizumab, platinum compounds, and 5-fluorouracil with hitherto standard therapy for R / M head and neck tumors, EXTREME protocol (platinum compounds + 5-fluorouracil + cetuximab). Patients with R/M tumors of the oropharynx, oral cavity, larynx, and hypopharynx, incurable for treatment with local therapy, were included. Randomization was performed in a 1: 1: 1 ratio, and stratification according to PD-L1 expression, p16 expression, and ECOG status. The results show that in patients with PD-L1 CPS expression (combined positive score) ≥20, the median survival was significantly better in the pembrolizumab monotherapy group compared to the EXTREME protocol, 14.9: 10.7 months (HR 0.61; p = 0.0007), while ORR (overall response rate) and PFS were not statistically significant. Furthermore, pembrolizumab + chemotherapy with platinum salts and 5-fluorouracil has a better survival median in the overall population, regardless of CPS expression, than the combination according to the EXTREME protocol, 13.0: 10.7 months (HR 0.77; p = 0.0034). Based on these results, pembrolizumab monotherapy is the treatment of choice in the relevant clinical guidelines for first-line treatment of R/M head and neck tumors in patients with high PD-L1 expression, and the combination of pembrolizumab and chemotherapy with platinum compounds for the same indication regardless of PD-L1 expression.

Based on the positive results of the use of PD-1 inhibitors in R/M tumors of the head and neck in phase III studies Checkmate-141 and KEYNOTE-048, numerous studies followed, most of which are ongoing, the use of combinations of PD-1, PD-L1 and CTLA-4 inhibitors, combinations of checkpoint inhibitors with SBRT (stereotactic body radiation therapy), applications of immunotherapy in locally advanced disease.

A randomized phase III EAGLE study was conducted on 736 patients with R/M head and neck cancers. It had three arms of therapy, monotherapy with PD-L1 inhibitor durvalumab, a combination of durvalumab and CTLA-4 inhibitors tremelimumab and standard therapy (cetuximab, taxanes, methotrexate, fluoropyrimidines). Randomization was performed in a 1:1:1 ratio. The primary goal of the study was overall survival (OS). No statistically significant OS improvements were observed for durvalumab compared to standard therapy (HR 0.88) or durvalumab plus tremelimumab compared to standard therapy (HR 1.04). The 12-month survival rates were 37.0% for durvalumab, 30.4% for durvalumab plus tremelimumab, and 30.5% for standard therapy. The combination of durvalumab and tremelimumab did not show greater efficacy. However, slightly higher survival rates of 12 to 24 months and response rates indicate clinical activity of durvalumab.

To date, the only randomized phase II study in 62 patients with metastatic head and neck cancers found no difference in efficacy in nivolumab and SBRT-treated patients compared to nivolumab-alone. Based on the results of the study, the authors concluded that the addition of nivolumab to SBTR did not affect the safety profile, but did not improve ORR, PFS, and OS. No abscopal effect was observed in patients treated with nivolumab and SBRT.

There were high expectations from a phase III study, JAVELIN H&N 100, conducted on 907 patients with locally advanced tumors of the oropharynx, oral cavity, larynx, and hypopharynx. The standard therapy for this

disease, concomitant chemotherapy (three-week cisplatin 100 mg / m² + IMRT 70Gy / 7 weeks) and placebo were compared with the same concomitant chemoradiotherapy and PD-L1 inhibitor avelumab 10 mg/kg one week before the start of chemoradiotherapy, during the chemoradiotherapy and as maintenance therapy at biweekly intervals of up to 12 months. The mean follow-up for progression-free survival was 14.6 months in the avelumab group and 14.8 months in the placebo group. Mean progression-free survival was not achieved (95% CI 16.9 months — not assessed) in the avelumab group and not achieved (23.0 months — not assessed) in the placebo group (HR 1.21; p). = 0.92). Serious treatment-related adverse reactions were reported in 124 (36%) patients in the avelumab group and in 109 (32%) patients in the placebo group. The primary goal of prolonging progression-free survival with avelumab with chemoradiotherapy, followed by maintenance of avelumab in patients with locally advanced head and neck squamous cell carcinoma, has not been met.

There are already reports of neoadjuvant use of immunotherapy in head and neck tumors. In a Phase I/II CheckMate 358 study in 52 patients with virus-related head and neck cancer, neoadjuvant nivolumab was evaluated in previously untreated, resectable HPV-positive or HPV-negative tumors. Nivolumab was administered at a dose of 240 mg iv on days 1 and 15, with surgery scheduled for day 29. Safety/tolerability (primary study outcome) was assessed by monitoring side effects (AE) and delaying surgery. The radiological response before surgery was measured using RECIST 1.1 criteria. Grade 3–4 side effects were registered in five (19.2%) HPV-positive patients and three HPV-negative patients (11.5%). 38 patients underwent surgical resection, 10 had post-nivolumab biopsy instead of surgery, and 4 did not undergo surgery or biopsy, including 2 with tumor progression. Radiological response rates in the 49 patients examined were 12.0% in HPV positive and 8.3% in HPV negative tumors. Of the 17 centrally assessed HPV-positive tumors, one (5.9%) achieved a complete pathological response, and three (17.6%) a partial pathological response. Neoadjuvant nivolumab was generally safe and led to pathological regression in HPV-positive (23.5%) and HPV-negative (5.9%) tumors.

Most clinical trials of immunotherapy involve a very heterogeneous population of patients with head and neck tumors. Based on the viral etiology, only oropharyngeal and epipharyngeal cancers can be included. Because of the limited number of patients, direct comparisons of treatment outcomes with cancer immunotherapy of viral and nonviral etiology are not entirely reliable. Given the immunosuppression in virus-related malignancies, treatment targeting the immune system is a reasonable option for clinical success but can be challenging. The majority of clinical studies with immunotherapy in head and neck tumors of viral etiology have been conducted on metastatic disease, and the results are encouraging. There are subgroups of patients who respond very well, while others have no response. The lack of response is probably multifactorial, very possibly also due to the evasion of the immune response of the tumors with the viral genome.

The application of immunotherapy has significantly changed the treatment of R/M head and neck cancer. Nevertheless, immunotherapy for the treatment of R/M head and neck tumors is still not on the HZZO list. Unfortunately, the results of studies conducted and published so far have not yielded positive results of the combination of two different checkpoint inhibitors in R/M tumors, the combination of PD-1 inhibitors and SBRT in metastatic disease as well as the application of immunotherapy in locally advanced head and neck cancers.

## LITERATURA


1. *Trivedi S, Sun L, Aggarwal C.* Immunotherapy for Head and Neck Cancer. Hematol Oncol Clin North Am. 2021 Oct;35(5): 1021–1037. doi: 10.1016/j.hoc.2021.05.010. Epub 2021 Jul 7. PMID: 34244017 Review.
2. *Mandal R, Şenbabaoğlu Y, Desrichard A, Havel JJ, Dalin MG, Riaz N, Lee KW, Ganly I, Hakimi AA, Chan TA, Morris LG.* The head and neck cancer immune landscape and its immunotherapeutic implications. JCI Insight. 2016 Oct 20;1(17):e89829. doi: 10.1172/jci.insight.89829. PMID: 27777979
3. *Ferris RL, Blumenschein G Jr, Fayette J et al.* Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. Oral Oncol. 2018 Jun;81:45–51. doi:10.1016/j.oraloncology. 2018.04.008. Epub 2018 Apr 17.PMID: 29884413 Free PMC article. Clinical Trial.
4. *Burtness B, Harrington KJ, Greil R,et al.; KEYNOTE-048 Investigators.* Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019 Nov 23;394(10212):1915–1928. doi: 10.1016/S0140-6736(19)32591-7. Epub 2019 Nov 1.
5. *Ferris RL, Haddad R, Even C et al.*. Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III study. Ann Oncol. 2020 Jul;31(7):942–950. doi: 10.1016/j.annonc.2020.04.001. Epub 2020 Apr 12. PMID: 32294530 Clinical Trial.
6. *McBride S, Sherman E, Tsai CJ et al.* Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2021 Jan 1;39(1):30–37. doi: 10.1200/JCO.20.00290. Epub 2020 Aug 21. PMID: 32822275 Clinical Trial.

7. *Lee NY, Ferris RL, Psyrri A et al.* Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol. 2021 Apr;22(4):450–462. doi: 10.1016/S1470-2045(20)30737-3. PMID: 33794205 Clinical Trial.
8. *Ferris RL, Spanos WC, Leidner R et al.* Neoadjuvant nivolumab for patients with resectable HPV-positive and HPV-negative squamous cell carcinomas of the head and neck in the CheckMate 358 trial. J Immunother Cancer. 2021 Jun;9(6):e002568. doi: 10.1136/jitc-2021-002568. PMID: 34083421
9. *Pharaon RR, Xing Y, Agulnik M, Villaflor VM.* The Role of Immunotherapy to Overcome Resistance in Viral-Associated Head and Neck Cancer. Front Oncol. 2021 Jul 16;11:649963. doi: 10.3389/fonc.2021.649963. eCollection 2021. PMID: 34336649 Free PMC article. Review.
10. *Wang H, Zhao Q, Zhang Y et al.* Immunotherapy Advances in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma and Its Relationship With Human Papillomavirus. Front Immunol. 2021 Jul 8;12:652054. doi: 10.3389/fimmu.2021.652054. eCollection 2021. PMID: 34305889
11. *Farlow JL, Brenner JC, Lei YL, Chinn SB.* Immune deserts in head and neck squamous cell carcinoma: A review of challenges and opportunities for modulating the tumor immune microenvironment. Oral Oncol. 2021 Sep;120:105420. doi: 10.1016/j.oraloncology.2021.105420. Epub 2021 Jul 1. PMID: 34218062 Review.
12. *Buchwald ZS, Schmitt NC.* Immunotherapeutic Strategies for Head and Neck Cancer. Otolaryngol Clin North Am. 2021 Aug; 54(4):729–742. doi: 10.1016/j.otc.2021.04.004. Epub 2021 Jun 9. PMID: 34116846 Review

## SVEOBUHVATNO GENSKO PROFILIRANJE KOD TUMORA GLAVE I VRATA

VAZDAR LJ.[1]

[1]Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*

ljubica.vazdar@gmail.com

Standardno sustavno liječenje raka glave i vrata je ograničeno na primjenu kemoterapije, anti-EGFR i imunoterapije. Odluke o terapijskom pristupu temeljenje su na lokalizaciji tumora, histološkom tipu i stadiju bolesti, a ne na biologiji bolesti čime molekularna složenost i intratumorska heterogenost nisu aktivno integrirani u odluke o liječenju.

Moguće pomake u liječenju pruža nam genomska era s ogromnom količinom informacija molekularne raznolikosti tumora, postavlja nove terapijske ciljeve, a primjena personalizirane medicine obećava poboljšanje kontrole bolesti i duže preživljenje.

Sekvencioniranje gena (*Next-Generation Sequencing*,NGS) je moćan alat za proučavanje genoma i razumijevanje molekularnih procesa u tumorogenezi, a omogućava sekvencioniranje cijelog ili ciljanog područja genoma.

Poznati biobiljezi koji trenutno imaju važnost u ciljanoj terapiji raka glave i vrata obuhvaćaju PD-L1 ekspresiju (eng. *programmed cell death*-1), MSI-H (eng. microsatellite instability-high), TMB-H (eng. tumor mutational burden), pozitivnost na androgen receptor (AR+), NTRK fuziju gena i HER2 pretjeranu ekspresiju. Osim ovih biobiljega poznato je više mutacija gena odgovornih za malignu transformaciju i napredovanje bolesti u raku glave i vrata. Najčešće je prisutna mutacija TP53 (35–80%), češće u HPV negativnih tumora, NORCH1 mutacija (do 30%), najčešće u Azijske populacije te PIK3CA (do 25%), češće kod HPV pozitivnog raka. Prijelaz od otkrića ovih mutacija do kliničke prakse je spor.

Važan biobiljeg u kliničkoj onkologiji je NTRK fuzija gena (NTKR, neurotrofična tropomiozin receptorska tirozin kinaza) koji promovira proliferaciju različitih tumora, a poglavito mamarnog analognog sekretornog karcinoma (MASC, *Mammary analogue secretory carcinoma*) tumora žlijezda slinovnica gdje je ovaj biobiljeg prisutan u preko 90% slučajeva te u raku štitnjače s pozitivnom fuzijom NTRK gena do 25%. U ostalim tumorima glave i vrata NRK fuzija zastupljena je ispod 5%.

Na temelju rezultata istraživanja ALKA, STARTRK-1 i STARTRK-2 odobreni su od regulatornih tijela FDA (*Food and Drug Administration*) i EMA (*European Medicines Agency*) NTRK inhibitori larotrektinib i entrektinib. Larotrektinib kao selektivni NTRK inhibitor postiže ukupnu stopu odgovora do 79% te djeluje i na moždane metastaze sa stopom odgovora (RR 71%). Entrektinib, pan NTRK inhibitor, ROS1 i ALK inhibitor postiže stopu odgovora do 57%, a centralna aktivnost mu je manja u odnosu na larotrektinib (RR 54%).

Najčešće nuspojave inhibicije NTRK su umor, neuropatija, kognitivni poremećaji, hiperfagija, parestezija, ataksija, poremećaj osjeta boli. Nuspojave su najčešće blagog stupnja, kod larotrektiniba dominira umor (33%), a entrektiniba promjena osjeta okusa (47%).

Temeljni cilj genskog profiliranja je stratifikacija bolesti, personalizacija strategija liječenja i otkrivanje potencijalnih lijekova. Odluke temeljene na genotipu i fenotipu bolesnika pružaju mogućnost učinkovitijeg, preciznijeg liječenja.

## COMPREHENSIVE GENE PROFILING OF HEAD AND NECK TUMORS

VAZDAR LJ.[1]

[1] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*
ljubica.vazdar@gmail.com

Standard systemic treatment for head and neck cancer is limited to the use of chemotherapy, anti-EGFR therapy and immunotherapy. Decisions on the therapeutic approach are mostly based on tumor localization, histological type and stage of the disease and not on the disease biology.

Possible breakthroughs in treatment are provided by the genomic era with a huge amount of information about the molecular diversity of tumors. It sets new therapeutic goals and the application of new personalized medicine shows improvement in disease control and longer survival of patients. Next-Generation Sequencing (NGS) is a powerful tool for studying genomes and understanding molecular processes in tumorogenesis, it allows sequencing of the entire genome or target area. Known biomarkers, currently relevant in targeted therapy of head and neck cancer, include PD-L1 expression (programmed cell death-1), MSI-H (microsatellite instability-high), TMB-H (mutational burden tumor), androgen receptor positivity (AR+), NTRK gene fusion and HER2 overexpression. In addition to these biomarker there are more known gene mutations responsible for the malignant transformation and progression of the disease in head and neck cancer. Most frequently found is a mutation of TP53 (35–80%), usually in HPV negative tumors, NORCH1 mutations (up to 30%), most often found in Asian populations and PIK3CA (up to 25%), more common in HPV positive cancer. The transition from the discovery of these mutations to clinical practice is slow.

An important biomarker in clinical oncology is NTRK gene fusion (NTKR, neurotrophic tropomyosine receptor tyrosine kinase) that promotes the proliferation of various tumors and especially mammary analogue secretory carcinoma (MASC) of salivary gland where it is present in over 90% of cases and in thyroid cancer with positive fusion in up to 25% of patients. In other head and neck tumors NTRK fusion is found in less than 5% of cases.

Based on the results of the ALKA, STARTRK-1 and STARTRK-2 studies, regulatory authorities of the FDA (Food and Drug Administration) and EMA (European Medicines Agency) approved NTRK inhibitors larotrektinib and entrektinib. Larotrektinib as a selective NTRK inhibitor achieves an overall response rate of up to 79% and also acts on brain metastases with response rate of 71%. Entrektinib, pan NTRK inhibitor, ROS1 and ALK inhibitor achieves a response rate of up to 57%, and its central activity is lower than with larotrectinib (54%). The most common side effects of NTRK inhibitors are fatigue (found in 33% of patients on larotrektinib), neuropathy, cognitive disorders (change in taste sensation is found in 47% of patients on entrektinib), hyperphagy, paresthesia, ataxia and pain sensation disorders. Side effects are most often mild in degree.

The main goal of gene profiling is disease stratification, personalization of treatment strategies and discovery of new potential drugs. Decisions based on the genotype and phenotype of patients provide the possibility for more effective precise treatment.

### LITERATURA

1. *Rebecca C Hoesli, Megan L.* Genomic Sequencing and Precision Medicine in Head and Neck Cancers.Eur J Surg Oncol. 2017 May; 43(5): 884–892. doi:10.1016/j.ejso.2016.12.002.
2. *Giefing M, Wierzbicka M.* Moving towards Personalized Therapy in Head and Neck Squamous Cell Carcinoma through Analysis of Next Generation Sequencing Data.Eur J Cancer. 2016 March ; 55: 147–157. doi:10.1016/j.ejca.2015.10.070.
3. *Malone E, Siu LL.*Precision Medicine in Head and Neck Cancer: Myth or Reality? https://doi.org/10.1177/1179554918779581
4. *Farah CS.* Next-Generation Sequencing Applications in Head and Neck Oncology.Next Generation Sequencing in Cancer Research, Volume 2 pp 401–422

## PRIKAZ SLUČAJA IZ STVARNOG ŽIVOTA – SUSTAVNO LIJEČENJE METASTATSKOG HPV P16 POZITIVNOG KARCINOMA OROFARINKSA

KOTROMANOVIĆ D.[1], Ladenhauser T.[1]

[1] Klinički bolnički centar Osijek
• *Zavod za onkologiju*
kotromanovic93@gmail.com

**Uvod**: Karcinom pločastih stanica glave i vrata (HNSCC) jedan je od češćih karcinoma. Incidencija u Europi je 140000, a mortalitet 65000. Najčešći je karcinom grkljana, nepčane tonzile, jezika i dna usne šupljine. Alkohol, pušenje i HPV najčešći su etiološki čimbenici. Oko 30–35% svih orofaringealnih karcinoma su HPV pozitivni. Pacijenti s HPV + rakom imaju povoljnije prognoze: 2-godišnje preživljenje 95 % nasuprot HPV– 62 %; medijan vremena do pojave metastaza je veći. 11 % ih razvije udaljene metastaze, a one su češće na atipičnim mjestima – mozak, bubreg, muskulatura. 1.29 puta je vjerojatniji odgovor na imunoterapiju od HPV negativnih.

**Prikaz slučaja**: Muškarac, 52 godine, urednih navika i bez komorbiditeta, dolazi na ORL zbog grlobolje i disfagije. Obradom se nađe karcinom pločastih stanica orofarinksa, HPVp16+, T3N1M0, stadija II. MDT indicira kemoiradijaciju kao primarno liječenje, 3 ciklusa konkomitantnog cisplatina 100 mg/m² svaka 3 tjedna uz EBRT do 70Gy/33x. Nakon inicijalnog liječenja lokoregionalni nalaz bio je u potpunoj regresiji kroz 6 mjeseci, a potom se radiološkom obradom nađu presadnice pluća i medijastinuma. Liječen je cisplatinom, 5-FU-om i cetuksimabom kroz 6 ciklusa, ali tada dolazi do daljnje progresije bolesti u plućima, medijastinumu, kostima i mozgu. Bolesnik je uključen u kliničku studiju faze II s pembrolizumabom i nanocisplatinom u 2.liniji. Testiran je PD-L1: TPS 5 %, CPS 25 %, a pacijent randomiziran na pembrolizumab 200mg svaka 3 tjedna. Nakon 2 ciklusa se na CT nađe daljnja progresija bolesti u jetru uz kliničko pogoršanje te je isključen iz studije. Provedena je palijacijska radioterapija. Planirano liječenje docetakselom nije započeto jer je pacijent preminuo od plućne embolije.

**Zaključak**: Pacijent iz prikaza imao je trajanje odgovora na primarno liječenje 6 mjeseci, na prvu liniju za metastatsku bolest 6 mjeseci i na drugu 2 mjeseca – opserviran je atipični, agresivniji tijek bolesti s bržim nastupom metastaza i s kratkim odgovorima na iduće linije liječenja. Temeljem studije KEYNOTE-048, u EU standard prve linije za mHNSCC s CPS ≥1 postaje pembrolizumab. Naš ga je pacijent ulaskom u studiju primio u drugoj liniji, čime smo, unatoč nedostupnosti lijeka, stekli određena iskustva u ovoj indikaciji, a pacijent dodatnu priliku za terapijski odgovor.

## CASE REPORT – A SYSTEMATIC TREATMENT OF A METASTATIC HPV P16 POSITIVE OROPHARYNGEAL CANCER

KOTROMANOVIĆ D.[1], Ladenhauser T.[1]

[1] University Hospital Centre Osijek
• *Department of Oncology*
kotromanovic93@gmail.com

**Introduction**: Head and neck squamous cell carcinoma (HNSCC) is one of the common carcinoma. The incidence rate in Europe is 140000 and mortality rate 65000. The most common is the larynx, palatine tonsil, tongue, and the mouth floor carcinoma. Alcohol, smoking and HPV are the most frequent etiologic factors. Around 30 – 35% of all oropharyngeal carcinoma are HPV positive. Patients with HPV+ cancer have a better prognosis: a two year survival rate of 95% in comparison to 62% in HPV- patients; median time to metastases occurrence is longer; 11% develops distant metastases and they are, most frequently, at some non-typical places such as brain, kidney, musculature. They respond to immunotherapy 1.29 times stronger than HPV- patients.

**Case study**: Man, 52 years old, a person with healthy routines and no prior comorbidities, comes to the Clinic for Otorhinolaringology due to sore throat and dysphagia. After further medical examination an oropharyngeal squamous cell carcinoma was found, HPVp16 +,T3N1M0,stage II. MDT indicates chemoradiation as a primary treatment, 3 cycles of concomitant cisplatin (100 mg/m² every 3 weeks) with EBRT(70Gy/33x). After the initial treatment a locoregional test result showed a complete regression during 6 months. However, radiological screening found metastases in the lungs and mediastinum. The patient was treated with cisplatin, 5- FU as well as cetuximab throughout 6 cycles, but then it came to the disease progression in the lungs, mediastinum, bones and brain. The patient was included in a clinical study of the phase II with pembrolizumab and nanocisplatin in second line.

PD-L1 was tested: TPS 5%, CPS 25% and the patient was randomly assigned to 200 mg of pembrolizumab every 3 weeks. After 2 cycles, a CT scan showed a further disease progression on the liver, and the patient was excluded from the study, due to a deterioration of his general condition. A palliative radiotherapy was implemented. The treatment with docetaxel was not started because the patient died of pulmonary embolism.

**Conclusion**: The patient from the case study had a response to primary treatment in duration of 6 months; to the first line for a metastatic disease 6 months and to the second line 2 months – a non-typical, aggressive course of disease with the quicker occurrence of metastases and short responses to the following lines of treatments has been observed. Based on the study KEYNOTE-048, in the EU a standard in the first line for mHNSCC with CPS ≥1 has become pembrolizumab. Our patient got it in the second line when entering the clinical study. Despite the drug's unavailability, we have obtained some experience in this indication and our patient got an additional opportunity for a therapeutic response.

## SMJERNICE ZA DIJAGNOSTIKU I PRAĆENJE KARCINOMA GLAVE I VRATA

LINARIĆ P.[1], Vazdar Lj.[1], Tečić Vuger A.[1], Pavlović Mavić M.[1], Lepetić P.[1], Šeparović R.[1,2]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
[2] Sveučilište Jurja Dobrile u Puli
• *Medicinski fakultet u Puli*
petralinaric22@gmail.com

Planocelularni karcinom glave i vrata razvija se iz epitelnih stanica tkiva usne šupljine, farinksa i larinksa. Smatra se da je godišnja incidencija ovih tumora preko 700 000 slučajeva, uz stopu smrtnosti procijenjenu na oko 350 000 u 2018. godini, što ga čini sedmim najčešćim karcinomom diljem svijeta.

Simptomi poput kronične grlobolje, perzistirajuće promuklosti, dugotrajne neugodnosti jezika uz prisutnost ulkusa usne šupljine, prisutstvo kroničnih promjena na sluznici usne šupljine po tipu leukoplakije/eritroplakije, poteškoće gutanja ili palpabilne mase na vratu, zahtijevaju promptnu procjenu kliničara radi otkrivanja uzroka. Klinička evaluacija uključuje uzimanje detaljne anamneze navedenih simptoma, klinički pregled koji uključuje fiberendoskopiju, palpaciju vrata, stomatološki pregled, procjenu funkcije govora i gutanja, uz obaveznu procjenu performans statusa (ECOG), nutritivnog rizika te eventualnu psihosocijalnu evaluaciju. Potrebno je učiniti kompletnu laboratorijsku obradu koja uključuje krvnu sliku, biokemijske i koagulacijske pretrage te TSH. Radi dobivanja konačne patohistološke dijagnoze potrebno je učiniti transoralnu ili endoskopsku biopsiju tumorskog tkiva. Radi procjene lokoregionalne zahvaćenosti nužna je dijagnostika primarnog tumora te limfnih čvorova vrata MR-om (magnetskom rezonancijom) ili CT-om (kompjuteriziranom tomografijom). Kompjuterizirana tomografija smatra se superiornom za evaluaciju tumora larinksa, radi određivanja odnosa tumora prema kostima glave i vrata. Za prikaz mekih česti, usne šupljine, orofarinksa i svih malih tumora sluznice, MR je metoda izbora. UZV vrata, kao komplementarna metoda za određivanje suspektnih limfnih čvorova također se primjenjuje, a suspektne limfne čvorove potrebno je punktirati i citološki verificirati. Također, potrebna je radiološka procjena prsnog koša radi isključenja udaljene diseminacije osnovne bolesti kao i detekcije drugog primarnog tumora pluća kod bolesnika s anamnezom dugogodišnjeg pušenja. Kod bolesnika s dokazanim orofaringealnim karcinomom preporučena je HPV evaluacija imunohistokemijskim određivanjem surogatnog markera p16, te u slučaju pozitivnog nalaza, dodatna dijagnostika radi određivanja HPV statusa (PCR, in situ hibridizacija – ISH). HPV status kod ovog tipa tumora, za razliku od laringealnog, hipofaringealnog, i karcinoma usne šupljine, ima prognostičku vrijednost. Radi definiranja konačnog terapijskog pristupa, patohistološka evaluacija mora uključivati veličinu tumora, dubinu invazije kod karcinoma usne šupljine, ukupan broj odstranjenih limfnih čvorova kao i broj i točnu lokalizaciju zahvaćenih limfnih čvorova. Obavezna je procjena kirurških margina, proboja kapsule limfnog čvora te perineuralne i limfovaskularne invazije tumorskih stanica. Preporučljivo je određivanje PD-L1 statusa tumora, posebice kod rekurentne/metastatske bolesti.

Po provedenom liječenju, potrebno je blisko praćenje bolesnika radi ranog otkrivanja povrata bolesti, kao i praćenja dugoročnih nuspojava i toksičnosti primijenjene terapije. U tijeku prve godine praćenja potreban je kompletan klinički pregled koji uključuje fiberendoskopsku evaluaciju svakih 1–3 mjeseci, u tijeku druge godine svakih 2–6 mjeseci, od treće do pete godine praćenja svakih 4–8 mjeseci, te svakih 12 mjeseci nakon pete godine. Kod lokalno proširene bolesti, potrebna je radiološka procjena (MR ili CT) glave i vrata inicijalno 3 mjeseca po

provedenom liječenju, potom svaka 3–4 mjeseca, ili ranije u slučaju kliničkih simptoma ili abnormalnosti detektiranih kliničkim pregledom. Kod bolesnika sa zahvaćenošću limfnih čvorova vrata preporučen je PET/CT, alternativno MSCT toraksa, abdomena i zdjelice radi uvida u stanje bolesti, 3 mjeseca po završetku kemoradioterapijskog liječenja. Po provedenom radioterapijskom liječenju, potrebna je redovita stomatološka evaluacija, te praćenje vrijednosti TSH u prvoj, drugoj i petoj godini praćenja. U oporavku ovih bolesnika, velika je važnost multidisciplinarnog pristupa, te osim upućivanja specijalističkim službama za rehabilitaciju govora i gutanja te praćenja nutritivnog rizika, potrebna je i psihološka potpora, te pomoć i savjetovanje u smislu apstinencije od duhana i alkohola.

## HEAD AND NECK CANCER: DIAGNOSIS AND FOLLOW-UP RECOMMENDATIONS

LINARIĆ P.[1], Vazdar Lj.[1], Tečić Vuger A.[1], Pavlović Mavić M.[1], Lepetić P.[1], Šeparović R.[1,2]

[1] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*
[2] Juraj Dobrila University of Pula
• *School of Medicine*
petralinaric22@gmail.com

Squamous cell carcinoma of the head and neck (SCCHN) arises from epithelial cells and occurs in the oral cavity, pharynx and larynx. SCCCHN has annual incidence of approximately 700 000 cases and a mortality rate estimated at 350 000 in 2018. It is estimated that SCCHN is the seventh most common cancer in the world.

Symptoms like persistent hoarseness, chronic sore tongue or non-healing ulcers present in oral cavity, as well as red/white patches in the mouth, chronic pain in the throat, painful or difficult swallowing and neck masses, should require prompt clinical evaluation. It should include a detailed history of the symptoms, complete physical examination including neck palpation and fibreoptic endoscopy, as well as evaluation of patients performance status (ECOG), nutritional risk status, dental examination, speech and swallowing function and sometimes, psychosocial evaluation. Full panel blood test, with biochemical profile (serum creatinine, liver panel), coagulation tests, as well as thyroid-stimulating hormone (TSH) should be routinely done. Either transorally or using an endoscopic route, biopsy should be carried out for pathological confirmation. Computed tomography (CT) scan and/or magnetic resonance imaging (MRI) is used for locally advanced disease assessment (primary tumor, as well as regional lymph nodes). It is considered that computed tomography is superior in laryngeal cancer for assessing involvement of adjacent structures, in contrast to MRI which is better for evaluation of oral cavity, oropharynx, and small mucosal tumors. Ultrasound is complementary method of lymph nodes imaging, and cytological analysis should be done in case of suspicious findings. Chest imaging is recommended to assess the presence of distant metastases or a second lung primary in heavy smokers. On all patients with newly diagnosed oropharyngeal SCC, HPV evaluation using p16 immunohistochemistry (IHC) should be carried (p16 IHC is a reliable surrogate marker for HPV positivity in the oropharynx, but in case of positive result, other test should be performed for confirmation, such as PCR or ISH – in situ hybridization). The prognostic value of p16 has only been observed in oropharyngeal SCC, not in laryngeal, hypopharyngeal or oral cavity tumours. Pathological assessment is important to determine the postoperative adjuvant treatment, and should include the size of tumor, as well as depth of invasion (especially in oral cavity cancer), and lymph nodes evaluation (total number of lymph nodes removed, number and location of invaded lymph nodes). Presence of extracapsular nodal extension, perineural and lymphatic infiltration, and surgical margins are also important features and should be examined. Tumor programmed death-ligand 1 (PD-L1) expression should be evaluated, especially in recurrent or metastatic SCCHN.

Close patients follow-up is necessary for early locoregional recurrence as well as new primary tumors detection. There are many potential treatment toxicities and side effects that should be closely evaluated. In year one after treatment completion, clinical examination, flexible endoscopy including, should be done every 1–3 months, then every 2–6 months in the second year of follow up, every 4–8 months in years 3–5, then annually after 5 years of the follow-up. For locally advanced disease, head and neck imaging is recommended 3 months after the primary treatment, then every 3–4 months, or more frequently in case of symptoms occurrence or abnormal clinical findings. In node-positive disease, FDG-PET/CT, alternatively full body CT scan, is recommended 3 months after chemoradiotherapy (CRT). After radiation therapy, frequent dental evaluation is required, as well as TSH monitoring in first, second and fifth year of the follow-up. In this specific population, multidisciplinary approach is key for full patient

recovery. Speech/swallowing specialists should be included, as well as psychological specialists and dietitians, and tobacco and alcohol withdrawal counselling should be recommended.

**LITERATURA**

1. *Machiels J-P, Leemans CR, Golusinski W, Grau CL.* Licitr on behalf of the EHNS Executive Board, ESMO Guidelines Committee, ESTRO Head Office. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up.Published in 2020 – Ann Oncol (2020)
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Head and Neck Cancers, version 3.2021. – April 27,2021
3. *Silovski T, Pleština S, Belev B, Dobrila Dintinjana R, Kurbel S, Županc D, Vrdoljak DV, Škegro M, Vidović M, Šeparović R, Vrbanec D.* Praćenje onkoloških bolesnika – kliničke preporuke Hrvatskog društva za internističku onkologiju HLZ-a IV. dio: planocelularni rak glave i vrata, rak jednjaka, rak želuca, rak debelog i završnog crijeva.

# SEKCIJA RAK PLUĆA / LUNG CANCER SESSION

## PRIKAZ SLUČAJA – CILJANA TERAPIJA KOD ROS1 I PD-L1 POZITIVNOG TUMORA

Trivanović D.[1], VRBANEC J.[1]

[1] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
dtrivanovic@obpula.hr

U ovom prikazu slučaja opisujemo liječenje pacijentice s proširenim adenokarcinomom pluća s pozitivnim PD-L1 i ROS 1 biomarkerima. Pacijentica se inicijalno prezentirala sa suhim kašljem u trajanju od 4 mjeseca te se učinila slikovna obrada koja je pokazala proširenu neoplazmu pluća sa sekundarnom lezijom jetre. Radi se o pacijentici mlađe životne dobi bez komorbiditeta s anamnezom pozitivnom na pušenje. Imunocitokemijska analiza nakon učinjene bronhoskopije pokazala je adenokarcinom pluća uz ALK negativne, PD-L1 pozitivne (50–80%) i ROS1 pozitivne maligne stanice. Također se učinio CT mozga koji nije pokazao patološki nalaz i scintigrafija kostiju koja je pokazala vjerojatni sekundarizam u 8. Rebru uz moguću infiltraciju bolesti u 9. i 10. rebro. Razmatrala se mogućnost liječenja biološkom i imunoterapijom te se u skladu sa smjernicama, a s obzirom na ROS1 pozitivan nalaz uz preporuku iz klinike započinje se liječenje crizotinibom. Liječenje se provodi kroz šest mjeseci, uz inicijalno dobar parcijalni odgovor na terapiju, do progresije bolesti potvrđene PET-CTom. U nastavku se indicira liječenje loratinibom uz preporuku od strane kliničke bolnice. Liječenje loratinibom se do pisanja ovog prikaza slučaja provodi kroz tri mjeseca uz dobar klinički odgovor. Kroz ovaj prikaz slučaja prezentiramo plan liječenja pacijenta s više pozitivnih biomarkera koji mogu biti predmet ciljane onkološke terapije.

## CASE REPORT – TARGETED THERAPY IN A ROS1 AND PD-L1 POSITIVE TUMOR

Trivanović D.[1], VRBANEC J.[1]

[1] General Hospital Pula
• *Department of Medical Oncology and Hemathology*
dtrivanovic@obpula.hr

In this case report, we describe the treatment of a patient with advanced lung adenocarcinoma with positive PD-L1 and ROS 1 biomarkers. The patient initially presented with a dry cough of 4 months. Diagnostic imaging was performed which showed an advanced lung neoplasm with a secondary liver lesion. The patient is of younger age and without comorbidities, with a history of smoking. Immunocytochemical analysis after bronchoscopy revealed lung adenocarcinoma with ALK negative, PD-L1 positive (50–80%) and ROS1 positive malignant cells. A CT scan of the brain did not show a pathological finding and bone scintigraphy showed probable metastasis in the 8th rib with possible infiltration of the disease in the 9th and 10th rib. The possibility of treatment with biological or immunotherapy was considered and treatment with crizotinib was started. The decision was in accordance with the

guidelines, considering the ROS1 positive finding, and the recommendation from the clinic was secured. Treatment was carried out for six months, with an initially good partial response to therapy, until the progression of the disease confirmed by PET-CT scan. Treatment with loratinib was indicated as a second line and recommendation from a clinical hospital was obtained. Until the writing of this case report, loratinib treatment is continued for three months with a good clinical response. In conclusion, through this case report, we present a treatment plan for a patient with multiple positive biomarkers that may have been the target of specific oncology therapy.

## PRIKAZ SLUČAJA BOLESNIKA S KRONIČNOM LIMFOCITNOM LEUKEMIJOM I METASTATSKIM KARCINOMOM PLUĆA LIJEČENOG PEMBROLIZUMABOM

KOVAČ PEIĆ A.[1], Canjko I.[2], Coha B.[1]

[1] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*
[2] Klinički bolnički centar Osijek
• *Zavod za onkologiju*
akovacpeic@gmail.com

**Uvod**: Cilj ovog prikaza slučaja je pokazati uspješno liječenje metastatskog adenokarcinoma pluća pembrolizumabom u prvoj liniji uz zbrinjavanje imunološki posredovanih nuspojava

**Prikaz slučaja**: Bolesniku s koronarnom bolesti,preboljelim infarktom miokarda i paroksizmalnom fibrilacijom atrija 2019.g.u dobi 71 godine dijagnosticirana B kronična limfocitna leukemija, velike tumorske mase (paketi limfnih čvorova, ingvinalno 8x5 cm)u B stadiju po Binet-u, intermedijarnog rizika. Provedeno je VI ciklusa kemoimunoterapije po rituksimab-ciklofosfamid/fludarabin protokolu. U kontrolnoj obradi 10/2019 utvrđena remisija bolesti, no MSCTom opisan tumorski proces u posteriornom segmentu gornjeg plućnog režnja vel 20x17 mm uz obostrane sekundarizme do 11 mm. Citološki dokazan adenokarcinom pluća, EGFR neg[1], ALK neg, ROS1 neg, PD-L1 >50%. Upućen dogovorno u KBC Osijek Zavod za radioterapiju gdje je u 01/2020 započeta monoterapija pembrolizumabom u standardnoj dozi 200 mg intravenski. Na terapiju se pratila parcijalna remisija do 10 /2020. kada terapija prekinuta zbog razvoja pneumonitisa uz nejasnu disfagiju i gubitak na tjelesnoj težini od 20 kg, bez MSCTom dokazane progresije bolesti. Bolesnik se tada dogovorno nastavio liječiti u našoj ustanovi. Gastroskopski dokazan teški erozivni pangastritis uz aktivnu ulkusnu bolest dvanesnika Forrest III. Uvedena suportivna terapija i inhibitor protonske pumpe. Nakon potpune regresije pneumonitisa, poboljšanja općeg stanja uz nestanak disfagije te radiološki bez dokazane progresije karcinoma pluća, pembrolizumab ponovo uveden u 12/2021. U 01/2021 dijagosticirana hipotireoza te započeta nadomjesna terapija levotiroksinom. U 03/2021 eskcidiran tumorski proces desne temporalne regije uz rekonstrukciju s režnje, prema PHDu radio se o bazocelularnom karcinomu uz R0 resekciju. U 04/2021 se javio svrbež kože bez potrebe za terapijom. Od 02/2021. kada ponovno uveden pembolizumab kontinuirano se prati regresivna dinamika uz potpuni oporavak općeg stanja, ECOG 0. Kronična limfocitna leukemija je u remisiji. Kod bolesnika s adenokaricnomom pluća postignuta je odlična kontrola bolesti tijekom 20 mjeseci liječenja u 1. liniji liječenja metastatske bolesti

**Zaključak**: Uspješno liječenje bolesnika temelji se na multidiscplinarnosti, pravovremenom prepoznavanju i zbrinjavanju nuspojava, liječenju komorbiditeta s ciljem produženja života uz kontrolu simptoma bolesti i očuvanja kvalitete života.

## A CASE REPORT OF PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND METASTATIC LUNG CANCER TREATED WITH PEMBROLIZUMAB

KOVAČ PEIĆ A.[1], Canjko I.[2], Coha B.[1]

[1] General Hospital „dr. Josip Benčević" Slavonski Brod
• *Department of Oncology and Hematology*
[2] University Hospital Centre Osijek
• *Department of Oncology*
akovacpeic@gmail.com

**Introduction**: The aim of this case report is to demonstrate the successful treatment of metastatic lung adenocarcinoma with pembrolizumab in the first line treatment with management of immune-related side effect.

**Case report**: A patient with past history od coronary heart disease, myocardial infarction and paroxysmal fibrillation in 2019at the ag of 71was diagnose with B chronic lymphocytic leukemia with large tumor masses (inguinal lymph nodes 8x5 cm), stage B according to Binet, interemedium risk. He was treated with VI cycles of chemoimunotherapy rituximab-cyclofosfamid/fludarabine. In the controlc 10/2019 remission was comfirmed, but MSCT described tumor in the posterior segment of upper lung lobe measuring 20x17 mm with bilateral metastases up to 11mm. Adenocarcinoma EGFR neg, ALK neg, ROS 1 neg,PD-L1>50% was diagnosed. He was referred to Clinical center Osijek where monotherapy with pembrolizumab in a standard dose of 200 mg intravenously was started on 01/2020. Patrial remission was confirmed at the time of 10/2020. when the therapy was discontinued due to development od pneumonitis, dysphagia and weight loss of 20kg without MSCT proves disease progression. At that time according to doctors aggrement continued treatment in our hospital. Gastroscopy shown erosive gastrtis with active ulcer of duodenum, Forrest III. Supportive therapy and proton pump inhibitor introduces. After complete regression of pneumonitis, improvement of general condition and dysphagia disappearance withou progression of lung cancer, pemborlizumab was reintroduced in 12/2021. Hypothyroidism was diagnosed in 01/2021 and levothyroxine replacement therapy was started. In 03/2021 he had operation of skin tumor un right temporal region with the lobe reconstruction. According to patological report it was basal cell carcinoma with R0 resection. Itchy skin occured in 04/2021 without need for be treated.From 02/2021 when pembrolizumab is reintroduced and regression in tumor size is continously confirmed with complete recovery of general condition, ECOG 0. Chronic lymphocytic leukemia is in remission. In our patient wthi metastatic lung adenocarcinoma excellent disease control was achieved during 20 months of treatment in fist line setting.

**Conclusion**: Successful treatment of patients is based on multidisciplinarity, early recognition and management of side effects, treatment of comorbidities with the aim of prolonging life, controlling symptoms of disease and preserving quality of life.

# SEKCIJA RAK DOJKE – SEKVENCIONIRANJE TERAPIJSKIH OPCIJA U LIJEČENJU METASTATSKOG RAKA DOJKE / BREAST CANCER SESSION

## PERSONALIZIRANA TERAPIJA TROSTRUKO NEGATIVNOG METASTATSKOG RAKA DOJKE – IZMEĐU ŽELJA I STVARNOSTI

NALBANI M.[1], Križić M.[2]

[1] Opća bolnica Dubrovnik
• *Odjel za onkologiju*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
marion@bolnica-du.hr

Trostruko negativni rak dojke (TNRD) je podtip raka dojke koji čini 11–20% od svih karcinoma dojke,a definiran je odsutnošću ekspresije receptora za estrogen (ER), progesteron (PR), i humani epidermalni faktor rasta 2 (HER2). Radi se o klinički agresivnom podtipu s većom stopom moraliteta, većom učestalosti relapsa u prve tri godine nakon dijagnoze, te najkraćim preživljenjem u proširenoj bolesti. U želji da se TNRD definira ne samo odsustvom prediktivnih biljega, u zadnjem desetljeću učinjeni su napori kako bi se kroz molekularno profiliranje razlikovali podtipovi TNRD koji bi imali ne samo prognostičke već i prediktivne implikacije kako za klasičnu kemoterapiju, tako još i važnije za otkriće različitih novih oblika ciljanog liječenja. Trenutno je najaktualnija podjela prema Lehnamm i sur. koja je definirala 4 glavna molekularna podtipa TNRD: basal-like 1(BL1), basal-like 2 (BL2), mezenhimalni (M) i luminal androgen receptor (LAR). Ova podjela za sada ima prognostičke, ali ne i jasne prediktivne i terapijske implikacije. Obzirom na limitirane opcije liječenja, kemoterapija i danas čini glavnu okosnicu liječenja TNBC, iako je u zadnje vrijeme je ostvaren veliki napredak u liječenju TNRD i otkrivene su nove ciljane terapije. Prvenstveno su to PARP inhibitori (prema eng. *poly (ADP-ribose) polymerase inhi-*

*bitors*) te inhibitori imunih kontrolnih točaka (prema eng. *immune checkpoint inhibitors*). TNRD je najčešći podtip karcinoma dojke povezan sa zametnom mutacijom (g) *BRCA 1/2*. PARP inhibitori su relativno nova skupina lijekova koja je svoje impozantne rezultate doživjela u liječenju karcinoma jajnika. PARP inhibitori kroz koncept sintetičke letalnosti dovode do apoptoze stanica s *BRCA* mutacijom. OlimpyAD i EMBRACA su studije faze 3 koje su pokazale učinkovitost PARP inhibitora olapariba i talazopariba, u produljivanju vremena do progresije bolesti, kod bolesnica sa (g) *BRCA1/2* mutacijom u HER2-negativnom karcinomu dojke kod bolesnica koje su prethodno primale kemoterapiju. Olaparib se nedavno pokazao učinkovit i kao adjuvantna terapija u TNRD s (g)*BRCA 1/2* mutacijama temeljem OlimpyA studije koja je pokazala je da adjuvantni olaparib smanjuje rizik od povrata bolesti za 42% naspram placeba. Ostaje nerazjašnjeno pitanje učinkovitosti PARP inhibitora u somatskim mutacijama (s) *BRCA1/2* i zametnim mutacijama drugih gena uključenih u proces homologne rekombinacije, a aktualno je i pitanje optimalnog sekvencioniranja i kombiniranja s drugim lijekovima, npr. s imunoterapijom. Bolesnice s pozitivnom (g) *BRCA 1/2* mutacijom imaju deficit homologne rekombinacije te se karboplatina, zbog svojeg mehanizma djelovanja, nametnula kao logičan kemoterapijski odabir. U proširenoj bolesti, suprotno rezultatima u lokalnim stadijima,TNT studija je definirala karboplatinu kao prvi kemoterapijski izbor u (g)*BRCA* mutiranih bolesnica. Uvođenje imunoterapije predstavlja možda i najveći napredak u liječenju TNRD. Zahvaljujući studiji IMpassion 130, atezolizumab u kombinaciji s nabpaklitakselom postao je 1. linija za sve bolesnice koje imaju ekspresiju receptora za PDL1 >1%. Nešto kasnije odobren je i pembrolizumab u kombinaciji s kemoterapijom u PDL1pozitivnih bolesnica u 1.liniji na temelju studije KEYNOTE-355. Obje studije imaju usporedivo vrijeme do progresije bolesti te produljuju ukupno vrijeme preživljenja. Dodatak imunoterapije pokazao se uspješan i u lokalnim stadijima. KEYNOTE-522 studija pokazala je da dodatak pembrolizumaba neoadjuvantno kemoterapiji koja je uključivala i karboplatinu povećava stopu pCR-a (prema eng. pathological complete response) uz trend poboljšanja dugoročnih ishoda.

Sacituzumab govitecan je konjugirano monoklonsko protutijelo, lijek usmjeren na glikoprotein Trop2 koji je često izražen u TNBC. Na temelju studije ASCENT, te produljenja ukupnog preživljenja odobren je kod bolesnica s uznapredovalim TNRD koje su prethodno tretirane s najmanje dvije linije terapije za metastatsku bolest. Disregulacija signalnog puta PI3K/AKT/mTOR često se pojavljuje kod TNRD, a ciljana terapija koja djeluje na ovaj signalni put ubrzano se istražuje. AKT inhibitori ipatasertib i capivasertib u kombinaciji s paklitakselom u 1.liniji su pokazali obećavajuće rezultate u fazama II istraživanja, dok studija faze III IPATunity, nije pokazala benefit u vremenu do progresije bolesti. Antagonisti androgenskih receptora (AR) nisu pokazali posebno obećavajuće rezultate u studijama faze II kod bolesnica s AR+ TNRD. Zaključno, heterogena priroda TNRD čini ga idealnim kandidatom za otkrivanje i uvođenje personalizirane terapije, ipak jedini do sada jasni prediktivni biomarkeri su status (g)*BRCA 1/*2 mutacije te PDL1 ekspresija. Paradigma temeljena na podtipovima te na ciljanim biomarkerima u budućnosti će nam pružiti još dublji uvid u molekularnu bit tumora i doprinijeti učinkovitom liječenju bolesnica s TNRD.

## PERSONALIZED THERAPY FOR METASTATIC TRIPLE-NEGATIVE BREAST CANCER – BETWEEN DESIRES AND REALITY

NALBANI M.[1], Križić M.[2]

[1] General Hospital Dubrovnik
• *Department of Oncology*
[2] University Hospital Centre Zagreb
• *Department of Oncology*
marion@bolnica-du.hr

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that accounts for 11–20% of all breast cancers and is defined by the absence of estrogen receptor (ER), progesterone (PR), and human epidermal growth factor 2 (HER2) expression. It is a clinically aggressive subtype with a higher mortality rate, a higher frequency of relapses in the first three years after diagnosis, and the shortest survival in advanced disease. To define TNBC not only by the absence of predictive markers, efforts have been made in the last decade to distinguish through molecular profiling TNBC subtypes that would have, not only prognostic but also predictive implications for both classical chemotherapy and more importantly for the discovery of various new forms of targeted treatments. Currently, the most accepted molecular classification is according to Lehnamm et al., which defined 4

main molecular subtypes of TNBC: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M) and luminal androgen receptor (LAR). This division so far has prognostic but not clear predictive and therapeutic implications. Given the limited treatment options, chemotherapy still forms the main backbone of TNBC treatment, although great progress has recently been made in the treatment of TNBC and new targeted therapies have been discovered. These are primarily PARP (poly (ADP-ribose) polymerase) inhibitors and immune checkpoint inhibitors. TNBC is the most common subtype of breast cancer associated with the germline (g)*BRCA 1/2* mutation. PARP inhibitors are a relatively new group of drugs that have experienced impressive results in the treatment of ovarian cancer. PARP inhibitors through the concept of synthetic lethality lead to apoptosis of cells with *BRCA* mutations. OlimpyAD and EMBRACA are phase 3 trials that demonstrated the efficacy of PARP inhibitors olaparib and talazoparib, in prolonging progression-free survival (PFS), in HER2-negative patients with (g)*BRCA 1/2* mutation, who received prior chemotherapy. Olaparib has recently been shown to be also effective as adjuvant therapy in TNBC with (g)BRCA 1/2 mutations. OlimpyA trial showed that adjuvant olaparib reduces the risk of disease recurrence versus placebo by 42%. There are some questions that remain unsolved: the question of the effectiveness of PARP inhibitors in somatic (s)*BRCA 1/2* mutations and germline mutations of other genes involved in the process of homologous recombination, and the question of optimal sequencing and combination with other drugs, e.g. with immunotherapy. Patients with a positive (g)BRCA 1/2 mutation have a deficiency of homologous recombination, and carboplatin, due to its mechanism of action, has emerged as a logical chemotherapeutic choice. In advanced disease, in contrast to results at local stages, the TNT study defined carboplatin as the first chemotherapeutic choice in (g)*BRCA*-mutated patients. The introduction of immunotherapy represents perhaps the greatest advancement in the treatment of TNBC. According to the results IMpassion 130 trial, atezolizumab in combination with nabpaclitaxel became the 1st line treatment option for all patients with PDL1 receptor expression> 1%. Somewhat later, pembrolizumab was also approved in combination with chemotherapy in PDL1-positive first-line patients based on the KEYNOTE-355 trial. Both studies have a comparable PFS time and prolong overall survival (OS) time. The addition of immunotherapy has also been shown to be successful in the local stages. KEYNOTE-522 study showed that the addition of pembrolizumab to neoadjuvant chemotherapy that included carboplatin increased the pathological complete response (pCR) rate with a trend of improved long-term outcomes. Sacituzumab govitecan is a conjugated monoclonal antibody, a drug targeting the Trop2 glycoprotein that is commonly expressed in TNBC. Based on the ASCENT trial, and prolongation of OS, it is approved in patients with advanced TNBC who had been previously treated with at least two lines of chemotherapy for metastatic disease. Dysregulation of PI3K / AKT / mTOR signaling pathway often occurs in TNBC, and targeted therapy acting on this pathway is rapidly being investigated. The AKT inhibitors ipatasertib and capivasertib in combination with paclitaxel in first-line treatment showed promising results in a phase II trial, while the IPATunity phase III trial showed no benefit in PFS. Androgen receptor (AR) antagonists have not shown particularly promising results in phase II trials in patients with the AR+ TNBC. In conclusion, the heterogeneous nature of TNBC makes it an ideal candidate for the introduction of personalized therapy, yet the only clear predictive biomarkers so far are the status (g) of *BRCA 1/2* mutation and PDL1 expression. In the future, a treatment paradigm based on subtypes and targeted biomarkers, will provide us with an even deeper insight into the molecular essence of tumors and contribute to the effective treatment of patients with TNBC.

## LITERATURA

1. *Dent R, et al.* Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007;13(15 Pt 1):4429–34
2. *Lin NU, et al.* Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. Cancer. 2008;113(10):2638–45
3. *Lehmann BD, Jovanovic B, Chen X, Estrada MV, Johnson KN, Shyr Y, Moses HL, Sanders ME, Pietenpol JA.* Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection. PLoS ONE 2016, 11, e0157368. [CrossRef]
4. *Cipriano É, Mesquita A.* Emerging Therapeutic Drugs in Metastatic Triple-Negative Breast Cancer. Breast Cancer (Auckl). 2021;15:11782234211002491. Published 2021 Mar 22. doi:10.1177/11782234211002491
5. *Hossain F, Majumder S, David J, Miele L.* Precision Medicine and Triple-Negative Breast Cancer: Current Landscape and Future Directions. Cancers 2021, 13, 3739. https://doi.org/10.3390/cancers13153739

# BUDUĆNOST HORMONSKI OVISNOG HER2 NEGATIVNOG METASTATSKOG RAKA DOJKE – ŠTO NAKON CDK4/6 I PIK3 INHIBITORA

SALAMUN A.[1], Jazvić M.[2], Silovski T.[3]

[1] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
[2] Klinički bolnički centar Sestre milosrdnice
• *Klinika za onkologiju i nuklearnu medicinu*
[3] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
salamun.antonija@gmail.com

Okosnica liječenja metastatskog hormonski ovisnog (HR+) HER2 negativnog raka dojke je sekvencijska primjena endokrine terapije. Algoritam liječenja te prirodni tijek bolesti značajno su izmijenili CDK4/6 inhibitori, koji su u kombinaciji s endokrinom terapijom postali standard prve linije liječenja, približno udvostručujući vrijeme do progresije bolesti. Zasad u literaturi nema definiranog optimalnog slijeda terapija nakon progresije na prvu liniju. U kliničkoj praksi, endokrina monoterapija ili kemoterapija i dalje su terapijske opcije koje često koristimo, no prepoznati su mehanizmi rezistencije na endokrinu terapiju kao i na CDK4/6 inhibitore (i njihovu kombinaciju).

Disregulacijom, odnosno aktivacijom PI3K/AKT/mTOR puta u tumorskim stanicama dolazi do poremećaja u kontroli rasta i preživljenju stanica, do razvoja metastatskog potencijala, angiogeneze i otpornosti na terapiju. Terapijski se može djelovati na više mjesta ovog signalnog puta [1].

Primjena egzemestana u kombinaciji s mTOR inhibitorom everolimusom ispitivana je u brojnim studijama. BOLERO-2 studija usporedila je kombinaciju egzemestana i everolimusa s kombinacijom egzemestana i placeba, i pokazala je statistički i klinički značajno produljenje medijana preživljenja bez progresije bolesti (PFS-a), 10,4 prema 4,1 mjesec; HR: 0,36; $p < 0,001$, no bez učinka na produljenje ukupnog preživljenja (OS) 31,1 prema 26,6 mjeseci. Treba napomenuti kako se pokazalo da je terapijski odgovor bio neovisan o postojanju PIK3CA mutacije. Na temelju ove studije je everolimus u kombinaciji s egzemestanom odobren za liječenje HR+ HER2– metastatskog raka dojke rezistentnog na aromatazni inhibitor (AI) [2]. U jednom drugom istraživanju pokazalo se kako ova kombinacija polučuje značajnu korist – uz vrijeme do prestanka učinkovitosti liječenja od 13,2 mjeseci [3]. Studija naziva PrE0102 pokazala je kako je u bolesnika s rezistencijom na AI združenim liječenjem everolimusom i fulvestrantom udvostručen PFS. Iako su rijetke studije uključivale bolesnike čija je bolest napredovala na terapiju CDK4/6 inhibitorom, ipak postoje retrospektivni podaci i dokazi za primjenu ove strategije.

Drugi inhibitor PI3K puta koji je odobren je alpelisib, usmjeren na PI3K-alfa izoformu. SOLAR-1 studija je ispitivala fulvestrant s ili bez alpelisiba u bolesnica s uznapredovalim hormonski ovisnim, HER2 negativnim rakom dojke, a uključeni su bolesnici neovisno o statusu PIK3CA mutacije. U PIK3CA mutiranoj kohorti, liječenje kombinacijom alpelisiba i fulvestranta rezultiralo je gotovo udvostručenim PFS-om u odnosu na monoterapiju fulvestrantom (mPFS-a 11, odnosno 5,7 mjeseci, $p<0,001$). Stopa odgovora u mutiranoj kohorti također je udvostručena. Konačna analiza je pokazala produljenje sveukupnog preživljenja za 7,9 mjeseci koje nije doseglo statističku značajnost. Najveća korist zabilježena je u bolesnika s visceralnim metastazama i s mutacijom PIK3CA u ctDNA, dok u bolesnika bez PI3KCA mutacije nije zabilježen odgovor na liječenje [4].

U studiji faze II, BYLieve, alpelisib je kombiniran s fulvestrantom ili letrozolom u PIK3CA mutiranih, rezistentnih na CDK4/6 inhibitor. U ranoj analizi, stopa odgovora je bila nešto viša u kombinaciji s letrozolom (28%) u odnosu na fulvestrant (14%), no više bolesnika na fulvestrantu je imalo stabilnu bolest (59 vs 34%) [5,6]. Alpelisib je odobren u kombinaciji s fulvestrantom za PIK3CA mutirani, HR+, HER2 negativni metastatski rak dojke nakon progresije na prethodnu endokrinu terapiju te predstavlja novi standard u liječenju nakon terapije CDK4/6 inhibitorima.

Odgovor na pitanje koje su daljnje terapijske opcije pokušava se dobiti u nizu strategija i kliničkih istraživanja.

AKT je također dio PI3K signalnog puta i regulator normalnih staničnih procesa uključenih u progresiju raka. FAKTION studija, randomizirana studija faze II, istraživala je AKT inhibitor kapivasertib u kombinaciji s fulvestrantom u usporedbi s monoterapijom fulvestrantom kod HR+, HER2 negativnog metastatskog raka dojke rezistentnog na AI. Rezultat je udvostručenje PFS-a (10,3 vs 4,8 mjeseci, $p=0,0035$) uz trend produljenja OS-a (26,0 vs 20,0 mjeseci, $p=0,071$) [7]. Trenutno je u tijeku velika studija faze III kapivasertiba i fulvestranta vs fulvestrant u monoterapiji – CAPItello-391.

Pokazalo se kako su u više od četvrtine bolesnika s HR+ HER2– rakom dojke nakon progresije na CDK4/6, PI3K ili mTOR inhibitore, prisutne ESR1 mutacije. Aromatazni inhibitori i selektivni deregulatori estrogenskih receptora (SERD, npr. fulvestrant) najčešće su korištena antihormonska terapija. Dokazana je prednost fulvestranta u odnosu na AI u bolesnika s prisutnom ESR1 mutacijom temeljem SOFEA studije, kao i meta-analize iz 2018. godine. U tijeku je studija faze III (EMERALD) kojom se ispituje učinkovitost elacestranta, oralnog SERD-a, u liječenju ER+ HER2– metastatskog raka dojke nakon progresije na jednu ili više linija sustavne terapije.

Drugi su mogući terapijski pristupi, za koje se još očekuju rezultati u različitim kliničkim ispitivanjima i nastavak liječenja s istim CDK4/6 inhibitorom uz promjenu endokrinog partnera (ESR1 mutirani u fokusu), odnosno trostruka (triplet) terapija: nastavak liječenja CDK4/6 inhibitorom uz ET, ali i uz dodatak ciljane terapije (usmjerene na kolateralni signalni put); ili pak promjena CDK4/6 inhibitora.

U tijeku je studija faze I/II, TRINITI-1, koja ispituje učinkovitost egzemestana i everolimusa uz dodatak ribocikliba (triplet) nakon progresije na CDK4/6 inhibitor. Dokazana je klinička korist od 41% u 24. tjednu (rezultati lošiji kod ESR1 i PIK3CA mutiranih) [8].

Multicentrična, retrospektivna analiza učinkovitosti abemacikliba nakon progresije na palbociklib ili ribociklib, pokazala je korist u smislu trajanja odgovora od više od 6 mjeseci u jedne trećine bolesnika, uz produljenje PFS-a za 5,8 mjeseci. Ipak, u trećine ispitivanih bolesnika došlo je do brze progresije, što sugerira postojanje ukrižene rezistencije na različite CDK4/6 inhibitore. Prospektivne su studije u tijeku.

Jedna je strategija usmjerena i na BCL-2, anti-apoptotički protein koji je prekomjerno izražen u oko 80% HR+ raka dojke. Inhibitor BCL-2, venetoklaks, pokazao je u studiji faze Ib korist u kombinaciji s tamoksifenom u prethodno tretiranoj metastatskoj bolesti. Studija faze II, VERONICA je ispitivala venetoklaks u kombinaciji s fulvestrantom, no nije dokazala korist od navedene kombinacije.

Ostale su strategije usmjerene na FGFR inhibitore, CDK2 i CDK7 inhibitore, sacituzumab govitekan, te imunoterapiju u kombinaciji s CDK 4/6 inhibitorom i ET.

Endokrina terapija je terapija izbora u liječenju hormonski ovisnog raka dojke, a CDK4/6, mTOR i PI3K inhibitori pokazuju da je moguće poboljšati učinkovitost endokrine terapije i odgoditi endokrinu rezistenciju. Optimalno liječenje je i nadalje veliki izazov u zbrinjavanju bolesnika s proširenim HR+ HER2 negativnim rakom dojke te su stoga potrebni dodatni napori u definiranju optimalne kombinacije lijekova i optimalne sekvencijske terapije, a sve u cilju bolje skrbi za naše bolesnike.

## FUTURE OF HORMONE RECEPTOR SENSITIVE, HER2 NEGATIVE METASTATIC BREAST CANCER – TREATMENT STRATEGIES AFTER PROGRESSION ON CDK4/6 AND PIK3 INHIBITORS

SALAMUN A.[1], Jazvić M.[2], Silovski T.[3]

[1] General Hospital Pula
• *Department of Medical Oncology and Hematology*
[2] University Hospital Centre Sestre milosrdnice
• *Department of Oncology and Nuclear medicine*
[3] University Hospital Centre Zagreb
• *Department of Oncology*
salamun.antonija@gmail.com

The sequential use of endocrine therapies (ET) is the treatment backbone for hormone receptor positive (HR+) HER2 negative metastatic breast cancer. The treatment algorithm, as well as the natural history of the disease, have drastically changed with CDK4/6 inhibitors. In combination with endocrine therapies, they have doubled the time to disease progression. There are no defined guidelines for therapies after progression on CDK4/6 inhibitors, therefore, in clinical practice, endocrine monotherapy and chemotherapy are still very often used strategies, but the mechanisms of resistance to endocrine therapy, as well as to CDK4/6 inhibitors, and the combinations of those two, are well recognized.

The upregulation of PI3K/AKT/mTOR pathway in cancer cells leads to abnormal cell growth, tumour survival, angiogenesis, metastatic potential, and treatment resistance. Therapies can focus on more than one level of this pathway [1].

One therapeutic option is to give combination of exemestane and the mTOR inhibitor everolimus, which is supported by numerous studies. The BOILERO-2 study compared exemestane and everolimus combination with exemestane plus placebo, and showed progression free survival (PFS) benefit: the median progression-free survivals were 10.6 months and 4.1 months, respectively; hazard ratio 0.36. However, everolimus plus exemestane did not result in a significant improvement in overall survival (OS) compared with placebo plus exemestane in BOLERO-2. The results of this trial lead to approval of everolimus plus exemestane in HR+ HER2– metastatic breast cancer resistant to aromatase inhibitor (AI) [2]. Everolimus plus exemestane was effective in both PIK3CA-mutated and wild-type tumours. In another study everolimus plus exemestane treatment conveyed benefit in median time to treatment failure, which was 13.2 months [3]. In PrE102 trial, which included patients with resistance to AI, exemestane and everolimus combination doubled PFS. Although not many of the trials have included patients with disease progression after CDK4/6 inhibitor, there are many retrospective data that support this treatment strategy.

The second PI3K pathway inhibitor to be approved was the alpha-selective inhibitor alpelisib. SOLAR-1, the pivotal trial that evaluated fulvestrant with or without alpelisib, enrolled patients regardless of mutation status. In the subset of patients with PIK3CA mutations, median PFS was 11.0 months with alpelisib plus fulvestrant versus 5.7 months with fulvestrant alone (HR 0.65, p<0,001), with respective overall response rates of 26.6 versus 12.8%. Although the analysis did not cross the prespecified boundary for statistical significance, there was a 7,9-month numeric improvement in median OS. No benefit was shown in patients with wild-type disease [4].

BYLieve trial included a substantial proportion of patients with disease progression after a CDK4/6 inhibitor. It evaluated alpelisib in combination with fulvestrant or letrozole in PIK3CA mutated population. In an early analysis, response rates were somewhat higher with letrozole (28%) than fulvestrant (14%), but more patients had stable disease with fulvestrant (59% vs 34%) [5,6]. Alpelisib is approved in combination with fulvestrant for -PIK3CA-mutated HR+ HER2- advanced or metastatic breast cancer after disease progression on endocrine therapy. It presents a new standard of care after progression on CDK4/6 inhibitors.

Numerous studies try to find an answer to which are the optimal therapeutic options after further disease progression.

AKT, a component of the PI3K signaling pathway, is also a regulator of normal cellular processes involved in cancer progression. The phase II FAKTION trial evaluated the AKT inhibitor capivasertib plus fulvestrant vs fulvestrant alone in patients with hormone receptor–positive metastatic breast cancer resistant to an AI. The combination resulted in a doubling in PFS (10.3 vs 4.8 months; p=0.0035) and a trend for improved overall survival (26.0 vs 20.0 months; p= 0.071) [7]. The phase III CAPItello-291 trial, evaluating capivasertib with fulvestrant versus fulvestrant monotherapy, is now underway.

ESR1 mutations occur in more than 25% of patients with HR+ HER2- breast cancer after progression on CDK4/6, PI3K or mTOR inhibitors. Aromatase inhibitors and the selective ER downregulator (SERD) fulvestrant are the two most common endocrine agents for the treatment of metastatic breast cancer. SOFEA trial demonstrated an improved PFS associated with fulvestrant compared with AI treatment in patients with ESR1 mutation detected in circulating tumor DNA (ctDNA). A recent meta-analysis concluded that ESR1 mutation predicted a poor response to AIs, but not with fulvestrant. The phase III EMERALD trial evaluates efficacy of an oral selective SERD with activity against mutant ESR1, elacestrant, in patients with ER+, HER2– metastatic breast cancer who had previous CDK4/6 inhibitor plus AI or fulvestrant.

There are many other therapy options, and the results of several phase I and II trials are pending. One of the options is to continue the CDK4/6 inhibitor and switch the ET; another option is to continue both the ET and the CDK4/6 inhibitor and to target a collateral pathway with another agent, and the third option is to switch to a different CDK4/6 inhibitor.

The TRINITI trial is a single-arm phase I/II trial of ribociclib in combination with exemestane and everolimus (triplet therapy) in HR+ HER2– metastatic breast cancer, in ET refractory, post-CDK4/6 inhibitor population. It demonstrated a 41% clinical benefit rate at week 24. It was noted that patients with ctDNA ESR1 or PIK3CA mutation at baseline had a numerically shorter median PFS [8].

A multicentric, retrospective study of efficacy of abemaciclib after a previous CDK4/6 inhibitor showed benefit that in one third of the patients enrolled, treatment duration exceeded 6 months. Unfortunately, one third of patients had early disease progression, suggesting cross-resistance between CDK4/6 inhibitors. Prospective trials are underway.

One strategy involves BCL2, an antiapoptotic protein that is overexpressed in more than 80% of primary ER+ tumours. In a phase Ib trial, venetoclax plus tamoxifen led to clinical benefit in patients previously treated with tamoxifen, CDK4/6 inhibitors, or everolimus (plus endocrine therapy). VERONICA, phase II trial showed that adding venetoclax to fulvestrant does not improve outcomes for women with estrogen receptor-positive, HER2-negative locally advanced breast cancer resistant to endocrine and CDK4/6 inhibitor treatment.

Other strategies are being evaluated in clinical trials, like FGFR, CDK 2 and CDK7 inhibitors, sacituzumab govitecan, and immunotherapy in combination with CDK4/6 and ET.

Endocrine therapies are the standard of care in HR+ breast cancer, and CDK4/6, mTOR and PI3K inhibitors have shown that it is possible to improve endocrine therapy results as well as to delay endocrine resistance. The optimal treatment choice is still a great challenge in management of metastatic HR+ HER2– breast cancer. Significant efforts must be made to define the optimal drug combinations, as well as the optimal sequence of therapy.

**LITERATURA**


1. *Gul A, Leyland-Jones B, Dey N, De P.* A combination of the PI3K pathway inhibitor plus cell cycle pathway inhibitor to combat endocrine resistance in hormone receptor-positive breast cancer: a genomic algorithm-based treatment approach. Am J Cancer Res. 2018;8(12):2359–2376.
2. *Hortobagyi GN, Chen D, Piccart M et al.* Correlative Analysis of Genetic Alterations and Everolimus Benefit in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From BOLERO-2. J Clin Oncol. 2016 Feb 10;34(5):419–26.
3. *Giridhar KV, Choong GM, Leon-Ferre RA, et al.* Clinical management of metastatic breast cancer after CDK4/6 inhibitors: A retrospective single-institution study. 2018 San Antonio Breast Cancer Symposium. Abstract P6-18-09.
4. *André F, Ciruelos EM, Juric D, et al.* Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: Final overall survival results from SOLAR-1. Ann Oncol 2021;32:208–217.
5. *Jerusalem G, de Boer RH, Hurvitz S, et al.* Everolimus plus exemestane vs everolimus or capecitabine monotherapy for estrogen receptor-positive, HER2-negative advanced breast cancer: The BOLERO-6 randomized clinical trial. JAMA Oncol 2018;4:1367–1374.
6. *Rugo HS, Lerebours F, Ciruelos E, et al.* Alpelisib + fulvestrant in patients with PIK3CA-mutated hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer previously treated with cyclin-dependent kinase 4/6 inhibitor + aromatase inhibitor: BYLieve study results. ASCO20 Virtual Scientific Program. Abstract 1006.
7. *Jones RH, Casbard A, Carucci M, et al.* Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): A multicentre, randomized, controlled, phase 2 trial. Lancet Oncol 2020;21:345–357.
8. *Xi J, Ma CX.* Sequencing Endocrine Therapy for Metastatic Breast Cancer: What Do We Do After Disease Progression on a CDK4/6 Inhibitor? Curr Oncol Rep. 2020; 16;22(6):57.


## „NEW KIDS ON THE BLOCK" – NOVOSTI U KRAJOLIKU LIJEČENJA HER2 POZITIVNOG METASTATSKOG RAKA DOJKE


KARDUM FUCAK I.[1], Trajbar M.[2]

[1] Opća bolnica „dr. Tomislav Bardek" Koprivnica
• *Odjel za gastroenterologiju, onkologiju i hematologiju*
[2] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
ikardum@gmail.com


HER2 pozitivni metastatski rak dojke klinički je agresivniji oblik raka dojke u odnosu na ostale podtipove i kao takav predmet je brojnih istraživanja. Unatrag nekoliko godina preživljenje bolesnica s HER2 pozitivnim metastatskim rakom dojke značajno se produžilo upravo zbog mogućnosti primjene ciljane anti HER2 terapije u više linija liječenja. Standard u prvoj liniji liječenja i dalje je primjena taksana u kombinaciji s dualnom anti HER2 blokadom – pertuzumabom i trastuzumabom prema CLEOPATRA ispitivanju, a u 2. liniji liječenja prema rezultatima dobivenim iz EMILIA ispitivanja primjenjuje se ado – trastuzumab emtanzin (TDM1). Unatrag dvije godine u svijetu je odobreno nekoliko lijekova za treću i kasnije linije liječenja metastatskog HER2 pozitivnog raka dojke te se zahvaljujući njima očekuje da će ishod liječenja bolesnica u budućnosti biti značajno promijenjen. 2019. godine FDA i EMA odobrile su dva inhibitora tirozin kinaza – tukatinib i neratinib. Tukatinib je visokoselektivni oralni inhibitor HER2 tirozin kinaze, koji je, u kombinaciji s trastuzumabom i kapecitabinom, u ispitivanju faze II, HER2CLIMB pokazao benefit u sveukupnom preživljenju za 4,5 mjeseci u svim ispitivanim

podskupinama bolesnica, uključujući i one s metastazama u mozgu. Neratinib, pan – HER2 inhibitor tirozin kinaze, dokazao se učinkovitim u kombinaciji s kapecitabinom u smislu produljenja vremena bez progresije bolesti u bolesnica koje su već primile dvije linije ciljane anti HER2 terapije, pa čak i u onih sa stabilnim metastazama u mozgu. Prema NALA ispitivanju, najveću korist imala je podskupina bolesnica s HER2 pozitivnom, HR negativnom bolešću. Iako još nije odobren od FDA, sličnu učinkovitost i profil nuspojava kao već navedena dva tirozin kinazna inhibitora je pokazao i pirotinib. Lijek koji je postigao značajan odgovor u skupini bolesnica liječenih s više linija terapije svakako je i trastuzumab derukstecan TDXd, konjugat monoklonalnog protutijela i inhibitora topoizomeraze I. Na temelju ispitivanja faze II DESTINY Breast 01 FDA je 2019. godine odobrio njegovu primjenu. Ispitivanje faze III DESTINIY Breast 03 je ispitivalo učinkovitost trastuzumaba derukstekana u usporedbi s TDM1 u drugoj liniji liječenja metastatskog HER2 pozitivnog raka dojke. Rezultati ovog istraživanja recentno su objavljeni na ESMO-u ove godine i moguće je da će promijeniti paradigmu liječenja metastatskog HER2 pozitivnog raka dojke u drugoj liniji. Rezultati ovog istraživanja pokazali su da je u drugoj liniji liječenja TDXd statistički i klinički značajno produljio PFS u odnosu na TDM1 u bolesnika koji su prethodno bili liječeni trastuzumabom i taksanima zbog metastatskog HER2 pozitivnog raka dojke uz prihvatljiv toksični profil i značajno smanjenje tegoba kao posljedica intersticijskog pneumonitisa u odnosu na kasnije linije liječenja. Margetuksimab je anti HER2 monoklonalno protutijelo koje je u kombinaciji s kemoterapijom, u SOPHIA ispitivanju faze 3, statistički značajno poboljšao PFS uz prihvatljiv sigurnosni profil u usporedbi s trastuzumabom i kemoterapijom u bolesnica s metastatskim rakom dojke koje su prethodno već liječene s ciljanom anti HER2 terapijom. Konačni rezultati za ukupno preživljenje se očekuju. U tijeku su ispitivanja faze III koja će pomoći bolje razumjeti njegov profil nuspojava i jasnije pokazati njegovu poziciju u budućnosti. Uz sve veći izbor novih anti HER 2 lijekova u liječenju HER2 pozitivnog metastatskog raka dojke, onkolozima danas predstavlja izazov odabrati odgovarajuću ciljanu terapiju u određeno vrijeme liječenja.

## „NEW KIDS ON THE BLOCK" – NOVEL OPTIONS IN THE TREATMENT LANDSCAPE OF HER2 POSITIVE METASTATIC BREAST CANCER

KARDUM FUCAK I.[1], Trajbar M.[2]

[1] General Hospital „dr. Tomislav Bardek" Koprivnica
• *Department of Gastroenterology, Oncology and Hemathology*
[2] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*
ikardum@gmail.com

Compared to other subtypes of breast cancer, HER 2 positive subtype is much more aggressive than others and therefore is a subject of extensive scientific research. In the last few years, the survival of patients with metastatic HER 2 positive breast cancer has improved significantly, mainly due to multiple choices of antiHER 2 therapies in second and subsequent lines of treatment. Standard first-line treatment was established in the CLEOPATRA trial and is the combination of pertuzumab, trastuzumab, and a taxane, preferably docetaxel. Second-line treatment, according to results of the EMILA trial is TDM-1, ado-trastuzumab-emtansine. Two years back a couple new antiHER2 drugs were approved for third and subsequent lines. These new drugs are expected to change the survival advantages of HER 2 positive metastatic patients. In 2019 FDA and EMA approved two tyrosine kinase inhibitors – tucatinib and neratinib. Tucatinib is highly selective for the kinase domain of HER2. The drug was investigated in HER2CLIMB, phase II trial in combination with trastuzumab and capecitabine where it showed benefit in overall survival in 4.5 months in all patients' subgroups, including those with brain metastases. Neratinib is an irreversible pan-HER tyrosine kinase inhibitor that was proven effective in combination with capecitabine to the effect of prolonging progression-free survival even in heavily pretreated patients including those with stable brain metastases. According to the NALA trial, the greatest benefit was shown for HER2 positive HR negative subgroups. Pyrotinib, a new tyrosine kinase inhibitor that is not yet approved by FDA, showed similar efficacy and side effect profile as the previous two TKIs. Trastuzumab deruxtecan (TDXd) is an antibody-drug conjugate composed of an anti-HER 2 antibody and a cytotoxic topoisomerase I inhibitor. It achieved a significant response in a heavily pretreated group of patients. The drug was granted FDA approval in 2019 pursuant to the results of the phase II DESTINY Breast01 trial. Phase III DESTINY Breast 03 trial investigated the efficacy of trastuzumab deruxtecan compared to trastuzumab emtansine (TDM1) in the second line

treatment of metastatic disease setting. The results that were recently published on ESMO this year will probably change the paradigm of treatment sequence when it comes to second-line treatment. The results have shown clinical and statistical benefit in PFS of TDXd compared to TDM1 in patients previously treated with trastuzumab and a taxane. The toxicity profile was acceptable as well as relief of subjective disturbance due to interstitial pneumonitis. Margetuximab, an investigational HER 2 – directed monoclonal antibody, in combination with chemotherapy treatment in phase III, SOPHIA trial, statistically significant improvement in progression free survival (PFS) with an acceptable safety profile when compared to trastuzumab and chemotherapy combination In HER 2 positive advanced breast cancer (ABC) in previously treated patients. Phase III trials are currently ongoing to position the drug in treatment lines and further understand its toxicity profile. The clinical challenge is to optimally choose, utilize and sequence antiHER2 drugs in the treatment of metastatic HER 2 positive breast cancer given the constantly rising number of available drugs.

## PRISTUP ONKOLOŠKOM BOLESNIKU U ERI PRECIZNE MEDICINE

POPOVIĆ M.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
marina.baric11@gmail.com

Termin precizna onkologija odnosi se na identifikaciju specifičnih molekularnih promjena u tumorskim stanicama na koje možemo djelovati ciljanim terapijama. Cilj precizne onkologije je poboljšati ishod bolesti liječenjem usmjerenim prema osobnom genomskom profilu. Smatra se da je potrebno najmanje pet uzastopnih mutacija u genima odgovornim za kontrolu staničnog ciklusa da stanica postane zloćudna. Takve mutacije zovu se pogonske mutacije. Jedan od glavnih izazova precizne onkologije je razlučiti koje su pogonske mutacije rani klonski događaji, a koje kasniji subklonalni događaji. Za identifikaciju stečenih i zametnih mutacija možemo koristiti uzorke zdravog tkiva, tumorskog tkiva ili cirkulirajuću tumorsku DNA. Dubina informacija koja je potrebna da bismo dobili odgovore na složena pitanja o genomici prelazi mogućnosti tradicionalnih tehnologija sekvenciranja zbog čega se danas najčešće koriste nove metode kao što je NGS (eng. *Next Generation Sequencing*). Iako svaki tumor ima jedinstven genetski sastav, postoji ograničen set mutacijskih mehanizama koji oblikuju mutacijski krajolik genoma od kojih svaki generira karakterističan mutacijski potpis. Mutacijski potpisi nose potencijalnu kliničku vrijednost kao prediktori terapijskog odgovora tumora na ciljano liječenje. Radi optimalne upotrebe precizne onkologije u svakodnevnoj kliničkoj praksi kao pomoć liječnicima koji liječe onkološke bolesnike formiraju se odbori za molekularno profiliranje tumora (eng. „*Molecular tumor boards*“, MTBs). Uloga MTB-a je da raspravi klinički značaj pronađenih genetskih aberacija i utvrdi potencijalne terapijske strategije temeljene na dobivenoj genetskoj analizi i svim ostalim značajkama pacijenta. Na primjeru bolesnice oboljele od uznapredovalog trostruko negativnog raka dojke bit će ilustrirano djelovanje MBT-a i primjena precizne onkologije u kliničkoj praksi.

## PATIENT MANAGEMENT IN THE ERA OF PRECISION ONCOLOGY

POPOVIĆ M.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
marina.baric11@gmail.com

The term precision oncology refers to the identification of specific molecular changes in tumor cells that can be potential targets for genomic-based therapies. The goal of precision oncology is to improve disease outcome with treatment geared toward a personal genomic profile. At least five consecutive mutations in the genes responsible for controlling the cell cycle are required for a cell to become malignant. Such mutations are called driver mutations. One of the main challenges of precision oncology is to distinguish which driver mutations are early clonal events and which are subsequent subclonal events. Sequencing of a non-cancerous tissue samples, tumor

tissue and cell-free DNA samples can be done to reveal germline and somatic mutations. To get the information needed to answer complex genomics questions novel techniques of sequencing such as next-generation sequencing (NGS) are used. Although each tumor has a unique genetic composition, there are a limited set of mutational mechanisms that shape the mutational landscape of the genome, generating a characteristic mutational signature. Mutational signatures carry potential clinical value as predictors of response to targeted treatment. To assist physicians treating cancer patients implement precision oncology in everyday clinical practice, molecular tumor boards (MTBs) are formed. The role of MTB is to discuss the clinical relevance of the genetic aberrations found and to identify potential therapeutic strategies based on genetic analysis and other patient characteristics. A case of a patient with advanced triple negative breast cancer who has had her tumor sequenced as part of clinical management will be presented to illustrate the role that MTBs play on implementing precision oncology.

# SEKCIJA TUMORI PROBAVNIH ORGANA / GASTROINTESTINAL CANCER SESSION

## RAZVOJ PRECIZNE MEDICINE U GASTROINTESTINALNOJ ONKOLOGIJI

LIBRENJAK N.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
niksa.librenjak@gmail.com

Kako bi se optimiziralo liječenje raka kroz personaliziranu skrb, potrebno je provesti odgovarajuća molekularna testiranja u bolesnika koji ispunjavaju uvjete takvu terapiju, pri čemu ta potreba ostaje sve prisutnija u liječenju gastrointestinalnih tumora. Trenutni standardi molekularnih ispitivanja u metastatskom kolorektalnom karcinomu (mKRK) uključuju testiranje za aktivirajuće mutacije KRAS i NRAS, mutaciju BRAF V600E, kao i za proteine popravka DNA (MMR). Osim mutacija KRAS/NRAS/BRAF, druge promjene u RTK, PI3KCA ili PTEN također su vjerojatno uključene u rezistenciju na anti-EGFR terapiju. Prekomjerna ekspresija HER2 zbog amplifikacije ERBB2 gena nađena je u 2–6 % mKRK-a, a nekoliko studija to navodi kao negativan prediktor odgovora na anti-EGFR terapiju. Nadalje, nekoliko je studija istraživalo HER2 kao terapijski cilj u mKRK-u, pokazujući obećavajuće stope odgovora. U malog broja bolesnika (<2.5%) fuzije gena, uključujući one koje uključuju NTRK, ROS, ALK i RET ključni su onkogeni pokretači i klinički su zanimljivi jer su svi sada dostupni terapiji s potencijalom za postizanje boljih kliničkih ishoda naspram onih postignutih standardnom terapijom. Cirkulirajuće tumorske stanice (CTC), cirkulirajuća tumorska DNA (ctDNA) i egzosomi oslobođeni iz tumorskih stanica istražuju se kao biomarkeri koji mogu biti otkriveni primjenom tekućinske biopsije. Tekućinska biopsija može promijeniti pristup KRK u na nekoliko načina: otkrivanje i liječenje minimalne rezidualne bolesti (MRD), praćenje metastatske bolesti i odgovora na liječenje, procjena rezistencije na lijekove i dinamiku klonalnosti. Immunoscore, standardizirani sustav bodovanja temeljen na imunohistokemiji koji koristi gustoću infiltriranih CD3+ i CD8+ T limfocita u središtu tumora i na rubovima tumorske infiltracije, pokazao je prognostičku vrijednost u procjeni ishoda u ranim stadijima CRC-a. Vrlo heterogena priroda tumora bilijarnog trakta na genomskoj, epigenetskoj i molekularnoj razini dovela je do razvoja učinkovitih novih lijekova za bolesnike s tim rijetkim zloćudnim tumorima. U bolesnika s intrahepatalnim kolangiocelularnim karcinomom, IDH1 mutacije i fuzije gena FGFR2 bile su najčešće identificirane promjene. Manje uobičajene uključuju mutacije BRAF-a, fuzije NTRK i ROS1 i mikrosatelitsku nestabilnost (MSI-H). Većina danas dostupnih podataka odnosi se na aktiviranje fuzija ili preuređenja FGFR2, što je meta pemigatiniba i infigratiniba, prvih inhibitora FGFR-a odobrenih od FDA. Dodatno, inhibitor IDH1 ivosidenib povezan je s poboljšanim PFS u rezultatima faze 3 ispitivanja ClarIDHy, iako nije pokazao dramatične stope odgovora. Bolje poznavanje prognostičkih i prediktivnih biomarkera i personalizirani odabir liječenja, uz izbjegavanje terapija za koje nije vjerojatno da će koristiti pacijentima i potencijalno imaju ozbiljne nuspojave, moglo bi poboljšati ishode u bolesnika s gastrointestinalnim tumorima.

## PRECISION MEDICINE DEVELOPMENT IN GASTROINTESTINAL ONCOLOGY

LIBRENJAK N.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
niksa.librenjak@gmail.com

In order to optimise cancer treatment for personalized care, adequate molecular testing must be performed in patients who are eligible for these therapies, with this necessity becoming more and more prevalent in the treatment of gastrointestinal tumors. Current standards of molecular testing in metastatic colorectal cancer (mCRC) include testing for activating KRAS and NRAS mutations, BRAF V600E mutation and also for mismatch repair (MMR). Besides KRAS/NRAS/BRAF mutations, other alterations in RTK, PI3KCA, or PTEN are also likely involved in the resistance to anti-EGFR therapy. Overexpression of HER2 due to amplification of ERBB2 gene is found in 2–6 % of mCRCs and several studies report it as a negative predictor for response to anti-EGFR therapy. Also, several trials investigated HER2 as therapeutic target in mCRC showing promising response rates. In a small minority of patients(<2.5%) gene fusions including those involving NTRK, ROS, ALK and RET are key oncogenic drivers and are clinically interesting because they are all now pharmacologically actionable with the potential to confer better clinical outcomes than those achieved with standard-of-care therapies. Circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) and exosomes released from neoplastic cells are being explored as biomarkers detected using the liquid biopsy approach. Liquid biopsy has potential to change the management of CRC in several ways: detection and management of minimal residual disease (MRD), monitoring of metastatic disease and treatment response, assessment of drug resistance and clonal dynamics. Immunoscore, a standardized immunohistochemistry-based scoring system using the density of infiltrating CD3+ and CD8+ T lymphocytes in the tumor center and at the infiltrating margins, demonstrated prognostic value in assessing outcome in early-stage CRC. The highly heterogeneous nature of biliary tract tumors at the genomic, epigenetic, and molecular levels has led to the development of effective new treatments for patients with these rare malignant tumors. In patients with intrahepatic cholangiocarcinoma, IDH1 mutations and FGFR2 gene fusions have been the most frequent alterations identified. Less common targets include BRAF mutations, NTRK fusions, ROS1 fusions, and microsatellite instability-high (MSI-H) status. Today, we have most data currently available for activating FGFR2 fusions or rearrangements, which is the target of pemigatinib and infigratinib, first FDA approved FGFR inhibitors. Additionally, IDH1 inhibitor ivosidenib has been associated with improved PFS in data from the phase 3 ClarIDHy trial, although has not shown dramatic response rates. Better knowledge of prognostic and predictive biomarkers and personalized treatment selection, with avoidance of therapies that are unlikely to benefit patients and potentially have serious side effects, could improve outcomes in patients with gastrointestinal tumors.

## MOLEKULSKI PROFIL ADENOKARCINOMA GUŠTERAČE – TERAPIJSKE IMPLIKACIJE

BELEV B.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
borislavbelev@gmail.com

Karcinom gušterače je i dalje jedan od najzloćudnijih tumora i predstavlja veliki javnozdravstveni problem. Projekcije za iduće desetljeće govore da bi mogao postati drugi najčešći uzrok karcinomom-uzrokovane smrti. Svega 15–20% oboljelih imaju resektabilnu bolest, a kod onih koji su operirani i potom primili adjuvantnu kemoterapiju oko 30% doživi povrat bolest u 1. godini života. Kirurško je liječenje i dalje jedino kurativno. Oko 80% oboljelih imaju u samom trenutku postavljanja dijagnoze proširenu/metastatsku bolest. Zadnjih desetljeća 5-godišnje preživljenje nije se bitnije produljilo i iznosi najviše 10%. Specifična sustavna terapija započinje zapravo gemcitabinom, koji u kliničku praksu ulazi 1997.godine, pokazavši se superiornim prema 5-FU. Idućih 15-ak godina nema značajnijih pomaka, a tada se pojavljuj 2 studije koje mijenjaju sliku – PRODIGE 11, faze III, gdje se FOLFIRINOX pokazao superiornim prema gemcitabinu, te MPACT gdje je nab-paklitaksel pokazao superiornost prema gemcitabinu. Obje studije su faze III. Zanimljivo je da su sve ciljane terapije koje su testirane pokazale nedostatan učinak (negativne studije MEK-inhibitora, anti-HER2 terapije – trastuzumab i lapatinib,

mTOR-inhibitori itd. Premda je u molekulskoj klasifikaciji PDAC jasno da je većina PDAC-KRAS-poz., ali za njih, kao niti za p53-mutiran tumore odnosno CDKN2A još uvije nepoznata terapija, a neg. su studije gdje su bili markeri poput SMAD4, TGF-betaR1 i R2. Zapravo pravi pomak se događa uvođenjem PARP-inhibitora (POLO-studija), koja je dizajnirana na temeljeu ranijih iskustava BRACA poz.tumora karcinoma ovarija i dojke. POLO je ispitivao tzv.germ-line mutirane PDAC, koji ima oko 5–7%, a terapija se primjenjivala nakon indukcije kemoterapijom. Današnja je preporuka NCCN-a da bi svi oboljeli trebali biti testirani na BRCA neovisno da li imaju pozitivnu obiteljsku anamnezu. Postoje i druge mutacije koje su potencijalno zanimljive, poput KRAS-G12C, zatim BRAF mutacije kao i KRAS-wt tumori, gdje je pozitivna studija faze II gemcitabin+nimotuzumab u odnosu na gemcitabin. U posljednjih nekoliko godina predmet interesa su i tzv. fuzijski geni, koji se mogu detektirati koristeći RNA, od kojih je najpoznatija NTRK-fuzija, a za nju postoji i specifični inhibitor – larotrectinib, koji je dobio odobrenje FDA i EMA, te je prisutna u više tumora, no u razmjerno malo postotku. Od drugih fuzijskih gena, još su poznati ALK, RET, NRG, no svaki sa učestalošću od oko 1%. Što se imunoterapije tiče, PDA nije osobito pogodan za imunoterapiju iz više razloga. Prije svega niska je imunogeničnost tumora, niski je TMB (tumor mutational burden), a k tome desmoplastična stroma igra vrlo aktivnu ulogu stvarajući citokine koji smanjuju imunosni odgovor. Klinička implikacija novih ciljanih terapija uglavnom se oslanja na MSI, BRCA i fuzije što su ujedno i 3 najčešće alteracije koje su ujedno „targetabilne". Ostaje otvoreno pitanje da li će u budućnosti NGS za likvidnu biopsiju postati šire upotrebljavana metoda. Također će se trebati posvetiti više pozornosti stromi tumora i ekstracelularnom matriksu, koji igraju važnu ulogu u razvoju rezistencije na terapiju, ali i „pasivizaciji"imunih stanica.

## MOLECULAR PROFILE OF PANCREATIC ADENOCARCINOMA (PAC) – TREATMENT IMPLICATION

BELEV B.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
borislavbelev@gmail.com

Pancreatic adenocarcinoma (PAC) is still one of the most malignant tumors and means serious public health issue. Next 10-years projection suggest that it might become the second most frequent cancer-caused death. Only about 15–20% of patients have resectable disease, and those who have undergone surgery in about 30% have recurrent disease at one year. Surgery is still the only curative treatment. About 80% of patients at the time of diagnosis have advanced disease. Looking back on 10 years doesn't show significant improval of overall survival (OS), 5-year survival is still about 10%. Specific systemic treatment starts with gemcitabine that enters clinical practice in 1997. Two recent trials phase III finally changed clinical practice – PRODIGE 11 (comparing FOLFIRINOX to gemcitabine) and IMPACT (nab-paclitaxel compared to gemcitabine). So obviously, there was a need for further step forward looking for more efficient treatment. Interestingly, all targeted treatment failed (negative trials with MEK-inhibitors, anti-HER2 agents – trastuzumab and lapatinib, mTOR-inhibitors etc.). According to molecular classification of PAC, mostly there are KRAS-positive, p53-mutated nad CDKN2A-positive tumors, for which we do not have efficient treatment. There were also negative trials for marker slike SMAD4, TGF-betaR1 and -R2. Real progress was achieved by introducing PARP-inhibitors (POLO-trial), based on previous experience with BRCA-positive breast cancer and ovary-tumors. POLO examined germ-line mutated PAC, which is frequent as 5–7%, and treatment was introduced after chemotherapy. NCCN recommends BRCA-testing for all patients regardless of family history of disease. There are other mutations potentially targetable, like KRAS-G12C, then BRAF mutation and KRAS-wt tumors, where positive trials phase II was conducted comparing gemctiabin + nimotuzumab compared to gemcitabine. In the last few years the subject of research are so called fusion-genes, among which the most famous one was NTRK-fusion, with specifici inhibitor – larotrectinib. This molecule was approved recently by FDA and EMA, being presented in various tumors but in very low percentage. Among other fusion genes there are ALK, RET, NRG and other fusion-genes theri is incidence of about 1%. Regarding immunogenicity of tumors, PDA is not particulary suitable for immunotherapy, for many reasons. First of all, there is immunogenicety, TMB is very low, (tumor mutational burden). On the other side, desmoplatic stroma play very acitve role creating cytokines playing important citokines which diminish immuno response. Clinical imaplication of new drugs basicaly is relied on MSI, BRCA and fusion genes, which are three

most common alteration which are at the same time „targetable". There is still open question of NGS for liquid biopsy would become more acceptable method. More attention will be paid to tumor-stroma and extracellular matrix, which have important roles in development of resistance to treatment but also on development of „passive immune cells".

## MIJENJA LI SE PARADIGMA LIJEČENJA KARCINOMA JEDNJAKA/GE SPOJA?

KEKEZ D.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
domina.kekez@gmail.com

Karcinom jednjaka je šesti najčešći uzrok smrti od tumora u svijetu. Velika većina pacijenata se i dalje prezentira u uznapredovalom stadiju bolesti, čak 39% pacijenata ima uznapredovalu bolest prilikom dijagnoze. 5-godišnje preživljenje pacijenata s karcinomom jednjaka je 19.9 %, dok je preživljenje pacijenata s meastatskom bolesti samo 5.2%. Karcinom jednjaka ima 2 histološka podtipa, adenokarcinom i skvamozni karcinom jednjaka. Predominantni histološki podtip u svijetu je skvamozni karcinom jednjaka koji na svjetskoj razini čini 80% svih karcinoma jednjaka, no inci-dencija se značajno razlikuje u regijama svijeta, te je skvamozni karcinom jednjaka puno češći u Aziji i Africi nego u zapadnim zemljama. Adenokarcinom jednjaka je predominantni tip karcinoma jednjaka u zapadnim zemljema. Skvamozni karcinom jednjaka većinom nastaje u vratnom i torakalnom dijelu jednjaka, dok adenokarcinom jednjaka najčešće nastaje u donjem dijelu jednjaka i gastroezofagealnom spoju. Rizični čimbenici za razvoj karcinoma jednjaka se razlikuju za skvamozni karcinom i adenokarcinom, no pretilost, pušenje i prekomjerno korištenje alkohola su zajednički za oba histološka podtipa. U liječenju karcinoma jednjaka bitno je znati histološki i molekularni profil tumora kako bismo bolje odabrali terapijski pristup. Standardno testiranje prije početka liječenja je HER2 status, MSI-H/dMMR i PD-L1 za adenokarcinome jednjaka, dok kod skvamoznih karcinoma je to samo PD-L1. Principi liječenja karcinoma jednjaka se razlikuju ovisno o histološkom podtipu i stadiju bolesti. Kod skvamoznih karcinoma jednjaka u stadiju I bolesti primarni terapijski izbor je operacija, dok je u stadiju II/III bolesti je to trimodalni pristup (kemoradioterapija praćena operacijom). Jedna od terapijskih opcija je također i definitivna kemoradioterapija, pogotovo u bolesnika koji nisu najbolji kandidati za operativni zahvat (smanjena kardijalna i respiratorna rezerva). CROSS studija je postavila nove temelje perioperativne kemoradioterapije, te je navedeni pristup postigao CPR (*complete patologic response*) u gotovo 50% pacijenata. U pacijenata koji ne postignu CPR nakon KRT temeljem CheckMate 577 studije primjena nivolumaba je jedna od potencijalnih novih terapijskih opcija (udvostručenje DFS-a). Bolesnici koji nakon definitivne KRT ili trimodalnog pristupa dobiju lokalni recidiv reoperacija ili reiradijacija je terapijska opcija u jednog postotka tih bolesnika. U bolesnika s metastatskim skvamoznim karcinomom jednjaka sistemska terapija je jedina terapijska opcija. U 1. liniji liječenja se koristi kemoterapija bazirana na platini i 5FU uz pembrolizumab ili nivolumab (KEYNOTE 590 i Chec-kMatte 648 studija). U 2. liniji liječenja preporuča se pembrolizmab temeljem KEYNOTE 180 i 181 studije u bolesnika sa PD-L1 CPS>10, te nivolumab na temelju ATTRACTION-3 studije. Studija RATIONELE 302 je pokazala i učinkovitost tislelizumaba u 2. liniji liječenja u usporedbi s kemoterapijom, a ESCORT studija učinkovitost camrelizumaba. U ostalih bolesnika kemoterapija docetakselom, paklitakselom ili 5-FU je opcija liječenja. Što se adenokarcinoma jednjaka /GE tiče u stadiju I bolesti, jedina opcija liječenja je kirurgija u bolesnika koji su kandidati za operativni zahvat. KRT može biti terapijska opcija kod bolesnika s komorbiditetima koji onemogućavaju kirurško liječenje, no stopa odgovora nije kao kod skvamoznih karcinoma jednjaka. U stadiju II/III perioperativna kemoterapija (FLOT4 studija) ili KRT je terapijska opcija, s tim da 75% pacijenata ne postigne CPR. Obje opcije su dobar terapijski pristup, a temeljem NEO-AEGIS studije perioperativna kemoterapija nije inferiorna KRT, a definitivan odgovor na pitanje ima li jedna prednost pred drugom dati će nam ESOPEC studija koja je u tijeku. U bolesnika koji nisu postigli CPR perioperativim pristupom moguće je dati nivolumab temeljem CheckMate 577 studije gdje su bolesnici u ispitivanoj skupini u usporedbi s placebom imali značajnije duži DFS (24.4 mj naspram 11 mj). Bolesnici s adenokarcinomom jednjaka/GE spoja češće nakon provedenog neoadjuvantnog liječenja recidiviraju sistemski nego lokalno. Standardna 1. linija liječenja bolesnika s metastatskim adenokarcinomom jednjaka /GE spoja je kemoterapija bazirana na platini i 5-FU, s tim da se oksaliplatina preferira pred cisplatinom. Ovisno o nalazu HER2 statusa uz kemoterapiju se dodaje trastuzumab. KEYNOTE 811 studija koja je u tijeku će nam dati odgovor na

pitanje hoće li dodatak pembrolizumaba kombinaciji kemoterapije i trastuzumaba donijeti korist bolesnicima. Temeljem KEYNOTE 590 studije u Europi je pembrolizumab odobren za liječenje pacijenata koji imaju PD-L1 CPS>10. CheckMate 649 studija je pokazala učinkovitost nivolumaba u bolesnika s PD-L1 CPS >5, te je odobren od FDA u ovoj indikaciji. U 2. liniji liječenja se koristi paklitaksel s ramucirumabom, a 3. linija liječenja je trifluridin/tipiracil temeljem TAGS studije. Nekoliko je novih studija koje ispituju učinkovitost imunoterapije u karcinomima jednjaka i GE spoja. ESCORT 1-st studija ispitala je učinkovitost camrelizumaba u kombinaciji s kemoterapijom u 1. liniji liječenja skvamoznog karcinoma jednjaka. Ispitivana skupina je imala statistički značajno veći OS i PFS te ORR. U tijeku su studije u 1. liniji liječenja skvamoznog karcinoma jednjaka: RATIONALE 306 (kemoterapija sa ili bez tislelizumaba) i ORIENT 15 (kemoterapija sa ili bez sintilimaba). Dobro poznavanje biomarkera nam donosi bolje razumijevanje bolesti, te bolju odluku u izboru terapijskih postupaka. Novi tumorski biomarkeri koji se ispituju za karcinom jednjaka su TMB, MSI, TIL (*tumor infiltrating lymphocites*) i GEP (T cell inflamed gene expression *profile*). Prognoza karcinoma jednjaka je loša. Bolje poznavanje biologije bolesti, multidisciplinarni pristup te daljnje studije nam potencijalno nose nove opcije za ovu skupinu bolesnika.

## IS THE PARADIGM OF ESOPHAGEAL CANCER TREATMENT CHANGING?

KEKEZ D.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
domina.kekez@gmail.com

Esophageal cancer is the sixth most common cause of tumor related death in the world. The vast majority of patients still present at an advanced stage of the disease, as many as 39% of patients have advanced disease at diagnosis. 5-year survival of patients with esophageal cancer is 19.9%, and survival of patients with meastatic disease is only 5.2%. Esophageal cancer has 2 histological subtypes, adenocarcinoma and squamous cell carcinoma of the esophagus. The predominant histological subtype in the world is squamous cell carcinoma, which accounts for 80% of all esophageal carcinomas worldwide, but the incidence varies significantly in regions of the world, and squamous cell carcinoma is much more common in Asia and Africa than in Western countries. Esophageal adenocarcinoma is the predominant type of esophageal cancer in Western countries. Squamous cell carcinoma of the esophagus mostly occurs in the cervical and thoracic part of the esophagus, while adenocarcinoma of the esophagus most often occurs in the lower part of the esophagus and the gastroesophageal junction. Risk factors for the development of esophageal cancer differ for squamous cell carcinoma and adenocarcinoma, but obesity, smoking, and alcohol abuse are common to both histological subtypes. In the treatment of esophageal cancer, it is important to know the histological and molecular profile of the tumor in order to better select a therapeutic approach. Standard pre-treatment testing is HER2 status, MSI-H / dMMR, and PD-L1 for esophageal adenocarcinomas, whereas in squamous cell carcinomas it is only PD-L1. The principles of treatment of esophageal cancer differ depending on the histological subtype and stage of the disease. In squamous cell carcinoma of the esophagus in stage I of the disease, the primary therapeutic choice is surgery, while in stage II / III of the disease it is a trimodal approach (chemoradiotherapy followed by surgery). One of the therapeutic options is also definitive chemoradiotherapy, especially in patients who are not the best candidates for surgery (reduced cardiac and respiratory reserve). The CROSS trial laid the new foundations of perioperative chemoradiotherapy, and this approach achieved CPR (complete pathological response) in almost 50% of patients. In patients who do not achieve CPR after CRT based on the CheckMate 577 trial, the use of nivolumab is one of the potential new therapeutic options (doubling of DFS). In patients who experience local recurrence after definitive CRT or a trimodal approach reoperation or reradiation is a therapeutic option in one percent of these patients. In patients with metastatic squamous cell carcinoma of the esophagus, systemic therapy is the only therapeutic option. Platinum-based and 5FU-based chemotherapy with pembrolizumab or nivolumab is used in first line treatment (KEYNOTE 590 and Check-Matte 648 trials). In the 2nd line treatment, pembrolizmab based on KEYNOTE 180 and 181 trials is recommended in patients with PD-L1 CPS> 10, and nivolumab based on the ATTRACTION-3 trial. The RATIONELE 302 trial also showed the efficacy of tislelizumab in 2nd line treatment compared to chemotherapy, and the ESCORT trial the efficacy of camrelizumab. In other patients, chemotherapy with docetaxel, paclitaxel or 5-FU is valid treatment option. For esophageal adenocarcinoma / GE junction in stage I disease, the only treatment option is surgery in patients who are candidates for surgery. CRT may be a therapeutic option in

patients with comorbidities that prevent surgical treatment, but the response rate is not the same as in squamous cell carcinoma of the esophagus. In stage II / III, perioperative chemotherapy (FLOT4 trial) or CRT is a therapeutic option, with 75% of patients not achieving CPR. Both options are valid therapeutic approach, and based on the NEO-AEGIS trial, perioperative chemotherapy is not inferior to CRT. Definitive answer to the question of whether one has an advantage over the other will be given by the ongoing ESOPEC trial. In patients who did not achieve CPR with a perioperative approach, nivolumab can be given based on the CheckMate 577 trial, where patients reciveing nivolimab had significantly longer DFS compared to placebo (24.4 months versus 11 months). Patients with esophageal adenocarcinoma / GE junction recur more often systemically than locally after neoadjuvant treatment. The standard first-line treatment for patients with metastatic esophageal adenocarcinoma / GE junction is platinum-based and 5-FU-based chemotherapy, with oxaliplatin being preferred to cisplatin. Depending on the HER2 status, trastuzumab is added to chemotherapy. The ongoing KEYNOTE 811 trial will provide an answer to the question of whether the addition of pembrolizumab to a combination of chemotherapy and trastuzumab will benefit patients. Based on the KEYNOTE 590 trial, pembrolizumab has been approved for the treatment of patients with PD-L1 CPS> 10. The CheckMate 649 trial demonstrated the efficacy of nivolumab in patients with PD-L1 CPS> 5, and was approved by the FDA in this indication. Paclitaxel with ramucirumab are used in 2nd line treatment and trifluridine / tipiracil is used in 3rd line treatment based on the TAGS trial. There are several new trials examining the efficacy of immunotherapy in esophageal and GE junction carcinomas. An ESCORT 1-st trial examined the efficacy of camrelizumab in combination with chemotherapy in the first-line treatment of squamous cell carcinoma of the esophagus. The examined group had statistically significantly higher OS, PFS and ORR. 1 st line treatments trials are underway for squamous cell carcinoma of the esophagus: RATIONALE 306 (chemotherapy with or without tislelizumab) and ORIENT 15 (chemotherapy with or without syntilimab). Good knowledge of biomarkers brings us a deeper understanding of the disease, and alows us to choose better treatnet for patients. New tumor biomarkers being tested for esophageal cancer are TMB, MSI, TIL (tumor infiltrating lymphocytes) and GEP (T cell inflamed gene expression profile). The prognosis of esophageal cancer is poor. Better knowledge of disease biology, a multi-disciplinary approach, and further studies potentially bring us new options for this group of patients.

## LITERATURA


1. *Shapiro J et al.* Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015 Sep;16(9):1090–1098. doi: 10.1016/S1470-2045(15)00040-6. Epub 2015 Aug 5.
2. *Kelly RJ et al.* Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med. 2021 Apr 1;384(13):1191–1203. doi: 10.1056/NEJMoa2032125.
3. *Kato K et al.* KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Future Oncol. 2019 Apr;15(10):1057–1066. doi: 10.2217/fon-2018-0609. Epub 2019 Feb 8.
4. *Janjigian YY et al.* First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a ran-domised, open-label, phase 3 trial. Lancet. 2021 Jul 3;398 (10294):27–40. doi: 10.1016/S0140-6736(21)00797-2. Epub 2021 Jun 5.
5. *Kojima T et al.* Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Ad-vanced Esophageal Cancer. J Clin Oncol. 2020 Dec 10;38(35):4138–4148. doi: 10.1200/JCO.20.01888. Epub 2020 Oct 7.
6. *Shah MA et al.* Efficacy and Safety of Pembrolizumab for Heavily Pretreated Patients With Advanced, Metastatic Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus: The Phase 2 KEYNOTE-180 Study. JAMA Oncol. 2019 Apr 1;5(4):546–550. doi: 10.1001/jamaoncol.2018.5441.
7. *Reynolds JV et al.* ICORG 10-14: NEOadjuvant trial in Adenocarcinoma of the oEsophagus and oesophagoGastric junction International Study (Neo-AEGIS). BMC Cancer. 2017 Jun 3;17(1):401. doi: 10.1186/s12885-017-3386-2.

## KOLOREKTALNI KARCINOM U MLAĐIH BOLESNIKA

PROŠEV J.[1], Pavlović M.[1]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
jelena.raguz89@gmail.com

Kolorektalni karcinom u mlađih bolesnika označava pojavu kolorektalnog karcinoma (CRC) u osoba mlađih od 50 godina. Iako se incidencija CRC-a smanjuje u ukupnoj populaciji, u posljednjih nekoliko desetljeća u cijelom svijetu se bilježi porast incidencije u mlađih bolesnika. U Europi najbrži porast incidencije događa se u najmlađoj dobnoj skupini od 20 do 29 godina.

Vodeći uzroci porasta incidencije CRC-a u mlađih bolesnika i dalje su nepoznati, no najvjerojatnije se mogu pripisati genetskim faktorima i stilu života. Kod mlađih bolesnika također uvijek treba razmišljati o nasljednim sindromima koji su višestruko učestaliji u ovoj skupini bolesnika (najčešći su Lynchov sindrom i familijarna adenomatozna polipoza), no oni i dalje predstavljaju samo manji broj slučajeva. Budući da se prevalencija patogenih genetskih varijanti u populaciji ne mijenja značajno tijekom vremena, samo genetski čimbenici ne bi mogli objasniti nedavni porast incidence CRC-a. Što se tiče uzroka koji potječu iz okoliša i načina života, pokazalo se da su pretilost, uz prehranu s visokim udjelom masti, te sjedilački način života, najveći čimbenici rizika. Konkretno, djeca koja su pretila u mladosti i adolescenciji imaju veći rizik od razvoja CRC-a u svom odraslom životu. Neke teorije sugeriraju da genetske promjene zajedno s nezdravim načinom života mogu uzrokovati disbalans crijevnog mikrobioma koji potom može dovesti do kronične upale, a zatim do adenoma i na kraju kolorektalnog karcinoma.

U usporedbi sa starijim bolesnicima, mladi pacijenti s CRC-om se češće prezentiraju s alarmirajućim simptomima, kao što su rektalno krvarenje, opstrukcija ili bol u trbuhu. Također, u ovoj populaciji se često ne razmišlja inicijalno o CRC-u kao potencijalnoj dijagnozi što može odgoditi dijagnostički proces. Posljedično, veći udio CRC-a u mlađih prisutan je u kasnijoj fazi.

Dokazi o ishodima i učinkovitosti specifičnih režima liječenja u CRC-a u mlađih bolesnika i dalje su oskudni. Kao liječnici, suočeni smo s dilemom hoćemo li liječiti agresivno kako bismo postigli najbolji rezultat ili umjereno liječiti pacijenta i osigurati mu najbolju moguću kvalitetu života, s obzirom na to da većina mladih pacijenata s CRC-om ima obitelj, puno radno vrijeme i društveni život koji žele zadržati. Nekoliko je studija izvijestilo da je vjerojatnije da će se mladi pacijenti liječiti adjuvantnom kemoterapijom bez obzira na prisutnost udaljenih metastaza, ali nije bilo značajnog poboljšanja preživljavanja u odnosu na starije bolesnike. Na temelju retrospektivnih opservacijskih studija nije jasno je li trenutna klinička praksa sklona preagresivnom liječenju mlađih pacijenata s CRC-om u usporedbi s njihovim starijim bolesnicima (uz marginalnu korist) ili bi temeljna biologija CRC-a kod mlađih mogla biti agresivnija i zahtijevati agresivnije liječenje kako bi se optimizirali ishodi. Za sada niti jedna smjernica ne preporučuje izmjenu liječenja CRC-a na temelju mlađe dobi, a potrebne su dodatne prospektivne studije i randomizirana klinička ispitivanja kako bi se odredile optimalne sheme liječenja za mlađe pacijente.

Trenutno se istražuju budući pravci vezani uz određene mogućnosti liječenja. Nedavna opažanja također ističu značajnu razliku u stopi mutacija tumora uključenih u metilaciju i demetilaciju histona koje igraju važnu ulogu u patogenezi CRC a. S boljim razumijevanjem molekularnih razlika između CRC-a u mlađih i u starijih bolesnika, možda će biti moguće iskoristiti određene molekularne promjene za modificiranje liječenja u ovoj sobnoj skupini.

## COLORECTAL CANCER IN YOUNG ADULTS

PROŠEV J.[1], Pavlović M.[1]

[1] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*
jelena.raguz89@gmail.com

Young-onset CRC (yCRC), defined as CRC diagnosed in individuals younger than age 50, is a heterogeneous disease [1]. While the incidence of colorectal cancer (CRC) is declining in the overall population, over the last few decades there has been an increase in the incidence of yCRC worldwide. In Europe, the fastest rise in inci-

dence occurs in the youngest age group 20–29 [2]. The underlying cause(s) for the rise in incidence of yCRC remains unknown but it can most probably be attributed to genetic and lifestyle factors. Although germline genetic alterations can be implicated in one in five individuals with yCRC, hereditary syndromes (most often Lynch syndrome and familiar adipose polipose) account for only a minority of cases. Since the prevalence of pathogenic variants in a population does not change significantly over time, genetic factors alone would not explain the recent increase in CRC incidence. As for environmental and lifestyle causes, obesity along with high fat diet and sedentary living have been shown to be the highest risk factors for yCRC [3,4]. Specifically, children who are obese through young age and adolescence have a higher risk of developing yCRC in their adult life [4]. Some theories suggest that genetic alterations together with unhealthy lifestyle can cause to gut dysbiosis which can lead to chronic inflammation and then to adenomas and eventually colorectal cancer [5]. When compared to their older patients, young CRC patients tend to have a higher rate alarming symptoms, such as rectal bleeding, obstruction, or abdominal pain [5,8]. Failure to consider CRC as a potential diagnosis often delays the diagnostic process-Consequently, a higher proportion of yCRCs present at a later stage [6]. Evidence regarding outcomes and effectiveness of specific treatment regimens in yCRC remains unclear. At the moment, no evidence-based age-specific treatment regimens exist for CRC, although some recent reports do suggest differences in treatment outcomes between yCRC and older-onset CRC. As physicians we are encountered with the dilemma whether to treat aggressively in order to obtain the best result or to treat moderately a patient and ensure they have a best possible quality of life considering that the majority of patients with yCRC have a family, full time job and social life they want to keep. Several studies have reported that young patients are more likely to be treated with adjuvant chemotherapy regardless of the presence of distant metastases, but there was no significant improvement in survival compared to their older counterparts. Based on retrospective observational studies, it is unclear whether current clinical practice tends toward overtreatment of yCRC patients compared to their older counterparts (with marginal benefit) or whether the underlying biology of yCRCs may be more aggressive, requiring more aggressive treatment to match outcomes [7]. Currently, no guidelines recommend modifying CRC treatments based on young age and additional prospective studies and randomized clinical trials are needed to determine the optimal treatment regiments for younger patients. Specific treatment options for this group of patients are currently being explored. Several recent observations also highlight a possible difference in tumor mutation rates involved in histone methylation and demethylation which may play an important role in CRC pathogenesis [8]. With a better understanding of the molecular differences between yCRC and their older counterparts, it may be possible to exploit specific molecular alterations for the treatment of yCRC.

## LITERATURA


1. *Siegel RL, Miller KD, Fedewa SA i sur.* Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177–93
2. *Vuik FE, Nieuwenburg SA, Bardou M i sur.* Increasing incidence of colorectal cancer in young adults in Europe over the last 25 yearsGut 2019;68:1820–1826.
3. *Hidayat K, Yang CM, Shi BM.* Body fatness at an early age and risk of colorectal cancer. Int J Cancer. 2018;142(4):729–40.
4. *Rosato V, Bosetti C, Levi F i sur.* Risk factors for young-onset colorectal cancer. Cancer Causes Control. 2013;24(2):335–41.
5. *Saus E, Iraola-Guzmán S, Willis JR, Brunet-Vega A, Gabaldón T.* Microbiome and colorectal cancer: Roles in carcinogenesis and clinical potential. Mol Aspects Med. 2019 Oct;69:93–106.
6. *Chen FW, Sundaram V, Chew TA, Ladabaum U.* Advanced-stage colorectal cancer in persons younger than 50 years not associated with longer duration of symptoms or time to diagnosis. Clin Gastroenterol Hepatol. 2017;15(5):728–37.
7. *Manjelievskaia J, Brown D, Mc Glynn KA, Anderson W, Shriver CD, Zhu K.* Chemotherapy use and survival among young and middle-aged patients with colon cancer. JAMA Surg. 2017;152(5):452–9. 8. Gargalionis AN, Piperi C, Adamopoulos C, Papavassiliou AG. Histone modifications as a pathogenic mechanism of colorectal tumorigenesis. Int J Biochem Cell Biol. 2012;44(8):1276–89.

## KARCINOM REKTUMA – PRIKAZ SLUČAJA – ŠTO JE "OPTIMALNO" U LOKALNOJ/LOKALNO UZNAPREDOVALOJ BOLESTI

GORŠIĆ I.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
irmagoo@gmail.com

**Uvod**: Rak debelog i završnog crijeva je najčešći novodijagnosticirani rak u Hrvatskoj 2020. godine (3706 novih slučajeva). Po smrtnosti je na drugome mjestu s 2320 slučaja. Rizični čimbenici za nastanak kolorektalnog karcinoma, osim upalnih bolesti crijeva i nasljedne predispozicije, uključuju pušenje, konzumaciju crvenog i prerađenog mesa, alkohola, dijabetes, metabolički sindrom i pretilost. Optimalno zbrinjavanje ovih bolesnika zahtjeva pažljivo planiranje terapijskih i dijagnostičkih postupaka te multidisciplinarni pristup bolesniku. Od posebne je važnosti tim bolesnicima, uz liječenje karcinoma, očuvati funkciju i kontinuitet crijeva, analnu kontinenciju kao i prezervaciju genitourinarnih funkcija. Zbog svega navedeng potrebna je pažljiva selekcija bolesnika i korištenje sekvencijske, multimodalne terapije koja uključuje kemoterapiju, radioterapiju i kirurško liječenje.

**Prikaz slučaja**: bolesniku od 63 godine endoskopski je verificiran karcinom rektuma na 5–10 cm od anokutane granice. Patohistološki je potvrđen adenokarcinom. Učinjenom obradom isključena je metastatska bolest, nađena je fibroza u području mokraćnog mjehura i vezikoureteralnog ušća desno. Posljedično prisutna i desnostrana hidronefroza zbog koje je postavljena pijelonefrostoma. Prema magnetskoj rezonanci (MR) zdjelice radi se o T4N0 stadiju bolesti uz infiltraciju mezorektalne fascije, seminalnih vezikula i dorzalne konture mokraćnog mjehura. Provedena je neoadjuvantna kemoradioterapija (long course). Učinjena je kontrolna MR zdjelice prema kojoj postoji smanjenje tumorskog procesa rektuma uz i dalje pristunu infiltraciju mezorektalne fascije i progresiju infiltracije mokraćnog mjehura. Cistoskopski viđena infiltracija mokraćnog mjehura izvana. Učinjena je operacija po Milesu, prostatektomija, cistektomija i ileostoma po Brickeru. Prema nalazu patologa radilo se o kompletnom odgovoru na neoadjuvantno liječenje.

**Zaključak**: inicijalni terapijski plan valja redovito revidirati u okviru multidisciplinarnog tima te ga modificirati sukladno reevaluacijskim nalazima. S obzirom na nove spoznaje, paradigma liječenja ovih bolesnika se polako, ali sigurno mijenja.

## RECTAL CANCER – CASE REPORT – WHAT IS „OPTIMAL" IN LOCAL/LOCALLY ADVANCED DISEASE

GORŠIĆ I.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
irmagoo@gmail.com

**Introduction**: Colon and rectal cancer is the most common newly diagnosed cancer in Croatia in 2020 (3706 new cases). In terms of mortality, it is in second place with 2320 cases. Risk factors for developing colorectal cancer, in addition to inflammatory bowel disease and hereditary predisposition, include smoking, consumption of red and processed meat, alcohol, diabetes, metabolic syndrome, and obesity. Optimal care for these patients requires careful planning of therapeutic and diagnostic procedures and a multidisciplinary approach to the patient. It is of particular importance for these patients, in addition to cancer treatment, to ensure bowel function and continuity, anal continence as well as the preservation of genitourinary functions in these patients. All of the above requires careful patient selection and the use of sequential, multimodal therapy that includes chemotherapy, radiotherapy, and surgical treatment.

**Case report**: A 63-year-old patient was endoscopically verified for rectal cancer 5–10 cm from the anal verge. Adenocarcnioma has been confirmed by pathologic report. The radiological evaluation ruled out metastatic disease, but fibrosis was found in the area of the bladder and vesicoreteral junction on the right. Consequently, right-sided hydronephrosis was found, due to which a pyelonephrostomy was placed. According to magnetic resonance (MR) of the pelvis, it was T4N0 stage of the disease with infiltration of the mesorectal fascia, seminal

vesicles and the dorsal contour of the bladder. Neoadjuvant chemoradiotherapy (long course) was performed. A control MR of the pelvis was performed, according to which there is a reduction in the tumor process of the rectum with still present infiltration of the mesorectal fascia and progression of bladder infiltration. Cystoscopically, infiltration of the bladder from the outside was found. The patient underwent Miles surgery, prostatectomy, cystectomy and ileostomy (Bricker procedure). According to the pathologist's findings, there was a complete response to neoadjuvant treatment.

**Conclusion**: The initial therapeutic plan should be regularly revised within the multidisciplinary team and modified in accordance with the re-evaluation findings. Given the new data, the treatment paradigm of these patients is slowly but surely changing.

## IMUNOTERAPIJA GI TUMORA

PREJAC J.[1, 2]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Sveučilište u Zagrebu
• *Stomatološki fakultet*
juraj.prejac@gmail.com

Postoji velika razlika između imunoterapije i konvencionalne terapije, ponajviše određena visokom specifičnošću imunoterapije prema tumorskim antigenima. U posljednje vrijeme uspjeh imunoterapije u liječenju karcinoma postupno iz temelja mijenja terapijski pristup. U tom pogledu sve više obećava takav oblik liječenja i tumora probavnog sustava, poglavito u bolesnika s bolesti otpornom na kemoterapiju.[1,2] Glavna podijela tumora probavnog sustava uključuje karcinom jednjaka, želuca, gušterače, jetre i žučnih vodova te debelog crijeva, a pojam "imunoterapija" obuhvaća monoklonska protutijela u koja pripadaju inhibitori kontrolne točke, nadalje cjepiva, citokini i adoptivna stanična terapija. Inhibitori kontrolne točke najzastupljeniji su u kliničkoj praksi ipodrazumjevaju klasu protutijela koja blokira inhibiciju signalnih puteva posrednovanih PD-1, PD-L1 te CTLA-4. Karcinom jednjaka i želuca Pembrolizumab je odobren od FDA za liječenje karcinoma želuca nakon progresije na standardne linije liječenja temeljem rezultata ispitivanja KEYNOTE-059, dokje nivolumab odobren za prethodno liječene tumore u Japanu nakon ishoda ATTRACTION-2 [3]. Učinak pembrolizumaba istražen je nizom KEYNOTE studija kod raka jednjaka. KEYNOTE-180, ispitivanje faze II, bilo je prvo koje se usredotočilo na karcinom jednjaka i gastroezofagealnog spoja i uključilo 121 bolesnika s napredovanjem metastatskim rakom jednjaka. ORR je iznosio 9,9% (95% CI, 5,2–16,7%) uz djelomičan odgovor kod svih bolesnika. Medijan OS bio je 5,8 mjeseci i stopa 6-mjesečnog i 12-mjesečnog OS bila je 49%, odnosno 28%. [4] Nakon toga uslijedilo je KEYNOTE-181, ispitivanje faze III djelotvornosti pembrolizumaba kao agensa druge linije u uznapredovalom karcinomu jednjaka u odnosu na standardnu kemoterapiju pokazalo je značajnu u OS, osobito u PD-L1 pozitivnom tumorima [5]. KEYNOTE-590 kombinira pembrolizumab s kemoterapijom nasuprot standardne kemoterapije u prvoj liniji [6]. Checkmate-032 studija dokazala je da je kombinacja ipilimumaba s nivolumabom učinkovitija od monoterapije nivolumabom za liječenje uznapredovalih tumora gornjeg dijela probavnog sustava, uključujući jednjak. [7] ATTRACTION-2 pokazala je korist nivoulumaba u odnosu na placebo u ranije liječenih bolesnika [8], dok je ATTRACTION-3usporedila nivolumab s standarndom kemoterapijom za refraktorni karcinom jednjaka i pokazala značajno poboljšanje preživljavanja (medijan OS 10,9 mjeseci naspram 8,4 mjeseca) [9] U tijeku su brojna ispitivanja kako bi se ispitala učinkovitost različitih dostupnih imunoterapija. KEYNOTE-062 ukazuje na korist od upotrebe pembrolizumaba zajedno s kemoterapijom na bazi platine u prvoj liniji liječenja. Međutim, još jedno ispitivanje, KEYNOTE-061, koje testira pembrolizumab u odnosu na paklitaksel nije uspio postići superiornost u OS i PFS.[3] Kolorektalni karcinom U početku su inhibitori kontrolne točke imali ograničen uspjeh u CRC. U ispitivanju faze I PD-1 inhibitora nivolumaba na 14 bolesnika pokazao je trajan potpuni odgovor u samo jednom bolesniku [10]. Daljnjim ispitivanjima dokazano je da odgovor na nivolumab pokazuju tumori koji su dMMR/MSI-H. Tako su u ispitivanju CheckMate-142, 74 bolesnika s dMMR/MSI-H metastatskim CRC liječenih nivolumabom, postigli zadovoljavajuću kontrolu bolesti i dugotrajan odogovor na terapiju (31% pacijenata sa objektivnim odgovorom i 69% s kontrolom bolesti nakon 12 mjeseci) [11]. Rezultati su bili ohrabrujući i u istraživanju kombinacije PD-1/CTLA-4 kombinacije sa stopom preživljavanja bez progresije od 71% u 12 mjeseci te kontrolom bolesti od 80% tijekom više od 12 tjedana [12]. Slične pozitivne rezultate ostvario

je i pembrolizumab u skupini bolesnika s dMMR/MSI-H tumorima [13]. Najznačajniji rezultati dolaze iz studije prve linije liječenja, KEYNOTE-177 koja je ispitivala pembrolizumab u odnosu na standardnu kemoterapiju. Pembrolizumab se pokazao boljim od kemoterapije u vidu PFS (medijan 16,5 mjeseci naspram 8,2 mjeseca; HR 0,60). Stope PFS-a nakon 12 i 24 mjeseca bile su 55,3% i 48,3% u korist pembrolizumaba naspram 37,3% i 18,6% u grani s kemoterapijom. ORR iznosio je 43,8% naspram 33,1% [14]. Inhibicija kontrolne točke ima ograničenu aktivnost u mikrosatelitski stabilnim (MSS) tumorima zbog čega se istrauju različite kombinacije kao što je kombiniranje regorafeniba i nivolumaba uz ORR-om od 29% [15]. Karcinom gušterače Karcinom gušterače predstavlja najveći izazov za imunoterapiju od svih probavnih tumora. Smatra se da je to posljedica nedostatka imunogenosti, niskog mutacijskog opterećenja u kombinaciji s jedinstvenim vaskularnim i stromanim mikrookruženjem [16]. Odgovori na inhibitore kontrolnih točaka, osobito monoterapiju su razočaravajući. Ipilimumab je testiran u ispitivanju faze II na 20 bolesnika, bez objektivnog odgovora [17]. Slično se pokazalo i u kasnijim studijama pembrolizumaba [18] kao i kod kombinacijskih terapija. Durvalumab, u kombinaciji s tremelimumabom, testiran je protiv monoterapije durvalumabom uz nešto bolji OS od 3,6 mjeseci u odnosu na 3,1 mjesec. [19] Zanimljiva je, međutim, populacija MSI-H. Kao i kod raka debelog crijeva, bolesnici s rakom gušterače koji je MSI-H/dMMR mogu biti populacija koja će odogovriti na inhibitore kontrolne točke. Nažalost, ovo stanovništvo čini samo do 3% ukupne populacije [20]. Hepatocelularni karcinom Jetra ima jedinstven imunološki mikrookoliš sa brojnim stanicama koje prezentiraju antigen (uključujući sinusoidne endotelne stanice jetre) u dobro vaskulariziranoj stromi. Unatoč tome, međutim, u jetri dominiraju signali koji suprimiraju imunološki odgovor [21]. Imunosupresivno mikrookruženje čini inhibiciju kontrolne točke privlačnom metom za imunoterapiju HCC-a. Mještovit je uspjeh kada je korišten jedan agens. CheckMate-040 pokazala je učinkovitost nivolumaba s ORR-om od 20% [22]. CheckMate-459 usporedio je nivolumab sa sorafenibom u prvoj liniji (ORR 15% naspram 7%) no unatoč poboljšanom ORR–u nije postignut statistički značaj u poboljšanju OS [23]. Drugi inhibitor PD-1, pembrolizumab, testiran je u KEYNOTE-240. Unatoč postizanju ORR-a od 17%, studija nije uspjela zadovoljiti glavne ciljeve OS-a i PFS-a. [24]. U tijeku su kombinirane terapije koje uključuju inhibiciju PD-1 i CTLA-4 istraženo u tekućim ispitivanjima (HIMALAYA) [25]. U ovom trenutku kao standard prve linije liječenja HCC-a je kombinacija atezolizumaba (anti PD-L1) i bevacizumaba (anti VEGF). Navedena kombinacije odobrena je globalno za bolesnike s neresektabilnom HCC koji nisu primili prethodnu sustavnu terapiju, na temelju rezultata IMbrave150. Nakon medijana od 8,6 mjeseci praćenja, ispunjena su oba primarna cilja, pri čemu su statistički i klinički značajna bolji OS (HR 0,58) i PFS (HR 0,59) uočeni kod atezo + bev u odnosu na sorafenib. [26] Karcinomi žučnog stabla Trenutne dostupne terapijske opcije su ograničene učinkovitosti, a određeni uspjeh može se očekivati u MSI-H populaciji [27]. Inhibicija kontrolne točke pembrolizumabom ispitivana je u KEYNOTE-028 za bolesnik s PD-L1 ekspresijom. Od 24 pacijenta, 4 je postiglo djelomičan odgovor, a 4 su imali stabilnu bolest. [28,29]. KEYNOTE-158 nastavlja istraživati pembrolizumab kolangiocelularnom karcinomu [29]. Nivolumab je također testiran kao monoterapija sa sličnim rezultatima – od 29 ispitanih pacijenata 5 je postiglo djelomičan odgovor, as 11 pacijenata stabilnu bolest [30]. Kao i kod HCC-a, kombinacije su danas predmet istraživanja.

## IMMUNOTHERAPY OF GI TUMORS

PREJAC J.[1,2]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] University of Zagreb
• *School of Dental Medicine*
juraj.prejac@gmail.com

There is a great difference between immunotherapy and conventional therapy, mostly determined by the high specificity of immunotherapy against tumor antigens. Recently, the success of immunotherapy in the treatment of cancer has gradually fundamentally changed the therapeutic approach. In this regard, such a form of treatment and tumors of the digestive system is increasingly promising, especially in patients with chemotherapy-resistant diseases. [1,2] The main divisions of gastrointestinal tumors include cancer of the esophagus, stomach, pancreas, liver, bile ducts, and colon, and the term "immunotherapy" includes monoclonal antibodies that include checkpoint inhibitors, including vaccines, cytokines, and adoptive cell therapy. Checkpoint inhibitors are

the most common in clinical practice and involve a class of antibodies that block the inhibition of PD-1, PD-L1 and CTLA-4-mediated signaling pathways. Oesophageal and gastric cancer Pembrolizumab was approved by the FDA for the treatment of gastric cancer after progression to standard lines of treatment based on the results of the KEYNOTE-059 trial, while nivolumab was approved for previously treated tumors in Japan after the outcome of ATTRACTION-2.[3] The effect of pembrolizumab has been investigated by a series of KEYNOTE studies in esophageal cancer. KEYNOTE-180, a phase II study, was the first to focus on esophageal and gastroesophageal junction cancer and included 121 patients with advanced metastatic esophageal cancer. The ORR was 9.9% (95% CI, 5.2–16.7%) with a partial response in all patients. The median OS was 5.8 months and the 6-month and 12-month OS rates were 49% and 28%, respectively. [4] This was followed by KEYNOTE-181, a phase III study of the efficacy of pembrolizumab as a second-line agent in advanced esophageal cancer compared to standard chemotherapy showed significant in OS, especially in PD-L1-positive tumors [5]. KEYNOTE-590 combines pembrolizumab with chemotherapy versus standard first-line chemotherapy [6]. A Checkmate-032 study demonstrated that the combination of ipilimumab with nivolumab was more effective than nivolumab monotherapy for the treatment of advanced tumors of the upper gastrointestinal tract, including the esophagus. [7] ATTRACTION-2 showed a benefit of nivolumab over placebo in previously treated patients [8], while ATTRACTION-3 compared nivolumab with standard chemotherapy for refractory esophageal cancer and showed a significant improvement in survival (median OS 10.9 months versus 8, 4 months) [9] Numerous trials are underway to examine the effectiveness of the various immunotherapies available. KEYNOTE-062 indicates the benefit of using pembrolizumab in combination with platinum-based chemotherapy in first-line treatment. However, another study, KEYNOTE-061, testing pembrolizumab over paclitaxel failed to achieve superiority in OS and PFS. [3] Colorectal cancer Initially, checkpoint inhibitors had limited success in CRC. In a phase I study of PD-1 inhibitor nivolumab in 14 patients, it showed a sustained complete response in only one patient [10]. Further studies have shown that the response to nivolumab is shown by tumors that are dMMR / MSI-H. Thus, in the CheckMate-142 study, 74 patients with dMMR / MSI-H metastatic CRC treated with nivolumab achieved satisfactory disease control and long-term response to therapy (31% of patients with objective response and 69% with disease control after 12 months) [11]. The results were also encouraging in a study of the PD-1 / CTLA-4 combination with a progression-free survival rate of 71% at 12 months and disease control of 80% over more than 12 weeks [12]. Similar positive results were achieved with pembrolizumab in the group of patients with dMMR / MSI-H tumors [13]. The most significant results come from a first-line treatment study, KEYNOTE-177 that examined pembrolizumab versus standard chemotherapy. Pembrolizumab was shown to be better than chemotherapy in the form of PFS (median 16.5 months versus 8.2 months; HR 0.60). PFS rates after 12 and 24 months were 55.3% and 48.3% in favor of pembrolizumab, respectively, versus 37.3% and 18.6% in the chemotherapy arm. The ORR was 43.8% versus 33.1% [14]. Checkpoint inhibition has limited activity in microsatellite-stable (MSS) tumors, leading to various combinations such as the combination of regorafenib and nivolumab with a 29% ORR [15]. Pancreatic cancer Pancreatic cancer is the biggest challenge for immunotherapy of all digestive tumors. This is thought to be due to a lack of immunogenicity, a low mutational load combined with a unique vascular and stromal microenvironment [16]. Responses to checkpoint inhibitors, particularly monotherapy, are disappointing. Ipilimumab has been tested in a phase II study in 20 patients without an objective response [17]. Similar results were shown in later studies of pembrolizumab [18] as well as in combination therapies. Durvalumab, in combination with tremelimumab, was tested against durvalumab monotherapy with a slightly better OS of 3.6 months compared with 3.1 months. [19] However, the MSI-H population is interesting. As with colon cancer, patients with pancreatic cancer who have MSI-H / dMMR may be a population that will respond to checkpoint inhibitors. Unfortunately, this population makes up only up to 3% of the total population [20]. Hepatocellular carcinoma The liver has a unique immune microenvironment with numerous antigen-presenting cells (including sinusoidal endothelial cells of the liver) in a well-vascularized stroma. Nevertheless, however, the liver is dominated by signals that suppress the immune response [21]. The immunosuppressive microenvironment makes checkpoint inhibition an attractive target for HCC immunotherapy. Successful success is when one agent is used. CheckMate-040 showed an efficacy of nivolumab with an ORR of 20% [22]. CheckMate-459 compared nivolumab with first-line sorafenib (ORR 15% vs. 7%) but despite improved ORR, no statistical significance was achieved in OS improvement [23]. Another PD-1 inhibitor, pembrolizumab, was tested in KEYNOTE-240. Despite achieving an ORR of 17%, the study failed to meet the main objectives of the OS and PFS. [24]. Combination therapies involving inhibition of PD-1 and CTLA-4 are under investigation in ongoing trials (HIMALAYA) [25]. At present, the standard of first-line HCC treatment is a combination of atezolizumab (anti PD-L1)

and bevacizumab (anti VEGF). The above combination was approved globally for patients with unresectable HCC who had not received prior systemic therapy, based on IMbrave150 results. After a median of 8.6 months of follow-up, both primary targets were met, with statistically and clinically significant better OS (HR 0.58) and PFS (HR 0.59) observed with atezo + bev compared to sorafenib. [26] Biliary tract cancer The currently available therapeutic options are of limited efficacy, and some success can be expected in the MSI-H population [27]. Pembrolizumab checkpoint inhibition was tested in KEYNOTE-028 for a patient with PD-L1 expression. Of the 24 patients, 4 achieved a partial response and 4 had stable disease. [28,29]. KEYNOTE-158 continues to investigate pembrolizumab cholangiocellular carcinoma [29]. Nivolumab has also been tested as monotherapy with similar results – out of 29 patients examined, 5 achieved a partial response and 11 patients a stable disease [30]. As with HCC, combinations are the subject of research today.

## LITERATURA


1. *Hazama S, Tamada K, Yamaguchi Y i sur.* Current status of immunotherapy against gastrointestinal cancers and its biomarkers: perspective for precision immunotherapy. Ann Gastroenterol Surg 2018;2:289–303.
2. *Grierson P, Lim K-H, Amin M.* Immunotherapy in gastrointestinal cancers. J Gastrointest Oncol 2017;8:474–84.
3. *Taghizadeh H, Lampichler K, Beer A, Preusser M, Ilhan-Mutlu A.* A case report of pseudo-progression after pembrolizumab in metastatic gastric cancer and a review of immunotherapy in gastroesophageal tumors. Memo – Mag European Med Oncol 2019; 12:51–9.
4. *Shah MA, Kojima T, Hochhauser D i sur.* Efficacy and safety of pembrolizumab for heavily pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: the phase 2 KEYNOTE-180 study. JAMA Oncol 2019;5:546–50.
5. *Kojima T, Muro K, Francois E i sur.* Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: Phase III KEYNOTE-181 study. J Clin Oncol 2019;37:2–.
6. *Kato K, Shah MA, Enzinger P i sur.* KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Future Oncol 2019;15:1057–66.
7. *Janjigian YY, Bendell J, Calvo E i sur.* CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. J Clin Oncol 2018;36:2836–44.
8. *Kang YK, Boku N, Satoh T i sur.* Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:2461–71.
9. *Kato K, Cho BC, Takahashi M i sur.* Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:1506–17.
10. *Topalian SL, Hodi FS, Brahmer JR i sur.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.
11. *Overman MJ, McDermott R, Leach JL i sur.* Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182–91.
12. *Overman MJ, Lonardi S, Wong KYM i sur.* durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 2018;36:773–9.
13. *Le DT, Uram JN, Wang H i sur.* PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.
14. *Shiu K-K, Andre T, Kim TW i sur.* KEYNOTE-177: Phase III randomized study of pembrolizumab versus chemotherapy for microsatellite instability-high advanced colorectal cancer. Journal of Clinical Oncology 2021 39:3_suppl, 6–6
15. *Fukuoka S, Hara H, Takahashi N i sur.* Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): An open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO, EPOC1603). J Clin Oncol 2019;37:2522–.
16. *Torphy RJ, Zhu Y, Schulick RD.* Immunotherapy for pancreatic cancer: Barriers and breakthroughs. Ann Gastroenterol Surg 2018;2:274–81.
17. *Royal RE, Levy C, Turner K i sur.* Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010;33:828–33.
18. *Brahmer JR, Tykodi SS, Chow LQ i sur.* Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455–65.
19. *O'Reilly EM, Oh D-Y, Dhani N i sur.* A randomized phase 2 study of durvalumab monotherapy and in combination with tremelimumab in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): ALPS study. J Clin Oncol 2018;36:217
20. *Le DT, Durham JN, Smith KN i sur.* Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409–13.
21. *Johnston MP, Khakoo SI.* Immunotherapy for hepatocellular carcinoma: Current and future. World J Gastroenterol 2019;25:2977–89.
22. *Kudo M, Matilla A, Santoro A i sur.* Checkmate- 040: Nivolumab (NIVO) in patients (pts) with advanced hepatocellular carcinoma (aHCC) and Child-Pugh B (CPB) status. J Clin Oncol 2019;37:327–.

23. *Yau T, Park JW, Finn RS i sur.* CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Ann Oncol 2019;30:v874–5.
24. *Finn RS, Ryoo B-Y, Merle P i sur.* Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). J Clin Oncol 2019;37:4004–.
25. *Abou-Alfa GK, Chan SL, Furuse J i sur.* A randomized, multicenter phase 3 study of durvalumab (D) and tremelimumab (T) as first-line treatment in patients with unresectable hepatocellular carcinoma (HCC): HIMALAYA study. J Clin Oncol 2018;36:TPS4144-TPS.
26. *Finn RS, Qin S, Ikeda M i sur.* IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894–1905.
27. *Saeed A, Park R, Al-Jumayli M, Al-Rajabi R, Sun W.* Biologics, immunotherapy, and future directions in the treatment of advanced cholangiocarcinoma. Clin Colorectal Cancer 2019;18:81–90.
28. *Alley EW, Lopez J, Santoro A i sur.* Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncol 2017;18:623–30.
29. *Bang Y-J, Ueno M, Malka D i sur.* Pembrolizumab (pembro) for advanced biliary adenocarcinoma: Results from the KEYNOTE-028 (KN028) and KEYNOTE-158 (KN158) basket studies. J Clin Oncol 2019;37:4079.
30. *Kim R, Kim D, Alese O i sur.* O-009A Phase II multi institutional study of nivolumab in patients with advanced refractory biliary tract cancers (BTC). Ann Oncol 2018;29.

# SEKCIJA UROGENITALNIH TUMORA / UROGENITAL CANCER SESSION

## GENOMSKO PROFILIRANJE U KARCINOMU PROSTATE

GRUBIŠIĆ-ČABO F.[1]

[1] Opća bolnica Šibenik
• *Odjel interne medicine*
fgrubisic@yahoo.com

Karcinom prostate je drugi najčešći rak kod muškaraca prema podacima GLOBOCAN-a, baze podataka Svjetske zdravstvene organizacije. Svrstava se u zloćudne novotvorine kod kojega genetska predispozicija igra značajnu ulogu u nastanku bolesti.1 Različitost naravi karcinoma prostate očituje se u mogućnosti postojanja kako indolentne tako i vrlo agresivne bolesti; pojavnosti multifokalnosti raka unutar prostate u 80% oboljelih; postojanju inter i intratumoralne heterogenosti te činjenicom kako metastaze pokazuju, kao i primarni tumor, genomsku i fenotipsku heterogenost. S obzirom na genetsko naslijeđe možemo podijeliti oboljele od karcinoma prostate u 3 grupe. U prvoj grupi pripadaju bolesnici oboljeli od hereditarnog raka, koji se javlja u 5–10% slučajeva, nastao mutacijom (varijacijom) univerzalnih gena za popravak dvostrukih lomova deoksiribonukleinskih kiselina (DNK), a tipično su prisutne varijacije gena BRCA1, BRCA2, ATM, CHEK2, PALB2. Najčešća je, među navedenim, varijacija BRCA2 gena. Osim navedenih i varijacije reparatornih gena MLH1, MSH2, MSH6, PMS2 dovode do povećanog rizika od nastanka raka prostate, a kao posebno rizična se izdvaja varijacija gena HOXB13. U drugu grupu pripadaju oboljeli od raka prostate, gdje se ne može utvrditi točna genetska varijacija koja je dovela do pojave raka, ali se ipak rak prostate češće javlja u obitelji oboljelih. U tu grupu pripada otprilike 15–20% od svih oboljelih od raka prostate. U treću grupu, 70–80% od svih oboljelih, karcinom prostate nastaje sporadično te članovi obitelji nemaju višu incidenciju pojavnosti ove bolesti. Prema Hopkinsovi kriterijima za hereditarnost, nastali karcinom prostate mora imati jedan od 3 obilježja kako bi se mogao držati hereditarnim, i to: a) 3 ili više oboljelih rođaka u „ prvom koljenu“ (otac, brat,sin); b) Oboljeli rođaci u 3 uzastopne generacije s majčine ili očeve strane te c) najmanje dvoje rođaka koji su oboljeli u dobi od 55 godina ili mlađi.2 Osim nasljednih varijacija gena, koje onda zahvaćaju sve stanice u tijelu te se prenose s generacije na generaciju, varijacije gena mogu nastati i tijekom života, kada se nazivaju somatske, a otkrivaju se u samom tumoru. Sukladno činjenici kako rastom tumora nastaju dodatne varijacije gena, utvrdilo se postojanje varijacija rekombinantnih gena u oko 5% oboljelih od lokaliziranog raka prostate te 12% oboljelih od metastatke bolesti.3 Prema smjernicama evropskog društva za medicinsku onkologiju indicirano je genetsko profiliranje u metastatskoj bolesti, dok „američke“ smjernice preporučavaju i genetsko profiliranje u nemetastatskoj bolesti ukoliko se radi o karcinomu visokog

rizika, odnosno tamo gdje postoji učestala pojava karcinoma u obitelji. Već danas nalazi dobiveni određivanjem genomike karcinoma prostate mogu nam poslužiti i prije postavljanja dijagnoze, u smislu procjene rizika od nastanka bolesti, a jednako tako i nakon postavljanja dijagnoze, svojom mogućom prognostičkom i prediktivnom vrijednošću.

## GENOMIC PROFILING IN PROSTATE CANCER

GRUBIŠIĆ-ČABO F.[1]

[1]General Hospital Šibenik
• *Department of Internal Medicine*
fgrubisic@yahoo.com

Prostate cancer is the second most common cancer in men, according to GLOBOCAN, the World Health Organization's database. It is classified as a malignant neoplasm in which genetic predisposition plays a significant role in the development of the disease.[1] The diversity of the nature of prostate cancer is manifested in the possibility of the existence of both indolent and very aggressive diseases; the incidence of multifocal cancer within the prostate in 80% of patients; the existence of inter and intratumoral heterogeneity and the fact that metastases show, as well as the primary tumor, genomic and phenotypic heterogeneity. Given the genetic inheritance, we can divide patients with prostate cancer into 3 groups. The first group includes patients with hereditary cancer, which occurs in 5–10% of cases, caused by mutation (variation) of universal genes for the repair of double breaks of deoxyribonucleic acids (DNA), and typically there are variations of genes BRCA1, BRCA2, ATM, CHEK2, PALB2. The most common, among the above, is a variation of the BRCA2 gene. In addition to the above, variations in the reparative genes MLH1, MSH2, MSH6, PMS2 lead to an increased risk of prostate cancer, and variation of the HOXB13 gene is particularly risky. The second group includes patients with prostate cancer, where the exact genetic variation that led to the appearance of cancer cannot be determined, but still prostate cancer occurs more often in the family of patients. Approximately 15–20% of all prostate cancer patients belong to this group. In the third group, 70–80% of all patients, prostate cancer occurs sporadically and family members do not have a higher incidence of this disease. According to the Hopkins criteria for heredity, the resulting prostate cancer must have one of 3 characteristics in order to be considered hereditary, namely: a) 3 or more affected relatives in the "first generation" (father, brother, son); b) affected relatives in 3 consecutive generations on the mother's or father's side and c) at least two relatives who became ill at the age of 55 or younger.[2] In addition to hereditary gene variations, which then affect all cells in the body and are passed from generation to generation, gene variations can also occur during life, when they are called somatic, and are detected in the tumor itself. Consistent with the fact that tumor growth results in additional gene variations, recombinant gene variations have been found in about 5% of localized prostate cancer patients and 12% of metastatic disease patients.[3] According to European Society of Medical Oncology guidelines, genetic profiling in metastatic disease is indicated, while the "american" guidelines also recommend genetic profiling in non-metastatic disease if it is a high-risk cancer, but also when there is a frequent occurrence of cancer in the family. Already today, the findings obtained by determining the genomics of prostate cancer can serve us before diagnosis, in terms of risk assessment of the disease, as well as after diagnosis, with its possible prognostic and predictive value.

### LITERATURA

1. *Mucci LA, Hjelmborg JB, Harris JR i sur.* Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. JAMA 2016; 315(1): 68–76.
2. *Ruijter E, van de Kaa C, Miller G i sur.* Molecular genetics and epidemiology of prostate carcinoma. Endocr Rev 1999; 20(1): 22–45.
3. *Pritchard CC, Mateo J, Walsh MF i sur.* Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med 2016; 375(5): 443–53.

## NEOADJUVANTNA KEMOTERAPIJA UROTELNOG KARCINOMA – PRIKAZ SLUČAJA

BUŠELIĆ Š.[1], Antunac Golubić Z.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
simebuselic@gmail.com

**Uvod**: Mišićno-invazivni urotelni karcinom mokraćnog mjehura (MIKM) agresivna je novotvorina s pojavom lokalnog ili udaljenog recidiva u do 50% slučajeva te relativno niskim petogodišnjim preživljenjem, čak i nakon radikalne cistektomije. Primjena perioperativne sistemske kemoterapije, prije (neoadjuvantna, NAK) ili nakon (adjuvantna) kirurškog zahvata je stoga ključna u smanjenju rizika povrata bolesti, što se objašnjava uništenjem mikrometastaza nedetektabilnih u vrijeme postavljanja dijagnoze. Kombinirana kemoterapija temeljena na cisplatini je već desetljećima standard sistemskog liječenja urotelnog karcinoma. Prednost se daje primjeni neoadjuvantne kemoterapije u usporedbi s adjuvantnom terapijom ili radikalnom cistektomijom bez dodatne terapije. U nastavku je prikazan slučaj pacijentice kod koje je analizom operacijskog materijala zabilježen potpuni odgovor na primijenjenu NAK.

**Prikaz slučaja**: 54-godišnjoj bolesnici je zbog hematurije u dva navrata učinjena transuretralna resekcija tumora mokraćnog mjehura te je postavljena dijagnoza MIKM (pT2, visoki gradus). Inicijalnom slikovnom obradom u svrhu "staginga" se opisuje zadebljanje desne posterolateralne stijenke mjehura, bez dokaza udaljenog rasapa bolesti. Odlučeno je provesti liječenje NAK s 4 ciklusa po ddMVAC protokolu ("dose-dense" metotreksat, vinblastin, doksorubicin, cisplatina) te po završetku liječenja učiniti radikalnu cistektomiju. Reevaluacijski CT nakon 3. ciklusa opisuje stacionaran nalaz, a kao nus-nalaz opisana je plućna embolija zbog čega se odustalo od primjene posljednjeg planiranog ciklusa NAK. Uvedena je terapija dalteparinom. Radikalni kirurški zahvat (egzenteracija zdjelice s formiranjem "neobladdera") učinjen je dva mjeseca nakon završetka NAK. Unatoč ranijem perzistiranju radiološkog nalaza, patohistološkom analizom ne nalazi se rezidualnog urotelnog karcinoma u stijenci mokraćnog mjehura niti u ostalim uklonjenim strukturama.

**Zaključak**: Primjena NAK kod pacijentice je dovela do potpunog patološkog odgovora (ypT0), što predstavlja pozitivni prognostički čimbenik. Opisani slučaj je primjer uspješne primjene NAK s ciljem redukcije patološkog stadija te govori u prilog ove terapijske opcije u liječenju mišićno-invazivnog karcinoma mokraćnog mjehura.

## NEOADJUVANT CHEMOTHERAPY OF UROTHELIAL CARCINOMA – CASE REPORT

BUŠELIĆ Š.[1], Antunac Golubić Z.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
simebuselic@gmail.com

**Background**: Muscle-invasive urothelial bladder cancer (MIBC) is an aggressive disease with a high rate of local and distant recurrence, up to 50% of cases, and poor 5-year survival rates, even after radical cystectomy. Therefore, perioperative chemotherapy, given either before (neoadjuvant, NAC) or after (adjuvant) surgery, is essential in reducing the risk of disease recurrence, probably due to eradication of micrometastatic disease undetectable at the time of diagnosis. For decades, combined cisplatin-based chemotherapy has been the mainstay of systemic urothelial cancer treatment. In recent years, there has been increasing evidence in favor of neoadjuvant chemotherapy compared to adjuvant therapy or radical cystectomy alone. Here we present the case of a female patient in whom surgical specimen analysis showed complete response to the applied NAC.

**Case report**: 54-year old female patient was diagnosed with MIBC (pT2, high grade) after repeated transurethral resection of the bladder tumor following diagnostic workup of hematuria. Initial staging was performed, which described right-sided posterolateral bladder wall thickening with no clear evidence of distant metastases. The decision was made to administer NAC, four cycles of ddMVAC ("dose-dense" methotrexate, vinblastine, doxorubicin, cisplatin). After completion of chemotherapy, radical cystectomy was planned to be performed. Re-evaluation CT scan after third cycle showed unchanged dimensions of the bladder wall thickening, also, pulmonary embolism was diagnosed. Therefore, the last cycle was not administered. Anticoagulation therapy with

dalteparin was commenced. Radical surgical procedure (pelvic exenteration with "neobladder" formation) was performed two months later. Although there was persistence of radiologic finding, histopathological examination found no residual urothelial cancer in the bladder wall nor in any of the removed tissue.

**Conclusion**: NAC administration in this case has led to complete pathologic response (ypT0), which has positive predictive value. This is an example of successful use of NAC with the aim of pathologic downstaging and further favors this treatment option in the management of muscle-invasive bladder cancer.

## PROMJENE U KLINIČKOJ PRAKSI STANDARDNOG LIJEČENJA KARCINOMA BUBREGA

KOŠI KUNAC A.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
anakosi@gmail.com

Zadnjih godina došlo je do revolucionarnih pomaka u sferi onkološkog liječenja bolesnika s karcinomom bubrega. Povijesno je karcinom bubrega zbog svoje visoke kemorezistencije karakteriziran kao maligna bolest s izrazito niskom uspješnosti onkološkog liječenja. Tirozin kinazni inhibitori (TKI), kao prva etablirana terapija karcinoma bubrega, pokazali su visoku stopu odgovora na liječenje te uspoređujući s prijašnjom terapijom značajno dulje preživljenje bolesnika. Rane studije s citokinskom terapijom utrle su put još jednom modalitetu liječenja, u vidu imunoterapije. Nekoliko studija uspoređivalo je imunoterapiju sa standardom liječenja, tirozin kinaznim inhibitorom sunitinibom, naspram kojeg pokazuje višu stopu odgovora, duži period bez progresije bolesti, te bolje sveukupno preživljenje. Navedene uključuju kombinaciju dva imunoterapeutika (nivolumab i ipilimumab), te kombinacije imunoterapije s tiroznim kinaznim inhibitorima (aksitinib i pembrolizumab, kabozantinib i nivolumab te najnovije lenvatinib i pembrolizumab). Kombinacija dva imunoterapeutika je u istraživanjima pokazala očekivano visoku imunotoksičnost te nešto nižu stopu odgovora i perioda bez progresije bolesti uzevši u obzir rezultate kombinacije imunoterapije i tirozin kinaznog inhibitora. Kao prednost kombinacije imunoterapeutika ističe se mogućnost prekida terapije u određenoj fazi liječenja. Iako se došlo do obećavajućih rezultata u pogledu odgovora na terapiju te sveukupnog preživljenja bolesnika, ostaje značajna praznina u kontekstu odabira navedenih kombinacija, s obzirom da još uvijek nedostaju adekvatne studije njihove međusobne usporedbe. Najdalje se došlo u istraživanju kombinacije dva imunoterapeutika, gdje podaci već sada dozvoljavaju adekvatnu analizu te donošenje relevantnih zaključaka. Važno je spomenuti i nove opcije liječenja karcinoma bubrega, posebno u vidu trostruke terapije (kombinacija dva imunoterapeutika i tiroznim kinaznog inhibitora) te HIF-2 (hypoxia- inducible factor- 2) inhibitora. Stopa odgovora HIF-2 inhibitora belzutifana od 25 % u visoko refraktornoj populaciji bolesnika je vrlo ohrabrujuća kao podloga za daljnji razvoj i analize. Za bolesnike kod kojih dođe do progresije bolesti nakon prve linije liječenja, odabir daljnje terapije prvenstveno ovisi o inicijalnom tretmanu. Dok je situacija relativno jednostavna kod inicijalne monoterapije tirozin kinaznim inhibitorom, gdje je u daljnjem tijeku indicirana imunoterapija, stvari postaju zamršenije kada incijalno liječenje sadrži imunoterapiju. Uz zahtjevno i kompleksno onkološko liječenje metastatskog karcinoma bubrega, nedostatak etabliranog adjuvantnog režima samo doprinosi sveukupnoj lošijoj prognozi te maligne bolesti. Naime, većina onkoloških tretmana učinkovitih u domeni metastatske bolesti, ne pokazuje zadovoljavajući učinak kao adjuvantni tretman. Iako još uvijek u iščekivanju adekvatnih rezultata, pembrolizumab u studiji KEYNOTE-564 je dosadašnjom analizom pokazao potencijal da se etablira kao standanrdno adjuvantno liječenje karcinoma bubrega. Unatoč velikim pomacima, očigledno je da postoji mnogo nedoumica u sferi onkološkog liječenja karcinoma bubrega. Spoj analize nekonvencionalnih patofizioloških mehanizama kontrole uz podlogu visoko sofisticionirane tehnologije, mogao bi u budućnosti dovesti do potpune destigmatizacije i kontrole te maligne bolesti

## CHANGES IN CLINICAL PRACTICE OF STANDARD RENAL CELL CARCINOMA TREATMENT

KOŠI KUNAC A.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
anakosi@gmail.com

In recent years, there have been revolutionary advances in the field of oncological treatment of patients with kidney cancer. Historically, renal cell carcinoma has been characterized as a malignant disease with extremely low oncology treatment success due to its high chemoresistance. Tyrosine kinase inhibitors (TKIs), as the first established therapy for renal cell carcinoma, showed a high response rate to treatment and in comparison with previous therapy significantly longer patient survival. Early studies with cytokine therapy paved the way for another treatment modality, in the form of immunotherapy. Several studies have compared immunotherapy with a standard of care, the tyrosine kinase inhibitor sunitinib, against which it shows a higher response rate, a longer period without disease progression, and better overall survival. These include a combination of two immunotherapeutics (nivolumab and ipilimumab), and a combination of immunotherapy with tyrosine kinase inhibitors (axitinib and pembrolizumab, cabozantinib and nivolumab, and most recently lenvatinib and pembrolizumab). The combination of two immunotherapeutics in the studies showed expectedly high immunotoxicity and a slightly lower response rate and progression-free period taking into account the results of the combination of immunotherapy and a tyrosine kinase inhibitor. The advantage of a combination of immunotherapeutics is the possibility of stopping therapy at a certain stage of treatment. Although promising results have been obtained in terms of response to therapy and overall patient survival, a significant gap remains in the context of selection of these combinations, as adequate studies of their comparison are still lacking. The farthest research has come in the combination of two immunotherapeutics, where the data already allow for adequate analysis and making relevant conclusions. It is important to mention new treatment options for kidney cancer, especially in the form of triple therapy (a combination of two immunotherapeutics and a tyrosine kinase inhibitor) and HIF-2 (hypoxia-inducible factor-2) inhibitors. The response rate of the HIF-2 inhibitor belzutifan of 25% in the highly refractory patient population is very encouraging as a basis for further development and analysis. For patients who show disease progression after first line treatment, the choice of further therapy depends primarily on the initial treatment. While the situation is relatively simple with initial monotherapy with a tyrosine kinase inhibitor, where immunotherapy is indicated in the further course, things become more complicated when the initial treatment involves immunotherapy. In addition to the demanding and complex oncological treatment of metastatic renal cell carcinoma, the lack of an established adjuvant regimen only contributes to the overall poor prognosis of this malignant disease. Namely, most oncological treatments effective in the field of metastatic disease do not show a satisfactory effect as adjuvant treatment. Although still awaiting adequate results, pembrolizumab in the KEYNOTE-564 study to date has shown the potential to establish itself as a standard adjuvant treatment for renal cell carcinoma. Despite the great shifts, it is obvious that there are many doubts in the field of oncological treatment of kidney cancer. The combination of analysis of unconventional pathophysiological control mechanisms based on highly sophisticated technology could in the future lead to complete destigmatization and control of this malignant disease.

## MJESTO RADIOTERAPIJE KOD NELOKALIZIRANOG/OLIGOMETASTATSKOG KARCINOMA PROSTATE

SOLARIĆ M.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
mladen.solaric@gmail.com

U nastojanju poboljšanja učinkovitosti androgene deprivacije (ADT) danas se široko istražuje dodatna lokalna terapija kod bolesnika s metastatskim rakom prostate.

Zračenje prostate kod bolesnika s metastatskom bolesti (konsolidacijska radioterapija) je istraživana u nizu opservacijskih studija temeljenih na registrima bolesnika. Većina studija je upućivala na dužu kontrolu bolesti i preživljenje kod bolesnika koji su uz ADT bili lokalno liječeni. Postoje dvije obavljene prospektivne randomizirane studije koje su istraživale učinkovitost radioterapije prostate kod bolesnika s primarno metastatskim rakom prostate. Studija STAMPEDE i studija HORRAD nisu pokazale značajan učinak zračenja na cijeloj populaciji bolesnika. Međutim, podgrupna analiza u studiji STAMPEDE je pokazala kako radioterapija prostate značajno produžuje preživljenje u bolesnika s malim volumenom bolesti. U STOPCAP M1 meta analizi pokazana je bolja biokemijska kontrola bolesti zračenih bolesnika, a kod onih sa manje od 5 metastaza na scintigrafiji kostiju, značajno bolje preživljenje. Većina smjernica za liječenje raka prostate uključila je zračenje prostate uz kontinuiranu ADT kao jednu od terapijskih opcija u liječenju bolesnika s primarno metastatskim rakom prostate malog volumena. Očekuje se kako će konačnu potvrdu ovakvog pristupa pružiti rezultati studije PEACE1 i studije Jugozapadne onkološke skupine (SWOG, NCT03678025).

Na metastaze usmjerena radioterapija (MDT) uglavnom je istraživana kod bolesnika s oligometastatskom bolesti (manje od 5 metastaza ograničenih na kosti ili limfne čvorove) kao recidiva nakon ranijeg radikalnog lokalnog liječenja. Kod većine bolesnika se radilo o kastracijski osjetljivoj bolesti, a cilj istraživanja je bio odgoda uvođenja ADT i razvoja kastracijske rezistencije. Objavljeno je šest prospektivnih studija od koji su dvije bile randomizirane. U studijama ORIOLE i STOMP, koje su ukupno uključile samo 116 bolesnika, stereotaksijska ablativna radioterapija metastaza je značajno odgodila uvođenje ADT. Temeljem objavljenih smjernica, MDT još valja smatrati nestandardnim liječenjem. Međutim, 75% eksperata na Konsenzus konferenciji o uznapredovanom raku prostate (APCCC 2019.) smatralo je MDT opravdanim kod oligometastatskog relapsa uz ADT. Pouzdanija ocjena vrijednosti MDT će biti moguća temeljem rezultata studija PLATO, PCS IX (NCT02685397) i STORM/PEACE V.

## THE ROLE OF RADIOTHERAPY IN NON LOCALISED/OLIGOMETASTATIC PROSTATE CANCER

SOLARIĆ M.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
mladen.solaric@gmail.com

In an effort to improve the efficacy of androgen deprivation (ADT), local therapy in patients with metastatic prostate cancer is now being widely investigated.

Prostate radiation in patients with metastatic disease (consolidation radiotherapy) has been investigated in a series of observational studies based on patient registries. Most studies have recorded longer disease control and survival in patients treated locally and receiving ADT. There are two prospective randomized studies that investigated the efficacy of prostate radiotherapy in patients with primary metastatic prostate cancer. The STAMPEDE study and the HORRAD study did not show a significant effect of radiation on survival in the entire patient population. However, a subgroup analysis in the STAMPEDE study showed that prostate radiotherapy significantly prolongs survival in patients with low volume disease. The STOPCAP M1 meta-analysis showed better biochemical disease control of irradiated patients. In those with less than 5 metastases on bone scintigraphy, significantly better survival was demonstrated. Most guidelines for the treatment of prostate cancer have included prostate radiation in combination with continuous ADT as one of the therapeutic options in the treatment of

patients with primary metastatic small-volume prostate cancer. The final confirmation of this approach is expected to be provided by the results of the PEACE1 study and the Southwest Oncology Group study (SWOG, NCT03678025).

Metastasis-directed radiotherapy (MDT) has been mainly investigated in patients with the oligometastatic disease (less than 5 metastases confined to bone or lymph nodes) as a recurrence after previous radical local treatment. Most patients had a castration-sensitive disease, and the aim of the study was to delay the introduction of ADT and the development of castration resistance. Six prospective studies were published, two of which were randomized. In the ORIOLE and STOMP studies that included only 116 patients, stereotactic ablative radiotherapy (SART) of metastases significantly delayed the introduction of ADT. Based on published guidelines, MDT should still be considered a non-standard treatment. However, 75% of experts at the Advanced Prostate Cancer Consensus Conference (APCCC 2019) considered MDT justified in oligometastatic relapse concomitantly used with ADT. A more reliable assessment of MDT values will be possible based on the results of the PLATO, PCS IX (NCT02685397) and STORM / PEACE V studies.

## RIJETKI TUMORI UROGENITALNOG TRAKTA – PRIKAZ SLUČAJA BOLESNIKA S NEUROENDOKRINIM RAKOM PROSTATE

SALAMUN A.[1], Antunac Golubić Z.[2]

[1] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
salamun.antonija@gmail.com

**Uvod**: Neuroendokrini rak prostate je vrlo agresivni tip raka prostate. Neuroendokrini karcinomi prostate obuhvaćaju vrlo rijetke karcinome verificirane pri dijagnozi bolesti (de novo) te one češće koji su nastali iz metastatskog, kastracijski rezistentnog adenokarcinoma prostate u kasnim stadijima bolesti, kao posljedica rezistencije na terapiju blokatorima androgenog receptora koja se javlja u 15–20% slučajeva. Prognoza de novo neuroendokrinog raka je lošija nego onog nastalog iz adenokarcinoma. U liječenju neuroendokrinog raka prostate koristi se kemoterapija bazirana na cisplatini.

**Prikaz slučaja**: 59-godišnjem bolesniku je zbog klinički suspektnog nalaza prilikom pregleda učinjena biopsija te je verificiran neuroendokrini rak prostate. Vrijednosti PSA, CEA i NSE su bile unutar referentnih vrijednosti. U sklopu inicijalne obrade je učinjen F18- FDG – PET/CT koji potvrđuje vrlo agresivni rak prostate, s aktivnim sekundarizmima u jednom limfnom čvoru desno opturatorno i dva limfna čvora u mezorektalnom masnom tkivu lijevostrano. Inicijalno je liječen s četiri ciklusa kemoterapije po PE (cisplatina/etopozid) protokolu, nakon čega je provedena radioterapija prostate i zdjelice te se bolesnik redovito kontrolirao. Dvije godine kasnije verificira se povrat bolesti u prostati, limfnim čvorovima te jetri. Ponovno je liječen s četiri ciklusa kemoterapije po PE protokolu, ponovno uz dobar odgovor na terapiju. Zbog recentno verificiranog povrata bolesti u prostati uz novonastale lezije uz prednju konturu gušterače te u abdomenu odlučeno je primjeniti stereotaksijsku radioterapiju novonastalih lezija.

**Zaključak**: Neuroendokrini rak prostate čini manje od 2% svih malignih tumora prostate, a prema histološkim i biološkim karakteristikama sličan je mikrostaničnom raku pluća. Klinička prezentacija neuroendokrinog raka prostate je rana pojava simptoma, prisutnost visceralnih metastaza, litičkih lezija kostiju, inicijalno metastatska bolest uz niske vrijednosti PSA i otpornost na hormonsku terapiju. Iako se obično postigne dobar odgovor na kemoterapiju, odgovor traje kratko, uz medijan preživljenja oko 10 mjeseci. U tijeku su istraživanja novih strategija liječenja, a razvojem personalizirane medicine nadamo se postići bolje rezultate u liječenju ove vrlo agresivne bolesti.

## RARE GENITOURINARY TRACT TUMOURS: NEUROENDOCRINE PROSTATE CANCER – A CASE REPORT.

SALAMUN A.[1], Antunac Golubić Z.[2]

[1] General Hospital Pula
• *Department of Medical Oncology and Hematology*
[2] University Hospital Centre Zagreb
• *Department of Oncology*
salamun.antonija@gmail.com

**Introduction**: Neuroendocrine prostate cancer is an aggressive variant of prostate cancer. Neuroendocrine prostate cancers include very rare cancers that arise de novo (they are verified at the time of the disease diagnosis) and the ones that develop in metastatic castration-resistant prostate cancer following previous androgen suppression therapy. The latter occur in up to 15–20% of patients, as a mechanism of treatment resistance. Poorer prognosis is seen in patients with de novo neuroendocrine prostate cancer. Cisplatin-based chemotherapy is considered standard first-line treatment.

**Case report**: A 59-year-old patient with a clinical suspicion of prostate cancer had undergone a prostate biopsy, in which neuroendocrine prostate cancer was verified. PSA, CEA as well as NSE were in normal ranges. Initial imaging, F18-FDG-PET/CT, confirmed a very aggressive prostate cancer, with active metastases in a lymph node in right obturator group and two lymph nodes in mesorectal fat area. After four cycles of chemotherapy with etoposide and cisplatin (PE regimen), the patient received whole-pelvic radiotherapy. Follow-up exams were performed regularly. Disease recurrence occurred two years after, with F18-FDG-PET/CT showing malignant disease in the prostate, lymph nodes, and the liver. The patient was again treated with four cycles of PE chemotherapy protocol, with good response. Recent imaging showed disease recurrence again (prostate, intraabdominal masses), and it was decided that the patient should undergo stereotactic radiotherapy of newly formed metastases.

**Conclusion**: The incidence of neuroendocrine prostate cancer is less than 2% of all malignant prostate cancers. According to histological and biological characteristics, it resembles small cell lung cancer. Its clinical features are early onset of symptoms, visceral metastases, lytic bone lesions, initially metastatic disease with low PSA levels, and resistance to hormone therapy. Trials of new treatment strategies are ongoing, and with the uprising of the personalized medicine, we hope to achieve better results in treatment of this overly aggressive disease.

# SEKCIJA MLADIH ONKOLOGA 2021: „Mladi za treću dob" / YOUNG ONCOLOGIST SESSION

## GERIJATRIJSKA PROCJENA ONKOLOŠKOG BOLESNIKA

KOŠI KUNAC A.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
anakosi@gmail.com

U kontekstu sveukupnog starenja populacije te relativno više incidencije i mortaliteta od malignih bolesti u dobnoj skupini >65 godina, javlja se potreba preciznije i sistematičnije onkološke procjene takvih bolesnika. Unatoč visokoj pojavnosti malignih bolesti u toj dobnoj skupini, takvi bolesnici su nedovoljno zastupljeni u kliničkim istraživanjima te postoji tek nekoliko smjernica za njihovo onkološko liječenje. Posljedično tome, manjkavi su podaci o rizicima i prednostima onkološkog liječenja u toj populaciji, što na kraju dovodi do manje vjerojatnosti pravovremenog i učinkovitog tretmana u usporedbi s mlađom populacijom. S obzirom da kronološka dob krije širok dijapazon potencijalnih slabosti bolesnika koje u situaciji agresivnog onkološkog tretmana nerijetko isplivaju na površinu, kliničaru su prijeko potrebni relevantni podaci o bolesniku, dohvatljivi po brzom i racionalnom postupku.

Takozvana sveobuhvatna gerijatrijska procjena (comprehensive geriatric assessment – CGA) je uobičajeni dio kliničke procjene starijeg bolesnika. U onkološkoj sferi već sada postoji više kliničkih istraživanja 3. faze, rezultati kojih sugeriraju širok spektar potencijalnih benefita takvih upitnika. Osim općenitog utjecaja na plan onkološkog liječenja, takvi su upitnici učinkoviti u predviđanju komplikacija i nuspojava liječenja, procjeni funkcionalnog pogoršanja tijekom liječenja te procjeni preživljenja. Oni pomažu u donošenju specifičnih terapijskih odluka te otkrivaju probleme koji ostaju prikriveni tijekom uzimanja rutinske anamneze i statusa bolesnika. Tijekom liječenja i praćenja takvih bolesnika se također pojavljuju prepreke koje se učinkovitije prepoznaju koristeći takve upitnike, što naposljetku dovodi do boljeg psihičkog i fizičkog statusa takvih bolesnika. Standardne domene CGA upitnika uključuju procjenu funkcionalnog statusa, komorbiditeta, kognitivnog i psihološkog statusa, socijalne potpore, nutritivnog ststusa te medikamentozne terapije. S obzirom da takva ekstenzivna evaluacija nerijetko predstavlja problem u uobičajenoj onkološkoj praksi, donošen je konsenzus da se bolesnici u dobnoj skupini >65 godina inicijalno evaluiraju konciznijim i vremenski manje zahtijevnim upitnicima. Rezultati takvih "pojednostavljenih" upitnika profilirali bi skupinu bolesnika kojima bi ekstenzivna gerijatrijska procjena donijela najviše dobrobiti, s naglaskom da oni ne mogu i ne smiju biti zamjena za krajnju sveobuhvatnu procjenu.

Zaključno, sveobuhvatna gerijatrijska procjena u perspektivi mora postati standardni dio rutinske onkološke prakse te sastavni dio kliničkih istraživanja. Njena implementacija dovela bi do učinkovitijeg predviđanja i rješavanja nuspojava liječenja te procjene ostalih interkurentnih zdravstvenih problema, a sve s ciljem poboljšane kontrole boli te očuvanja psihičkog i fizičkog statusa bolesnika.

## GERIATRIC ASSESSMENT OF AN ONCOLOGICAL PATIENT

KOŠI KUNAC A.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
anakosi@gmail.com

In the context of overall aging of the population and the relatively higher incidence and mortality from malignant diseases in the age group> 65 years, there is a need for a more precise and systematic oncological assessment of such patients. Despite the high incidence of malignancies in this age group, such patients are underrepresented in clinical trials and there are only a few guidelines for their oncological treatment. Consequently, data on the risks and benefits of oncology treatment in that population group are lacking, ultimately leading to less likelihood of timely and effective treatment compared to the younger population. Given that the chronological age hides a wide range of potential weaknesses of patients who often come to the surface in a situation of aggressive oncological treatment, the clinician desperately needs relevant information about the patient, available by rapid and rational procedure.

The so-called comprehensive geriatric assessment (CGA) is a common part of the clinical assessment of an elderly patient. There are already several phase 3 clinical trials in the oncology field, the results of which suggest a wide range of potential benefits of such questionnaires. In addition to the general impact on the oncology treatment plan, such questionnaires are effective in predicting treatment complications and side effects, assessing functional deterioration during treatment, and assessing survival. They help make specific therapeutic decisions and reveal problems that remain hidden while taking a routine history and patient status. During the treatment and follow-up of such patients, barriers also emerge that are more effectively identified using such questionnaires, which ultimately leads to a better mental and physical status of such patients. Standard domains of the CGA questionnaire include assessment of functional status, comorbidity, cognitive and psychological status, social support, nutritional status, and drug therapy. Given that such extensive evaluation is often a problem in common oncology practice, a consensus has been reached that patients in the age group> 65 years are initially evaluated with more concise and less time-consuming questionnaires. The results of such "simplified" questionnaires would profile the group of patients to whom extensive geriatric assessment would bring the most benefits, emphasizing that they cannot and should not be a substitute for the ultimate comprehensive assessment.

In conclusion, a comprehensive geriatric assessment in perspective must become a standard part of routine oncology practice and an integral part of clinical research. Its implementation would lead to more effective prediction and resolution of treatment side effects and assessment of other intercurrent health problems, all with the aim of improved pain control and preservation of the mental and physical status of patients.

## TOKSIČNOST SUSTAVNE TERAPIJE KOD ONKOLOŠKIH BOLESNIKA STARIJE ŽIVOTNE DOBI

KOVAČ BARIĆ M.[1], Canjko I.[1], Šambić Penc M.[1], Kotromanović D.[1], Perić L.[1], Flam J.[1]

[1] Klinički bolnički centar Osijek
• *Zavod za onkologiju*
kovacmaja04@gmail.com

Rizik od oboljenja od raka raste s dobi, oko 70% bolesnika koji boluju od raka starije je od 65 godina. Starenje je heterogen proces karakteriziran postupnim fiziološkim pogoršanjem funkcije organa koji, kod ljudi, napreduje različitom brzinom. Ovisno o biološkoj starosti organizma, razlikuje se očekivano životno preživljenje osoba iste životne dobi.

Manje od ¼ bolesnika u kliničkim studijama su bolesnici stariji od 70 godina koji većinom imaju manje komorbiditeta i funkcijskih oštećenja od prosječnog pojedinca starije životne dobi stoga su osnovni principi liječenja raka kod starijih bolesnika isti kao i kod mlađih bolesnika. Međutim, stariji bolesnici, koji imaju smanjenu funkciju organa posljedično starenju, zahtijevaju poseban pristup uzimajući u obzir rizik od toksičnosti sustavne terapije, očuvanje kvalitete života i očekivano životno preživljenje.

Većina bolesnika starije životne dobi ima multiple komorbiditete te je kod razmatranja primjene sustavne terapije potrebno procijeniti jetrenu i bubrežnu funkciju, rizik od hematološke i nehematološke toksičnosti, polifarmaciju i kvalitetu života. Za odluku o primjeni kemoterapije razvijeni su prediktivni modeli bodovanja kemoterapijske toksičnosti, CARG i CRASH koji u obzir uzimaju ranije navedene rizične čimbenike i koji su se, u kliničkoj praksi, pokazali znatno bolji prediktori toksičnosti kemoterapije od kliničke procjene KPS -a. Slični modeli procjene toksičnosti nisu razvijeni za ciljanu terapiju i imunoterapiju.

U nekoliko randomiziranih kontroliranih studija dokazano je da gerijatrijska procjena prije početka kemoterapije i intervencije poduzete ovisno o nalazu gerijatrijske procjene, smanjuju toksičnost sustavne terapije, više pacijenata završi planirano liječenje, poboljšavaju kvalitetu života te smanjuju duljinu hospitalizacije i komplikacija. Evaluacija učinkovitosti gerijatrijske procjene prije početka ciljane terapije i imunoterapije još je u tijeku.

Smjernice ASCO, SIOG i ESMO društava preporučuju rutinsku primjenu alata gerijatrijske procjene za starije bolesnike koji boluju od raka (definirani kao oni bolesnici koji imaju 65 ili više godina) prije početka sustavne terapije s ciljem donošenja odluke i individualnog plana liječenja i srbi za starije bolesnike koji boluju od raka.

## TOXICITY OF SYSTEMIC THERAPY IN GERIATRIC CANCER PATIENTS

KOVAČ BARIĆ M.[1], Canjko I.[1], Šambić Penc M.[1], Kotromanović D.[1], Perić L.[1], Flam J.[1]

[1] University Hospital Centre Osijek
• *Department of Oncology*
kovacmaja04@gmail.com

Age is one of the most important risk factor for dveloping cancer, around 70% of cancer patients are older than 65 years of age. Aging is a heterogeneous process characterized by a gradual physiological deterioration of organ functions that, in humans, progresses at different rates. There is a great difference in life expectancy depending on the biological age.

Less than ¼ patients enrolled in clinical studies are older than 70 years and are carefully selected patients with less comorbidities and functional impairments than the average elderly individual. Thus basic principles of cancer treatment in elderly patients are the same as in younger patients. However, elderly patients with deteriorating organ function due to aging, require a special approach taking into account the risk of toxicity of systemic therapy, preservation of quality of life and estimated life expectancy.

Elderly patients usually have multiple comorbidities and when considering systemic therapy, liver and renal function, risk of haematological and non-haematological toxicity, polypharmacy and quality of life should be assessed. CARG and CRASH are predicitive models of chemotherapy toxicity based on geriatric assessment and the implementation of these models into daily practice showed that they are significantly better in predicting chemoterapy toxicity than the assessment of KPS. Similar models of toxicity assessment of targeted therapy and immunotherapy have not been developed.

Several randomized controlled trials have shown that geriatric assessment and interventions prior to chemotherapy reduce systemic toxicity, increase completion of planned treatment, improve quality of life, reduce hospital stays and complications. Evaluations of effectiveness of geriatric assessment prior to targeted therapy and immunotherapy are still ongoing.

Consensus guidelines from the ASCO, SIOG and ESMO socities recommend the routine use of tools for geriatric assessment of elderly cancer patients (defined as age 65 or older) before the onset of systemic therapy in order to guide a decision making and individualising therapy plan and care for elderly cancer patients.

## RADIOTERAPIJA U STARIJIH BOLESNIKA: ULOGA HIPOFRAKCIONIRANE/EKSTREMNO HIPOFRAKCIONIRANE RADIOTERAPIJE

SOČE M.[1], Baučić M.[1], Šandrk S.[1], Nalbani M.[2]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Opća bolnica Dubrovnik
• *Odjel za onkologiju*
majana.soce@gmail.com

Liječenje starijih pacijenata s rakom predstavlja nam izazov jer se normalna funkcija organa smanjuje s godinama, a posljedično i raste broj potencijalnih komorbiditeta. Iz tog razloga se invazivni postupci, poput kirurgije, ne mogu provesti kod mnogih starijih bolesnika s ranim stadijem bolesti. S druge strane, stariji bolesnici s rakom, koji su fizički i psihički sposobni, često su diskriminirani zbog svoje kronološke dobi, te im je liječenje uskraćeno zbog bojazni da neće podnijeti liječenje.

Radijacijska onkologija značajno se razvila u posljednjih 20 godina zbog napretka u tehnikama snimanja i isporuci zračenja. Novije tehnike omogućuju nam isporuku visokih doza na tkivo tumora uz dobru poštedu okolnih organa od rizika, i time potencijalno izlječenje unatoč prisutnosti više komorbiditeta. Standardno zračenje može trajati 6–8 tjedana i utjecati na bolesnikovu kvalitetu života, pogotovo zbog ograničene pokretljivosti starijih bolesnika, a i koncentracije radioterapijskih centara u većim gradovima. Moguća rješenja za takve poteškoće su upotreba hipofrakcionirane ili ekstremno frakcionirane (stereotaksijske) radioterapije.

Kod nekim tumorskih sijela hipofrakcionirano zračenje koristi se već duži niz godina.

Starije bolesnike s glioblastomom zračimo po shemi 40Gy u 15 frakcija (+/– temozolomid). Novije studije istražuju i kraće sheme (npr. 36Gy u 6 frakcija, 3x tjedno) i dosadašnji rezultati su slični shemi 40Gy/15x koja je trenutno standard.

Ne-melanomski rak kože jedan je od najučestalih u starijih bolesnika (>80 godina). Za ovaj rak vrijedi "manje je bolje", te često korištena shema je 5–7Gy 2x tjedno, ukupno 10 frakcija.

Najčešći tumor današnjice, rak pluća, izazov je u liječenju u svim dobnim skupinama bolesnika. Iako je kirurško liječenje standard kod ranog raka pluća (T1/T2 tumori), često ga kod starijih bolesnika ne možemo provesti zbog komorbiditeta. Takve bolesnike možemo liječenje SBRT tehnikom (Stereotactic Body Radiation Therapy), koja pruža dobru stopu lokalne kontrole uz minimalnu toksičnost.

Neoadjuvantna terapija praćena totalnom mezorektalnom kirurgijom standard je liječenja lokalno uznapredovalog raka rektuma. NACRE studija na starijim bolesnicima s rakom rektuma je pokazala da hipofrakcionirana radioterapija (25Gy u 5 frakcija) nije inferiornija standardnoj radioterapiji (50Gy u 25 frakcija), uz sličnu podnošljivost i bolju suradljivost bolesnika kod kraćeg zračenja. Stopa ukupnog preživljenja je bila nešto veća u hipofrakcioniranoj grupi.

Hipofrakcionirana radioterapija u tumorima dojke i prostate je danas standard liječenja. U tumorima dojke najčešće koristimo shemu 40–42.5 u 15–16 frakcija. Čini se da bi kod starijih bolesnica s rakom dojke bila prikladna i shema ekstremno hipofrakcionirane radioterapije 1x tjedno, 26–27.5Gy u 4–5 frakcija, s odličnom stopom lokalne kontrole i prihvatljivom toksičnosti.

Nakon rezultata CHHiP studije, hipofrakcionirano zračenje bolesnika s rakom prostate (57–60Gy u 19–20 frakcija) je ušlo u svakodnevnu praksu. Podanaliza navedene studije, koja je izdvojila starije bolesnike, pokazala je da nije bilo razlike u učinkovitosti i podnošljivosti u odnosu na mlađe bolesnike.

Stariji bolesnici s rakom nisu dovoljno zastupljeni u kliničkim studijama i stoga su pravi dokazi za optimalno liječenje ograničeni. Također, nedostaju nam dokazi o usporedbi učinkovitosti i podnošljivosti radioterapije u starijih u odnosu na mlađe bolesnike.

Općenito, čini se da je učinkovitost podjednaka, dok neki izvještaji govore u prilog teže podnošljivosti u starijih bolesnika. Ipak, radioterapija je važan segment liječenja u starijih bolesnika s rakom, te uz dobru selekciju bolesnika i potpornu terapiju tijekom provođenja terapije mnogi bolesnici će imati koristi od radioterapije. Primjena novijih tehnika koje smanjuju toksičnost, a poboljšavaju učinkovitost, može proširiti mogućnosti radikalnog i palijativnog liječenja starijih bolesnika.

## RADIOTHERAPY IN ELDERLY PATIENTS: THE ROLE OF HYPOFRACTIONATED / EXTREMELY HYPOFRACTIONATED RADIOTHERAPY

SOČE M.[1], Baučić M.[1], Šandrk S.[1], Nalbani M.[2]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] General Hospital Dubrovnik
• *Department of Oncology*
majana.soce@gmail.com

Management of older cancer patients remains a challenge as normal organ function decreases with age and consequently increases the number of comorbidity factors. Therefore, invasive procedures, such as surgery, cannot be performed in many elderly patients with early-stage disease. On the other hand, elderly cancer patients, who are physically and mentally fit, are often discriminated because of their chronological age, and are denied treatment because of fear of not being able to tolerate treatments. Radiation oncology has evolved significantly over the past 20 years due to advances in imaging techniques and radiation delivery. Newer technologies allow us to deliver precisely higher doses to the tumor tissue with good sparing of the surrounding organs at risk, and thus potential cure despite the presence of multiple comorbidities. Standard radiation can last for 6–8 weeks and affect the patient's quality of life, especially due to the limited mobility of elderly patients, as well as the distribution of radiotherapy centers in larger cities. Possible solutions to such difficulties are the use of hypofractionated or extremely fractionated (stereotaxic) radiotherapy.

In various tumor sites, hypofractionated radiation has been used for many years.

Elderly patients with glioblastoma are irradiated according to the 40Gy in 15 fractions (+/– temozolomide). Recent studies also investigate shorter schemes (e.g. 36Gy in 6 fractions, 3x per week) and the results so far are similar to the 40Gy/15x scheme that is currently the standard. Non-melanoma skin cancer is one of the most common in elderly patients (> 80 years). For this cancer, "less is better" applies, and the frequently used scheme is 5–7Gy 2x a week, a total of 10 fractions.

The most common cancer of today, lung cancer, is a challenge in treatment in all age groups of patients. Although surgical resection is a standard treatment in early lung cancer (T1/T2 tumors), it is often not feasible in elderly patients owing to comorbidities. Such patients can be treated with the SBRT technique (Stereotactic Body Radiation Therapy), which provides a good local control rates with minimal toxicity.

Neoadjuvant therapy followed by total mesorectal surgery is the standard of care for locally advanced rectal cancer. A NACRE trial in elderly patients with rectal cancer showed that hypofractionated radiotherapy (25Gy in 5 fractions) was not inferior to standard radiotherapy (50Gy in 25 fractions), with similar tolerability and better patient compliance with shorter radiation. The overall survival rate was slightly higher in the hypofractionated group.

Hypofractionated radiotherapy in breast and prostate cancers is the standard of care today. In breast cancer we most often use the 40–42.5Gy in 15–16 fractions. It seems that in elderly patients with breast cancer, extremely hypofractionated radiotherapy once a week, 26–27.5Gy in 4–5 fractions, with an excellent rate of local control and acceptable toxicity, can be a good alternative.

Following the results of the CHHiP trial, hypofractionated radiation of prostate cancer patients (57–60Gy in 19–20 fractions) became a daily practice. A subanalysis of this trial, which focused on elderly patients, showed that there was no difference in efficacy and tolerability compared to younger patients.

Elderly cancer patients are underrepresented in clinical trials and therefore the real evidence for optimal treatment is limited. There is limited evidence comparing the efficacy and tolerability of radiotherapy in younger and older patients. In general, efficacy appears to be similar, with some reports suggesting that toxicity rates are increased in older patients. Nevertheless, radiotherapy is a valuable treatment option in elderly cancer patients, and with good patient selection and supportive therapy during treatment, many patients will benefit from radiotherapy. The application of new technologies that reduce toxicity while improving efficacy, may expand the possibilities of radical and palliative treatment in elderly patients.

**LITERATURA**


1. *Popescu T i sur.* Challenges Facing Radiation Oncologists in The Management of Older Cancer Patients: Consensus of The International Geriatric Radiotherapy Group. Cancers 2019, 11(3), 371; https://doi.org/10.3390/cancers11030371
2. *Chargari C i sur.* Feasibility of radiation therapy in patients 90 years of age and older: A French multicentre analysis. European Journal of Cancer Volume 50, Issue 8, May 2014; https://doi.org/10.1016/j.ejca.2014.02.012
3. *Perry James R i sur.* Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. N Engl J Med 2017; 376:1027–1037; DOI: 10.1056/NEJMoa1611977
4. *Greer L i sur.* Accelerated Hypofractionated Radiotherapy in the Era of Concurrent Temozolomide Chemotherapy in Elderly Patients with Glioblastoma Multiforme. Cureus. 2017 Jun; 9(6): e1388; DOI: 10.7759/cureus.1388
5. *Vennes M.* Hypofractionated radiotherapy in older patients with non-melanoma skin cancer: Less is better. Australas J Dermat. Volume 59, Issue 2, May 2018; https://doi.org/10.1111/ajd.12609
6. *Gunaratne A Dakshika, Venness M.* Efficacy of hypofractionated radiotherapy in patients with non-melanoma skin cancer: Results of a systematic review. J Med Imaging Radiat Oncol. 2018 Jun;62(3):401–411. doi: 10.1111/1754-9485.12718
7. *Watanabe K i sur.* Lung stereotactic body radiation therapy for elderly patients aged ≥ 80 years with pathologically proven early-stage non-small cell lung cancer: a retrospective cohort study. Radiat Oncol. (2021) 16:39 https://doi.org/10.1186/s13014-021-01769-7
8. *Teckie S i sur.* NACRE: A randomized study comparing short course radiotherapy with radiochemotherapy for locally advanced rectal cancers in the elderly—Preliminary results. JCO. Volume 39, Issue 3_ suppl
9. *Rain Fadoua i sur.* Extreme weekly locoregional hypofractionated radiation in elderly women with non-metastatic breast cancer. Radiotherapy and Oncology Volume 162, Sep 2021, Pages 156–161; https://doi.org/10.1016/j.radonc.2021.07.008
10. *Wilson M James i sur.* The Efficacy and Safety of Conventional and Hypofractionated High-Dose Radiation Therapy for Prostate Cancer in an Elderly Population: A Subgroup Analysis of the CHHiP Trial. Int J Radiation Oncol Biol Phys, Vol. 100, No. 5, pp. 1179e1189, 2018; https://doi.org/10.1016/j.ijrobp.2018.01.016


## ALK POZITIVAN NEMIKROCELULARNI KARCINOM PLUĆA – PRIKAZ SLUČAJA


RADMILOVIĆ VARGA Lj.[1]

[1] Opća bolnica Varaždin
• *Odjel za hematologiju, onkologiju i kliničku imunologiju*
ljubka.varga@gmail.com


**Uvod**: ALK (anaplastic lymphoma kinase) pozitivan NSCLC (non-small cell lung cancer) čini oko 5% svih NSCLC-a. Više od polovice tih bolesnika je mlađe od 50 godina (oko 34% je mlađe od 40 godina), najčešće su to nepušači i žene. Također, u oko 90% slučajeva u trenu dijagnoze radi se o metastatskoj bolesti. Petogodišnje preživljenje prema stadiju bolesti je do 67% za stadij I, do 55% za stadij II te oko 25% za stadij III nakon provedene operacije i adjuvantne kemoterapije.

**Prikaz slučaja**: Bolesnik je muškarac star 47 godina, nepušač koji nije bio teže bolestan, nema kroničnih bolesti niti uzima kroničnu terapiju. Kako je bio sudionik Domovniskog rata redovito se odaziva na sistematske preglede u OB Zabok (bolnica hrvatskih veterana). Na jednom takvom sistematskom pregledu je u 04/2017. godine učinjen rtg srca i pluća kojim je evidentirana mekotkivna tvorba u posteriornom segmentu DGR promjera 12 mm. Učinjen je zatim MSCT kojim je opisana ekspanzivna formacija desno u gornjem plućnom polju veličine 1.9 x 1.8 cm, djelomično je vezana za pleuru, bez medijastinalne limfadenopatije. Učinjena je bronhoskopija no maligne stanice nisu dobivene. Zatim mu je u 05/2017. učinjena VATS lobektomija desnog gornjeg režnja na Klinici za torakalnu kirurgiju Jordanovac. Patohistološki se radilo o ALK pozitivnom adenokarcinomu bronha s pozitivnom limfovaskularnom invazijom i dva limfna čvora s probojem kapsule (pT1N2, stadij IIIA). Zatim je od 06/2017. do 09/2017. godine primio ukupno 4 ciklusa adjuvantne kemoterapije po protokolu cisplatina/vinorelbin. U 09/2017. godine učinjen je PET CT kojim se nije evidentiralo znakova metabolički aktivne

maligne bolesti. Na kontrolnim nalazima MSCT-a i PET CT-a koji su rađeni svakih 6 mjeseci prve dvije godine od operacije, a kasnije jendom godišnje, zadnji u 06/2021. god. nije evidentirano povrata maligne bolesti pluća.

**Zaključak**: Relaps ALK pozitivnog NSCLC-a je češći u vidu udaljenih presadnica nego kao lokoregionalna bolest (15:60%), a više od 80% relapsa dogodi se u prve 2 godine nakon operacije i adjuvantne kemoterapije. Naš bolesnik je za sada dulje od 4 godine bez povrata bolesti.

## ALK POSITIVE NON-SMALL CELL LUNG CANCER – A CASE REPORT

RADMILOVIĆ VARGA LJ.[1]

[1]General Hospital Varaždin
• *Department of Medical Oncology and Hemathology, Clinical Imunology and Alergology*
ljubka.varga@gmail.com

**Introduction**: ALK-positive NSCLC accounts for about 5% of all NSCLC (non-small cell lung cancer). More than half of these patients are younger than 50 years (about 34% are younger than 40 years), most often non-smokers and women. Also, in about 90% of cases at the time of diagnosis, it is metastatic disease. Five-year survival by stage of the disease is up to 67% for stage I, up to 55% for stage II, and about 25% for stage III after surgery and adjuvant chemotherapy.

**Case report**: The patient is a 47-year-old man, a non-smoker who has not been seriously ill, has no chronic diseases, or is taking chronic therapy. As he was a participant in the Croatian War of Independence, he regularly responds to physical examinations at General Hospital Zabok (Croatian veterans hospital). At the physical examination in 04/2017. chest X-ray was performed and recorded soft tissue formation in the posterior segment of the upper lobe of the right lung with a diameter of 12 mm. An MSCT described an expansive tumor in the right upper lung field measuring 1.9 x 1.8 cm, partially attached to the pleura and without mediastinal lymphadenopathy. Bronchoscopy was performed but no malignant cells were obtained. In 05/2017. VATS lobectomy of the right upper lobe of the lung was performed at the Clinic for Thoracic Surgery Jordanovac. Pathohistologically, it was ALK-positive bronchial adenocarcinoma with positive lymphovascular invasion and two lymph nodes with capsule perforation (pT1N2, stage IIIA). From 06/2017. to 09/2017. a patient received four cycles of adjuvant chemotherapy (cisplatin/vinorelbine protocol). On 09/2017. PET CT did not record any signs of metabolically active malignant disease. On control findings of MSCT and PET CT performed every six months for the first two years after surgery, and later once a year, last at 06/2021., no recurrence of malignant lung disease has been reported.

**Conclusion**: Relapse of ALK-positive NSCLC is more common in the form of distant metastases than as a locoregional disease (15: 60%), and more than 80% of relapses occur in the first two years after surgery and adjuvant chemotherapy. Our patient has been without recurrence for more than four years now.

## ULOGA GERIJATRIJSKE PROCJENE U BOLESNICA S KARCINOMOM DOJKE: MJESTO I ZNAČAJ NEOADJUVANTNE ENDOKRINE TERAPIJE

NALBANI M.[1], Soče M.[2]

[1]Opća bolnica Dubrovnik
• *Odjel za onkologiju*
[2]Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
marion@bolnica-du.hr

Hormon receptor pozitivni (HR+) karcinom dojke obuhvaća 70% karcinoma dojke, odnosno 85% karcinoma dojke u bolesnica starijih od 70 godina. 85–90% novootkrivenih karcinoma dojke nalazi se u lokalnim stadijima bolesti. Prosjek godina kod bolesnica s HR+ karcinomom dojke je između 65 i 70. Sukladno preporukama stručnih društava gerijatrijska procjena savjetuje se kod svih bolesnika starijih od 70 godina. Sagledavajući generalnu populaciju onkoloških bolesnika dokazan je utjecaj gerijatrijske procjene i gerijatrijskih intervencija na poboljšanje kvalitete života, smanjenje toksičnosti sistemnog liječenja, a posljedično i na produljenje života,

međutim utjecaj rezultata gerijatrijske procjene na odabir terapije i dugoročne kliničke ishode u karcinomu dojke još uvijek nije jasno dokazan. Endokrina terapija (ET) okosnica je liječenja u metastatskom HR+ karcinomu dojke gdje dugoročno pokazuje bolje rezultate liječenja uz značajno bolju kvalitetu života spram kemoterapije. U lokalnim stadijima ET se uglavnom koristi u adjuvantnom liječenju HR+ karcinoma dojke. Neoadjuvantni pristup rezerviran je za manjinu bolesnica s inoperabilnim tumorima, koje zbog godina i komorbiditeta nisu kandidati za neoadjuvantnu kemoterapiju.

Našoj bolesnici, N.N. rođenoj 1948. g u dobi od 72 godine dijagnosticiran je lokalno uznapredovali HR + tumor dojke. Radi se o 6.5 cm velikom lobularnom karcinomu dojke, s visokom ekspresijom estrogenih (ER) 90% i progesteronskih receptora (PR) 50% receptora. Nije nađena ekspresija humanog epidermalnog faktora rasta 2 (HER-2) uz indeks proliferacije (Ki-67) 35%. Limfni čvorovi su klinički negativni. Unatoč povišenim tumorskim markerima inicijalna obrada nije našla znakova udaljene bolesti. Bolesnica je prividno dobrog općeg stanja, ali opterećena brojnim komorbiditetima: kronična opstruktivna plućna bolest, stanje po akutnom infarktu miokarda, fibrilacija atrija, dijabetes melitus neovisan o inzulinu, depresija. Kod bolesnice je napravljen gerijatrijski screening pomoću validiranog G8 upitnika koji je pokazao da je bolesnica vulnerabilna te da je nužna detaljnija gerijatrijska procjena. Podrobnije analize pokazale su, pomoću NRS 2002 upitnika, da je bolesnica u nutritivnom riziku te su dani primjereni dijetetski savjeti. Mini mental test je ukazao na razvoj demencije te je bolesnica upućena neurologu uz uvođenje memantina. Korigirana je polifarmacija kako bi se smanjilo tabletno opterećenje bolesnice. Obitelj je savjetovana o potrebi značajne potpore bolesnici, te su dani savjeti o prevenciji pada. Bolesnica je pregledana po kardiologu i pulmologu koji su našli zadovoljavajuće stanje srčane i plućne funkcije. Sve navedeno rezultiralo je u konačnici i značajnim poboljšanjem odnosa liječnik – pacijent. Završno, sukladno rezultatima gerijatrijske procjene bolesnici je savjetovana neoadjuvantna endokrina terapija (NAET). Trenutni zlatni standard NAET je primjena inhibitora aromataze (IA) kroz 4–8 mjeseci. Nedostaju velike randomizirane studije koje bi komparirale NAET s neoadjuvantnom kemoterapijom (NAKT) ali dosadašnji rezultati sugeriraju ekvivalentni učinak. U potrazi za biomarkerima koji bi definirali koja bolesnica bi bila najbolji kandidat za NAET, za sada je najbolje rezultate pokazao pad KI-67 nakon 2 do 4 tjedna primjene ET. Pad KI-67 na manje < 10%, idealno < 2.7% je dobar pokazatelj dugoročnih ishoda. PEPI score je validirani prognostički zbroj koji na temelju postoneoadjuvatnih vrijednosti ekspresije ER, veličine tumora, statusa limfnih čvorova te ekspresije KI 67% dijeli bolesnice prema riziku relapsa. Bolesnice s PEPI zbrojem 0 imaju mali rizik relapsa i nije potrebna adjuvantna kemoterapija. Dodatak novih terapija poput inhibitora o ciklinu ovisnih kinaza 4/6, za sada nije doveo do poboljšanja dugoročnih kliničkih ishoda. Naša bolesnica uzimala je anastrozol kroz mjesec dana prilikom čega je primijećeno kliničko poboljšanje bolesti te je ponovljena core biopsija koja je ukazala na pad KI 67 s inicijalnih 35% na 3%, stoga se odlučilo nastaviti s NEAT anastrozolom. Nažalost, bolesnica je oboljela od teškog oblik-a COVID 19 infekcije te je trenutno protrahirano hospitalizirana u jedinici intenzivnog liječenja. U slučaju oporavka planira se nastavak liječenja s Anastrazolom.

## THE ROLE OF GERIATRIC ASSESSMENT IN A PATIENT WITH BREAST CANCER: THE PLACE AND IMPORTANCE OF NEOADJUVANT ENDOCRINE THERAPY

NALBANI M.[1], Soče M.[2]

[1] General Hospital Dubrovnik
• *Department of Oncology*
[2] University Hospital Centre Zagreb
• *Department of Oncology*
marion@bolnica-du.hr

Hormon receptor-positive (HR +) breast cancer comprises 70% of breast cancers, and 85% of breast cancers in patients older than 70 years. 85–90% of breast cancers are diagnosed in the local stages of the disease. The average age in patients with HR + breast cancer is between 65 and 70. In accordance with the recommendations of professional societies, geriatric assessment is advised in all patients older than 70 years. The influence of geriatric assessment and geriatric interventions on improving the quality of life, reducing the toxicity of systemic treatment, and consequently on prolonging life has been proven in general oncology population, however, the impact of geriatric assessment results on therapy selection and long-term clinical outcomes in breast cancer has not yet been demonstrated. Endocrine therapy (ET) is the backbone of treatment in metastatic HR + breast can-

cer where it results in better long-term treatment, with a significantly better quality of life compared to chemotherapy. In the local stages, ET is mainly used as an adjuvant treatment of HR + breast cancer. The neoadjuvant approach is reserved for a minority of patients with inoperable tumors, who are not candidates for neoadjuvant chemotherapy due to age or comorbidities.

Our patient, N.N. born in 1948 is diagnosed at the age of 72 with locally advanced HR + breast cancer. It is a 6.5 cm large lobular breast cancer, with a high expression of 90% estrogen (ER) and 50% progesterone (PR) receptors. No expression of human epidermal growth factor 2 (HER-2) was found with a proliferation index (Ki-67) of 35%. Lymph nodes are clinically negative. Despite elevated tumor markers, initial investigations found no signs of distant disease. The patient is in a seemingly good general condition but burdened with numerous comorbidities: chronic obstructive pulmonary disease, acute myocardial infarction, atrial fibrillation, non-insulin-dependent diabetes mellitus, depression. The patient underwent geriatric screening using a validated G8 questionnaire which showed that the patient is vulnerable and that a more detailed geriatric assessment is necessary. More detailed analyzes showed, using the NRS 2002 questionnaire, that the patient is at nutritional risk and appropriate dietary advice was given. A mini-mental test indicated the development of dementia and the patient was referred to a neurologist with the prescription of memantine. Polypharmacy was corrected to reduce the patient's tablet load. The family was advised of the need for significant patient support and falls prevention advice was given. The patient was examined by a cardiologist and pulmonologist who found a satisfactory condition of cardiac and pulmonary function. All of the above ultimately resulted in a significant improvement in the doctor-patient relationship. Finally, following the results of the geriatric assessment, the patient was advised to take neoadjuvant endocrine therapy (NAET). The current gold standard of NAET is the administration of aromatase inhibitors (IA) for 4–8 months. Large randomized studies comparing NAET with neoadjuvant chemotherapy (NAKT) are lacking, but the results so far suggest an equivalent effect. In the search for biomarkers that define which patient would be the best candidate for NAET, so far the best results have been shown by a drop in KI-67 after 2 to 4 weeks of ET. A drop in KI-67 to less <10%, ideally <2.7% is a good indicator of long-term outcomes. The PEPI score is a validated prognostic score that divides patients according to the risk of relapse based on postneoadjuvant values of ER expression, tumor size, lymph node status, and KI-67 expression. Patients with a PEPI score of 0 have a low risk of relapse and no adjuvant chemotherapy is required. The addition of new therapies, such as cyclin-dependent kinase 4/6 inhibitors, has not so far not led to an improvement in long-term clinical outcomes. Our patient took anastrozole for a month during which clinical improvement was observed, and after which a core biopsy was repeated indicating a decrease in KI 67 from an initial 35% to 3%. It was decided to continue with anastrozole. Unfortunately, the patient had a severe form of COVID 19 infection and is currently hospitalized in the intensive care unit. In case of recovery, continuation of treatment with anastrazole is planned.

# SEKCIJA GINEKOLOŠKIH TUMORA / GYNECOLOGICAL ONCOLOGY SESSION

## PRVOLINIJSKO LIJEČENJE „HIGH GRADE" SEROZNOG ADENOKARCINOMA JAJNIKA – BEVACIZUMAB ILI OLAPARIB

KUHARIĆ J.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za ženske bolesti i porode, Zavod za ginekološku onkologiju*
josip.kuh@gmail.com

U nedavno objavljenim podacima petogodišnjeg praćenja SOLO 1 studije, koja je ispitivala PARP inhibitor (PARPi) olaparib u terapiji održavanja kod bolesnica oboljelih od uznapredovalog „high grade" seroznog adenokarcinoma jajnika koje su nosioci *BRCA* mutacije, a nakon uspješno provedenog liječenja kemoterapijom na bazi platine, utvrđen je značajan utjecaj na PFS u usporedbi sa placebom uz redukciju rizika od progresije bolesti za 70% (PFS: 56 vs. 13,8 mjeseci, HR=0.30). Učinkovitost olapariba već ranije je utvrđena u drugoj liniji liječenja

platina osjetljivog recidiva „high grade" seroznog adenokarcinoma jajnika u bolesnica sa *BRCA* mutacijom u SOLO 2 studiji, a navedeno je dovelo do registracije lijeka u Hrvatskoj prije nekoliko godina u navedenoj indikaciji. I drugi PARPi osim olapariba, poput niraparib i rucaparib pokazali su učinkovitost kao terapija održavanja, a nekada i kao monoterapija, kod bolesnica sa „high grade" serozim adenokarcinomom jajnika. PARPi su pokazali svoj učinak i onim slučajevima kada *BRCA* mutacija nije prisutna, a prisutna je deficijencija homologne rekombinacije (HRD deficijencija) dokazana genetskim sekvencioniranjem ili je prisutan samo odgovor na kemoterapiju na bazi platine, što se pokazalo kao bitan prediktivni čimbenik za terapiju održavanja PARPi.

Bevacizumab, monklonalno protutijelo koje veže vaskularni endotelijalni faktor rasta i time utječe na inhibiciju angiogeneze, pokazao je svoj učinak u liječenju bolesnica sa uznapredovalim adenokarcinomom jajnika u kombinaciji sa kemoterapijom na bazi platine u prvoj liniji liječenja u ICON7 i GOG 218 studijama, te u liječenju platina osjetljivog i rezistentnog recidiva bolesti (OCEANS i AURELIA studije). Također bevacizumab u kombinaciji sa kemoterapijom na bazi platine pokazao je učinkovitost i u neoadjuvantnom liječenju bolesnica sa inoperabilnom uznapredovalom bolešću u vidu povećanja stope kompletne resekcije i operabilnosti bolesnica (ANTHALYA i GEICO 1205/NOVA studije). Radi navedeng bevacizumab je više godina utvrđen kao opcija ciljanog liječenja uz kemoterapiju u neoadjuvatnom pristupu, adjuvantnom liječenju i liječenju platina osjetljivog i rezistentnog recidiva bolesti u Hrvatskoj i u svijetu, no valja navesti da su sada objavljeni rezultati olapariba u SOLO 1 studiji superiotniji u odnosu na bevacizumab u liječenju bolesnica sa *BRCA* mutacijom.

Još jedna zanimljiva studija je PAOLA 1 koja je ispitivala kombinaciju olapariba i bevacizumaba uz kemoterapiju na bazi platine u bolesnica sa uznapredovalim „high grade" seroznim adenokarcinom jajnika u neoadjuvantnom i adjuvatnom pristupu liječenju, u usporedbi sa kemoterapijom na bazi platine i bevacizumabom. Kombinacija se pokazala učinkovitijom u pogledu na PFS (PFS 22.1 vs 16.6 mj., HR=0.59) u ukupnoj populaciji, a najviše u bolesnica sa *BRCA* mutacijom (PFS 37.2 vs 21.7 mj., HR=0.31), no i u onih kod kojih je utvrđena i samo HRD deficijencija.

Navedeni izvrsni rezultati petogodišnjeg praćenja u SOLO 1 studiji doveli su u Hrvatskoj do registracije olapariba kao terapije održavanja u bolesnica sa uznapredovalim „high grade" seorznim adenokarcinomom jajnika i utvrđenom *BRCA* mutacijom nakon uspješno provedenog liječenja kemoterapijom na bazi platine. Isto je dovelo u pitanje mjesto bevacizumaba u prvoj liniji liječenja, dotada jasnog odabira za bolesnice sa uznapredovalom bolešću koje su zadovoljavale kriterije, obzirom na inferiornije rezultate bevacizumaba u odnosu na olaparib kod bolesnica sa *BRCA* mutacijom. Izvan Hrvatske, na bazi PAOLA 1 studije, kombinacija bevacizumaba i olapariba je opcija ako se bevacizumab koristio kao ciljano liječenje u prvoj liniji, no isto nije dostupno u Hrvatskoj. Radi navedenog, bitno je utvrditi poziciju bevacizumaba u prvoj liniji liječenja kod nas, obzirom na njegov učinak u neoadjuvantnom pristupu i u bolesnica sa uznapredovalom bolešću, i s obzirom da utvrđivanje *BRCA* statusa kod bolesnica u Hrvatskoj nekada traje i više mjeseci.

## NEOADJUVANTNI PRISTUP U LIJEČENJU KARCINOMA VRATA MATERNICE

CANJKO I.[1], Perić L.[1], Šambić-Penc M.[2], Kovač Barić M.[1], Kovač Peić A. M.[2]

[1] Klinički bolnički centar Osijek
• *Zavod za onkologiju*
[2] Sveučilište J.J. Strossmayera u Osijeku
• *Medicinski fakultet*
dr.ivanamarkovic@gmail.com

Neoadjuvantna kemoterapija (NACT) primjenjuje se u velikom broju malignih bolesti jer smanjuje primarni tumor, što poboljšava operabilnost te smanjuje potrebu za adjuvantnim liječenjem, poboljšava radioosjetljivost i smanjuje broj hipoksičnih stanica. Štoviše, neoadjuvantna kemoterapija (NACT) uklanja mikrometastaze te smanjuje rizik od recidiva. Učinak neoadjuvantne kemoterapije prije operacije ili radioterapije na prognozu raka vrata maternice opsežno je istražena. Dugoročna prognoza raka vrata maternice nakon neoadjuvantne kemoterapije i kirurškog liječenja i dalje je kontroverzna.

Kirurgija i konkomitantna kemoradioterapija (CCRT) jednako su vrijedne mogućnosti liječenja bolesnica s FIGO stadijem IB1 – IIA1 raka vrata maternice, a konkomitantna kemoradioterapija (CCRT) preporučuje se za

lokalno uznapredovali karcinom vrata maternice (FIGO IB2, II, III) jer poboljšava vrijeme bez povrata bolesti (DFS) i ukupno preživljenje (OS) u odnosu na radioterapiju.

Neoadjuvanti pristup najviše je istražen u bolesnica FIGO stadija IB2 – IIB karcinoma vrata maternice.

Meta-analiza koja je obuhvaćala 872 bolesnice s rakom vrata maternice ispitivala je primjenu neoadjuvantne kemoterapije prije kirurškog liječenja u odnosu na radioterapiju. Pokazala je smanjenje rizika od smrti za 35 % u korist neoadjuvantne kemoterapije. Nedostaci ove meta – analize su usporedba samo s radioterapijom koja nije standard u liječenju ovih bolesnica, suboptimalna doza radioterapije te podatak da je samo 27 % bolesnica primilo intrakavitarnu brahiterapiju.

Dvije su kliničke studije faze III koje istražuju primjenu neoadjuvantne kemoterapije praćene operacijom u odnosu na primarnu kemoradioterapiju:

EORTC Protocol 55994 i NCT00193739.

Prva studija (EORTC Protocol 55994) pokazala je da nema razlike u sveukupnom preživljenju između skupina, ali je potvrdila nešto bolje preživljenje bez progresije bolesti u bolesnica koje su primale konkomitantnu kemoradioterapiju. Veću su dobrobit od CCRT imale bolesnice FIGO stadija IIB i one starije od 50 godina, a korist od neoadjuvantne kemoterapije imale su bolesnice FIGO stadija IB2. Rana toksičnost zabilježena je u bolesnica koje su primale kemoterapiju, a kasna u onih koje su primile konkomitantnu radioterapiju.

U drugoj studiji (NCT00193739) koja je uključivala bolesnice samo jednog centra, jedna je skupina primala neoadjuvantnu kemoterapiju s 3 ciklusa paklitaksela i karboplatine u razmaku od 3 tjedna, potom kirurški zahvat te adjuvantno liječenje prema čimbenicima rizika, a druga skupina konkomitantnu kemoradioterapiju s tjednom cisplatinom tijekom 5 ciklusa. Studija je pokazala bolje vrijeme bez povrata bolesti (DFS) u bolesnica koje su primale konkomitantnu kemoradioterapiju.

Nedavno objavljena meta-analiza koja je uspoređivala neoadjuvantnu kemoterapiju praćenu kirurškim liječenjem u odnosu na kirurško liječenje pokazuje visoku kontrolu bolesti s neoadjuvantnom kemoterapijom te daje obećavajuće rezultate u liječenju bolesnica s rakom vrata maternice. Dodatna eksplorativna analiza patološkog odgovora pokazala je značajno smanjenje različitih patohistoloških značajki (zahvaćenost l.č, infiltracija parametrija), ali veliki postotak tih bolesnica ipak neće biti kandidatkinje za kirurški zahvat zbog toksičnosti ili neodgovarajućeg patološkog odgovora.

Nedavno je objavljena meta-analiza koja je uspoređivala tri modaliteta liječenja; NACT nakon koje slijedi operacija i adjuvantna terapija (NACT + operacija + AT), naspram operacije plus adjuvantne terapije (operacija + AT), NACT nakon koje slijedi operacija i adjuvantna terapija (NACT + operacija + AT) u usporedbi s istodobnom kemoradioterapijom ili radioterapijom ili kemoradioterapija (CCRT/RT/CRT) i NACT nakon koje slijedi kemoradioterapija (NACT + CRT) u odnosu na kemoradioterapiju (CRT).

Mjere ishoda bile su 3-godišnji i 5-godišnji PFS i OS u grupi s neoadjuvantnom terapijom u odnosu na kontrolnu skupinu. Neoadjuvantna kemoterapija nema utjecaj na 3-godišnji OS, PFS i 5-godišnji PFS. Ova meta-analiza pokazala je da NACT poboljšava 5-godišnji OS pacijentica s resektabilnim rakom vrata maternice. Bez obzira na to, ovaj nalaz trebao bi se potvrditi velikim multicentričnim kliničkim ispitivanjima.

Zlatni je standard u liječenju bolesnica s lokalno uznapredovalom bolesti konkomitantna kemoradioterapija uz tjednu cisplatinu kao najčešći korišteni kemoterapijski lijek, iako je meta-analiza pokazala dobrobit i s neplatinskim spojevima.

Neoadjuvantna kemoterapija primijenjena u kraćem vremenskom razdoblju (tjedna aplikacija tijekom 6 tjedana), posebno kod pacijentica FIGO IIIC 1 i IIIC2 stadija bolesti, uz standardnu kemoiradijaciju i brahiterapiju, pokazuje obećavajuće rezultate (INTERLACE studija).

Potrebne su dodatne kliničke studije koje bi opravdale neoadjuvanti pristup u liječenju bolesnica s karcinomom vrata maternice i njenu implementaciju u kliničku praksu.

Takav pristup liječenja trebao bi biti dio multidisciplinarnog tima.

**Ključne riječi**: neoadjuvantna kemoterapija, kirurško liječenje, radioterapija, kemoterapijski protokol

# A NEOADJUVANT APPROACH IN THE TREATMENT OF CERVICAL CANCER

CANJKO I.[1], Perić L.[1], Šambić-Penc M.[2], Kovač Barić M.[1], Kovač Peić A. M.[2]

[1] University Hospital Centre Osijek
• *Department of Oncology*
[2] University of J.J.Strossmayer Osijek
• *School of medicine*
dr.ivanamarkovic@gmail.com

Neoadjuvant chemotherapy (NACT) is used in a large number of malignancies because it reduces the primary tumor, which improves operability and reduces the need for adjuvant treatment. It also improves radiosensitivity and reduces the number of hypoxic cells. Furthermore, NACT removes micrometastases and reduces the risk of recurrence of the disease. The effect of neoadjuvant chemotherapy before surgery or radiotherapy on the prognosis of cervical cancer has been extensively investigated. The long-term prognosis of cervical cancer after neoadjuvant chemotherapy and surgical treatment remains controversial.

Surgery or concomitant chemoradiotherapy (CCRT) is an equally valuable treatment option for patients with FIGO stage IB1 – IIA1 cervical cancer. But on the other hand, CCRT is recommended for locally advanced cervical cancer (FIGO IB2, II, III) because it significantly improves the time without disease-free survival (DFS) and overall survival (OS) in comparison to radiotherapy.

The neoadjuvant approach has been most investigated in patients with FIGO stage IB2 – IIB cervical cancer.

A meta-analysis involving 872 patients with cervical cancer examined the use of neoadjuvant chemotherapy before surgical treatment compared to radiotherapy. It showed a 35% reduction in the risk of death in favor of neoadjuvant chemotherapy. The main shortcomings of this meta-analysis were comparison with radiotherapy alone (non-standard treatment option). Also, only 27% of patients received intracavitary brachytherapy and the doses that were used were suboptimal.

Two phase III clinical studies are investigating the use of neoadjuvant chemotherapy followed by surgery versus primary chemoradiotherapy: EORTC Protocol 55994 and NCT00193739.

The first study (EORTC Protocol 55994) showed no difference in overall survival between the groups but confirmed somewhat better progression-free survival in patients receiving concomitant chemoradiotherapy. FIGO stage IIB patients and those older than 50 years benefited more from CCRT, and FIGO stage IB2 patients benefited from neoadjuvant chemotherapy. Early toxicity was observed in patients receiving chemotherapy and late toxicity in those receiving concomitant radiotherapy.

In another study (NCT00193739) involving patients from only one center, one group received neoadjuvant chemotherapy with 3 cycles of paclitaxel and carboplatin 3 weeks apart, followed by surgery and adjuvant treatment according to risk factors. The other group received concomitant chemoradiotherapy with weekly cisplatin during 5 cycles. The study showed better disease-free survival (DFS) in patients receiving concomitant chemoradiotherapy.

A recently published meta-analysis comparing neoadjuvant chemotherapy followed by surgical treatment versus surgical treatment alone shows better disease control with neoadjuvant chemotherapy and yields promising results in the treatment of patients with cervical cancer.

Additional exploratory analysis of the pathological response showed a significant reduction in various pathohistological features (lymph node involvement, parametrial infiltration), but a large percentage of these patients will still not be candidates for surgery due to toxicity or inappropriate pathological response.

A meta-analysis comparing three treatment modalities was recently published; NACT followed by surgery and adjuvant therapy (NACT + surgery + AT), versus surgery plus adjuvant therapy (surgery + AT). Another treatment modality that was compared was NACT followed by surgery and adjuvant therapy (NACT + surgery + AT) compared to concomitant chemoradiotherapy or radiotherapy or chemoradiotherapy (CCRT / RT / CRT) and the last comparison was NACT followed by chemoradiotherapy (NACT + CRT) versus chemoradiotherapy (CRT).

Outcome measures were 3-year and 5-year progression-free survival (PFS) and OS in the neoadjuvant chemotherapy group compared to the control group. Neoadjuvant chemotherapy does not affect 3-year OS, PFS, and 5-year PFS. This meta-analysis showed that NACT improves the 5-year OS of patients with resectable cervical cancer. Nevertheless, this finding should be confirmed by large multicenter clinical trials.

The gold standard in the treatment of patients with locally advanced disease is concomitant chemoradiotherapy with weekly cisplatin as the most commonly used chemotherapeutic drug, although meta-analysis has shown benefit with non-platinum compounds as well.

Neoadjuvant chemotherapy administered over a shorter period (weekly administration over 6 weeks), especially in FIGO IIIC 1 and IIIC2 stage patients, with standard chemoradiation therapy and brachytherapy, shows promising results (INTERLACE study).

Additional clinical studies are needed to justify a neoadjuvant approach in the treatment of patients with cervical cancer and its implementation in clinical practice.

Such a treatment approach should be part of a multidisciplinary team.

**Keywords**: Neoadjuvant chemotherapy, Surgical treatment, Radiotherapy, Chemotherapy protocol

**LITERATURA**

1. *Incidencija raka u Hrvatskoj 2016.* Bilten br. 41. Zagreb: Hrvatski zavod za javno zdravstvo, 2019.
2. *NCCN guidelines*
3. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.Annals of oncology 28(Supplement 4):iv72–iv83,2017.
4. *European Organisation for Research and Treatment of Cancer – EORTC.* Chemotherapy followed by surgery vs radiotherapy plus chemotherapy in patients with stage Ib or II cervical cancer. EORTC Protocol 55994. https:// clinicaltrials.gov/ct2/show/NCT00039338 (29 April 2017, date last accessed).
5. *Gupta S.* Neoadjuvant chemotherapy followed by surgery versus concurrent chemoradiation in carcinoma of the cervix (NACTcervix). NCT00193739. https://clinicaltrials.gov/ct2/show/NCT00193739 NCT00193739 https://clinicaltrials.gov/ct2/show/NCT00193739 (29 April 2017, date last accessed).
6. *Rydzewska L, Tierney J, Vale CL, Symonds PR.* Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. Cochrane Database Syst Rev 2012; 12: CD007406.
7. *Xua Y, Zhangc M, Zhangc J i sur.* Neoadjuvant chemotherapy increases the 5-year overall survival of patients with resectable cervical cancer: A systematic review and meta-analysisTaiwanese Journal of Obstetrics and Gynecology Volume 60, Issue 3, May 2021, Pages 433–441

## NOVOSTI U ADJUVANTNOM LIJEČENJU RAKA MATERNICE

MALOŠEVAC S.[1]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
sanja.malosevac@gmail.com

Rak endometrija najčešći je ginekološki rak u razvijenim zemljama s konstantnim porastom incidencije. U više od 80% slučajeva dijagnosticira se kod žena u postmenopauzi (srednja dob pri postavljanju dijagnoze je 63 godine), ali u 10% slučajeva pacijenti su mlađi od 40 godina. U 80% slučajeva bolest se otkriva u stadiju I s petogodišnjom stopom preživljavanja od 95%, a u oko 10% bolesnika bolest je u stadiju IV, s petogodišnjom stopom preživljavanja od samo 17%. Klasična histopatološka klasifikacija karcinoma endometrija uzima u obzir lokaciju i veličinu tumora, histološki tip i stupanj, dubinu invazije miometrija, zahvaćenost vrata maternice, limfovaskularnu invaziju, zahvaćenost okolnih organa, status limfnih čvorova, dopunjen statusom receptora estrogena i statusom raka endometrija prije HER2 statusa. Godine 2013. objavljena je genomska klasifikacija raka endometrija (TCGA Research Network), nakon čega je uslijedila klasifikacija pomoću alternativnih, klinički primjenjivijih metoda za određivanje markera. Molekularna / genomska analiza definira četiri molekularne podskupine karcinoma endometrija (POLE mutiran, MMRd / MSI-H, p53abn, NSMP) koje imaju prognostički značaj i zahtijevaju različite terapijske pristupe. Molekularnu analizu treba provesti kod raka endometrija visokog stupnja i, ako je moguće, kod raka endometrija niske razine. PORTEC-3, multicentrična randomizirana studija faze 3, analizirala je dobrobit adjuvantne kemoradioterapije samo od radioterapije zdjelice kod žena s visokorizičnim stadijem I, II i III raka endometrija. Dokazano je značajno poboljšanje OS i PPP, definirano kao primarni cilj, ali s povećanom toksičnošću. Dodatne studije su u tijeku kako bi potvrdile učinkovitost različitih modaliteta adjuvantnog liječenja prema molekularnim podtipovima raka endometrija. RAINBO: Poboljšanje adjuvantnog liječenja u liječenju raka endometrija na temelju molekularnih značajki, TransPORTEC platforma – sastoji se od četiri studije čiji je primarni cilj RFS. Postoje tri randomizirane studije: Studija RED/p35abn ispituje učinak

adjuvantne kemoradioterapije nakon koje slijedi niraparib u odnosu na placebo liječenje; Studija GREEN/MMRd ispituje učinak adjuvantne radioterapije, a zatim liječenja dostarlimabom u odnosu na placebo; Studija ORANGE/NSMP uspoređuje adjuvantnu radioterapiju sa i bez endokrinih terapija. Četvrta je opservacijska studija, BLUE/POLE mut studija u kojoj se pacijenti prate nakon operacije. U dodatnim studijama ispituje se učinkovitost kemoterapije i radioterapije sa ili bez inhibitora PD1/PDL1, antihormonske terapije, mTOR inhibitora, CDK4/6 inhibitora, PARP inhibitora, antiHER2, antiVEGF terapije i drugih potencijalnih lijekova. Molekularne odrednice raka endometrija uključene su u nove smjernice ESGO/ESTRO/ESP, kao i u trenutne smjernice NCCN.

## ADVANCES IN UTERINE CANCER ADJUVANT TREATMENT

MALOŠEVAC S.[1]

[1]University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*
sanja.malosevac@gmail.com

Endometrial cancer is the most common gynecological cancer in developed countries with persistently rising incidence rates. In more than 80% of cases it is diagnosed in postmenopausal women (median age at diagnosis is 63 years) but in 10% of cases, patients are younger than 40 years. In 80% of cases, the disease is detected in stage I with 5-year survival rate of 95%, and in about 10% of patients, the disease is in stage IV, with 5-year survival rate of only 17%. The classical histopathological classification of endometrial cancer considers tumor location and size, histological type and grade, depth of myometrial invasion, cervical involvement, lymphovascular space invasion, surrounding organ involvement, lymph node status, supplemented with estrogen receptor status and HER2 status in advanced or recurrent endometrial cancers. In 2013, the genomic classification of endometrial cancer (TCGA Research Network) was published, followed by classification using alternative, more clinically applicable methods of marker determination. Molecular/genomic analysis defines four molecular subgroups of endometrial cancer (POLE mutated, MMRd/MSI-H, p53abn, NSMP) that have prognostic significance and require different therapeutic approaches. Molecular analysis should be done in high grade endometrial cancer, and if possible, in low grade endometrial cancer. PORTEC-3, a multicenter randomized phase 3 study, analyzed the benefit of adjuvant chemoradiotherapy over pelvic radiotherapy alone in women with high-risk stage I, II, and III endometrial cancer. Significant improvement in OS and PPPs, defined as primary targets, has been demonstrated, but with increased toxicity. Additional studies are underway to validate the effectiveness of different modalities of adjuvant treatment according to molecular subtypes of endometrial cancer. RAINBO: Improving adjuvant treatment in the treatment of endometrial cancer Based on molecular features, the TransPORTEC platform – consists of four studies whose primary goal is RFS. There are three randomized studies: The RED/p35abn study examines the effect of adjuvant chemoradiotherapy followed by niraparib vs placebo treatment; The GREEN/MMRd study examines the effect of adjuvant radiotherapy and then treatment with dostarlimab vs placebo; The ORANGE/NSMP study compares adjuvant radiotherapy with and without endocrine therapies. The fourth is an observational study, the BLUE / POLE mut study in which patients were observed after surgery. In additional studies the efficacy of chemotherapy and radiotherapy with or without PD1/PDL1 inhibitors, antihormone therapy, mTOR inhibitors, CDK4/6 inhibitors, PARP inhibitors, antiHER2 therapy, antiVEGF therapy and other potential drugs are being explored. The molecular determinants of endometrial cancer are included in the new ESGO/ESTRO/ESP guidelines as well as in the current NCCN guidelines.

# SEKCIJA MEZENHIMALNIH I KOŽNIH MALIGNIH TUMORA / MEZENCHIMAL AND SKIN CANCERS SESSION

## TROJNA KOMBINACIJSKA TERAPIJA MOŽE BITI BUDUĆI TERAPIJSKI STANDARD KOD NEKIH BOLESNIKA S UZNAPREDOVALIM BRAF-MUTIRANIM MELANOMOM

DABELIĆ N.[1], Marić Brozić J.[1,2], Fröbe A.[3,1]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za onkologiju i nuklearnu medicinu*
[2] Sveučilište u Zagrebu
• *Medicinski fakultet*
[3] Sveučilište u Zagrebu
• *Stomatološki fakultet*
nina.dabelic@kbcsm.hr

Trojne kombinacije anti-PD-1/PD-L1 imunoterapije s anti-BRAF i anti-MEK ciljanom terapijom obećavajuća su antitumorska strategija i sve se više primjenjuju u kliničkim studijama. U ovome preglednom radu, tvrdimo da trojne kombinacije mogu biti budući terapijski standard kod nekih bolesnika s neresektabilnim ili metastatskim melanomom.

Melanom je najagresivniji oblik raka kože. Stope incidencije su među najbrže rastućima među svim malignim tumorima. (1) Uznapredovali neresektabilni/metastatski melanom najubojitiji je oblik raka kože. Uslijed svoje velike heterogenosti i sposobnosti izbjegavanja imunološkog sustava, stanice melanoma često posjeduju fenotip povezan s rezistencijom na lijekove, pa je liječenje melanoma često vrlo otežano.

Nedavno su se pojavile nove terapijske opcije kod bolesnika s uznapredovalim melanomom. Inhibitori malih molekula ciljaju na B-Raf protoonkogen serin/treonin kinazu (BRAF) i/ili MAPK/ERK kinazu (MEK), dok imunoterapijski lijekovi ciljaju na molekule programirane stanične smrti 1 / ligand molekule programirane stanične smrti 1 (PD-1/PD-L1) ili citotoksični T-limfocitni antigen-4 (CTLA-4).

Ciljana terapija koja obuhvaća BRAF-inhibitore (vemurafenib, dabrafenib ili enkorafenib), sama ili, kasnije, uz dodatak i u kombinaciji s MEK-inhibitorima (trametinib, kobimetinib, binimetinib ili selumetinib) bila je dugo prvolinijska terapija kod metastatskog ili uznapredovalog BRAF V600 – pozitivnog melanoma. (2) Razvojem imunologije i imunoterapije raka, CTLA-4 inhibitor ipilimumab, a kasnije PD-1/PD-L1 inhibitori imunoloških kontrolnih točaka (ICI, od engl. *immune checkpoint inhibitors*), prvenstveno pembrolizumab i nivolumab, te atezolizumab, a u kliničkim studijama i durvalumab, avelumab i spartalizumab, također su korišteni u prvolinijskom liječenju uznapredovalog melanoma, samostalno ili kombinacijski. (3–7)

Imunonterapija i ciljana terapija obje imaju svoje značajne prednosti i nedostatke. Značajna prednost ciljane terapije nad imunoterapijom visoka je stopa objektivnih odgovora (ORR, od engl. *objective response rate*), te brz terapijski učinak. Međutim, njezin je glavni nedostatak često kratkotrajno trajanje terapijskog odgovora (DOR, od engl. *duration of response*). (8)

Jasna prednost imunoterapije nad ciljanom terapijom jest omogućavanje dugotrajnijih terapijskih odgovora putem inhibicijskog učinka na rast tumora koji može biti prisutan i prolongirano, nakon završetka imunoterapije. Međutim, najveći nedostatak imunoterapije niže su stope terapijskog odgovora, uz znatno niže stope bolesnika koji odgovore na imunoterapiju. Posljedično, postoji kontinuirana potreba za razvijanjem novih terapijskih strategija. (9)

S obzirom na komplementarnost prednosti i nedostataka imunoterapije i ciljane terapije, njihove kombinacije predložene su i ispitivane u kliničkim istraživanjima. (10) Podaci pokazuju da terapija BRAF- i MEK-inhibitorima povećava broj T-limfocita u tumorskom mikrookolišu i infiltraciju CD8+ T-limfocitima (tj. sposobnost T-limfocita da prodiru u tumor), smanjuje imunosupresivne citokine i povećava ekspresiju PD-1/PD-L1. Navedeno ukazuje da dodatak ciljane terapije imunoterapiji može poboljšati imunološki odgovor. (11, 12)

Unatoč obećavajućim rezultatima iz nekih nedavnih kliničkih istraživanja, pitanje – je li trojna kombinacija superiorna ostalom sustavnom liječenju – još je uvijek prijeporno. Klinička istraživanja trojnih kombinacija kod melanoma uključuju BRAF V600 pozitivne bolesnike neresektabilnog stadija III. ili stadija IV. kojima se daje

trojna terapija inhibicijom PD-1/PD-L1, te BRAF- i MEK-inhibicijom, naspram dvojne terapije ili monoterapije u kontrolnim skupinama.

Podrobnijim proučavanjem, ističe se nekoliko kliničkih istraživanja u ovom području koji su polučili različite rezultate – IMSpire-150 (vemurafenib i kobimetinib uz atezolizumab), (13) TRIdent (dabrafenib i trametinib uz nivolumab), (14) Keynote-022 (dabrafenib i trametinib uz pembrolizumab), (15) IMPemBra (dabrafenib i trametinib uz pembrolizumab), (16) COMBI-i (dabrafenib i trametinib uz spartalizumab). (17)

Sve su studije uključivale BRAF V600 pozitivne bolesnike kako u trojnim tako i u kontrolnim granama istraživanja. Samo je u studiji IMPemBra kod kontrolne skupine primijenjena monoterapija pembrolizumabom, dok su u studijama IMSpire-150, Keynote-022 i COMBI-i kontrolne skupine primale dvojnu kombinacijsku ciljanu terapiju BRAF- i MEK- inhibitorima.

Kliničko istraživanje s pozitivnim rezultatima koji su doveli do registracije trojne terapije u indikaciji liječenja uznapredovalog BRAF-mutiranog melanoma studija je IMSpire-150, u kojoj su primjenjivani vemurafenib i kobimetinib u kombinaciji s atezolizumabom.

IMSpire-150 klinička studija osmišljena je s ciljem evaluacije kombinacije BRAF- i MEK-inhibitora i inhibitora kontrolnih točaka imunološkog sustava u prvolinijskom liječenju bolesnika s BRAF V600 mutiranim uznapredovalim/metastatskim melanomom.

Riječ je o randomiziranoj, multicentričnoj, dvostruko slijepoj, placebom kontroliranoj studiji faze 3. Bolesnici s neresektabilnim stadijem IIIC ili stadijem IV. BRAF V600 pozitivnog melanoma randomizirani su u omjeru 1:1 u skupinu s atezolizumabom (primali su atezolizumab, vemurafenib i kobimetinib) i kontrolnu skupinu (primali su placebo, vemurafenib i kobimetinib). Tijekom prvih 28 dana tj. prvog ciklusa, svi su bolesnici primali samo ciljanu terapiju; atezolizumab ili placebo dodani su od drugog ciklusa terapije nadalje. Bolesnici su stratificirani prema razinama LDH i geografskoj regiji iz koje potječu. Primarni ishod koji se pratio bilo je preživljenje bez progresije bolesti, PFS (od engl. *progression-free survival*) procijenjeno od strane ispitivača. Bolesnici (N=514) su nasumično raspoređeni u skupinu s atezolizumabom (n=256) ili kontrolnu skupinu (n=258). Nakon medijana praćenja od 18,9 mjeseci, PFS je bio značajno produljen u skupini s atezolizumabom u usporedbi s kontrolnom skupinom (15,1 vs 10,6 mjeseci; omjer rizika [HR] 0.78; 95% CI 0.63–0.97; p=0.025). Krivulje PFS-a razdvojile su se nakon 9 mjeseci i ostale razdvojene tijekom dvogodišnjeg praćenja. Medijan trajanja odgovora također je bio dulji kod trojne terapije naspram kontrolne skupine – 21,0 mjeseci vs. 12,6 mjeseci. (13)

Obje skupine bolesnika imale su značajne stope toksičnosti gradusa 3 ili 4 – 79% kod trojne i 73% kod dvojne terapije. Česte nuspojave liječenja (>30%) u obje skupine bile su: povišene razine kreatin-fosfokinaza (CPK) (51,3% vs 44,8%), dijareja (42,2% vs 46,6%), osip (40,9% u obje skupine), artralgija (39,1% vs 28,1%), pireksija (38,7% vs 26,0%), povišene razine alanin-aminotransferaza (ALT) (33,9% vs 22,8%), povišene razine lipaza (32,2% vs 27,4%). Zanimljivo je da je više bolesnika u kontrolnoj skupini prekinulo liječenje zbog nuspojava (16%) nego u skupini s trojnom terapijom (13%). Ukupno je 14 bolesnika umrlo uslijed toksičnosti, sedam u skupini s atezolizumabom i sedam u skupini s placebom.

Ovakva toksičnost nameće potrebu za identifikacijom bolesnika koji imaju potencijal odgovora na ovu skupinu lijekova. U analizi podataka studije IMSpire-150 prezentiranoj na godišnjem sastanku ASCO 2021, interferon gama (IFNg) i tumorsko mutacijsko opterećenje, TMB (od engl. *tumor mutational burden*) bili su čimbenici koji su upućivali na dobit u PFS-u kod bolesnika na trojnoj terapiji. (18)

Bolesnici s urednim razinama LDH i visokim IFNg imali su najveću vjerojatnost postizanja dugotrajnih odgovora. Zaključak je bio da je dodatak atezolizumaba ciljanoj terapiji vemurafenibom i kobimetinibom siguran i dobro se podnosi te da značajno povisuje PFS kod bolesnika s BRAF V600 mutiranim uznapredovalim melanomom.

Međutim, trojna terapija nije povisila stopu objektivnog terapijskog odgovora. Također, prvih 6–8 mjeseci nije bilo razlike u krivuljama PFS-a između skupina; razvojile su se nakon toga. S obzirom da su podaci većine bolesnika analizirani prije no što je prošlo 18 mjeseci, „repovi" krivulja PFS-a kod obje studijske skupine zahtijevaju dulje praćenje. Trojna kombinacija dovela je do povećane ukupne toksičnosti, no navedeno nije dovelo do razlike u stopama prekida terapije između dviju studijskih skupina.

Bitno pitanje u ovom istraživanju, kao i u ostalim koji istražuju trojne kombinacije, izbor je kontrolne skupine. Činjenica jest da je, u trenutku planiranja studije (oko 2013–2015), ciljana kombinirana terapija BRAF- i MEK-inhibitorom bila standard liječenja kod bolesnika s BRAF V600 mutiranim melanomom. Stoga je u trenutku dizajniranja ovog istraživanja, ciljana kombinirana terapija bila logičan izbor kod BRAF V600 mutiranih

melanoma. Neke regulatorne agencije čak su zahtijevale da ova skupina bolesnika dobiva navedenu terapiju u prvoj liniji liječenja. Uslijedila je promjena ka široko prihvaćenoj primjeni inhibitora kontrolnih točaka imunološkog sustava u prvolinijskom liječenju bolesnika s uznapredovalim melanomom neovisno posjeduju li mutaciju BRAF V600. Moglo bi se stoga zaključiti da bi trojna kombinacija trebala biti uspoređivana s anti-PD1 monoterapijom, ili još bolje, s kombinacijskom imunoterapijom.

Temeljem rezultata studije IMSpire-150, 30. srpnja 2020., sjevernoamerička Agencija za hranu i lijekove, FDA (od engl. *Food and Drug Administration*), odobrila je atezolizumab u kombinaciji s kobimetinibom i vemurafenibom kod bolesnika s BRAF V600 mutiranim neresektabilnim ili metastatskim melanomom. Međutim, Europska agencija za lijekove, EMA (od engl. *European Medicines Agency*), nije to još učinila.

Keynote-022 kliničko istraživanje (dabrafenib+trametinib uz pembrolizumab) nije dostiglo svoj primarni cilj (poboljšanje medijana preživljenja bez progresije bolesti, PFS.

Međutim, postojao je pozitivan trend duljeg PFS-a dodatkom pembrolizumaba (medijan PFS-a 16,0 mjeseci kod trojne terapije naspram 10,3 mjeseca kod kontrolne skupine). Ažurirana analiza studije nakon 24-mjesečnog praćenja ukazala je na trojnu terapiju kao potencijalno superiornu terapijsku opciju kod bolesnika s BRAF-mutiranim uznapredovalim melanomom. Naime, stopa 24-mjesečnog PFS-a iznosila je 41% uz dodatak pembrolizumaba naspram 16,3% kod bolesnika na placebu. Medijan ukupnog preživljenja, OS (od engl. *overall survival*) nije bio dostignut uz dodatak pembrolizumaba naspram 26,3 mjeseca kod primjene placeba (HR: 0.64; 95% CI: 0.38–1.06). Stopa ukupnog preživljenja nakon 24 mjeseca bila je 63,3% uz pembrolizumab naspram 51,7% kod placeba (HR: 0.64).

Medijan trajanja odgovora, DOR (od engl. *duration of response*) iznosio je 25,1 mjeseci u skupini s pembrolizumabom naspram 12,1 mjeseci u skupini s placebom. Nuspojave gradusa 3–5 pojavile su se kod 58,3% bolesnika u skupini s pembrolizumabom naspram 25% u skupini s placebom. Najčešće nuspojave gradusa 3–5 bile su: pireksija (10,0% vs 3,3%), povišena vrijednost aspartat-aminotransferaza (67% vs 3,3%), te povišena vrijednost γ-glutamil-transferaza (67% vs 5,0%). (15)

TRIdent (dabrafenib+trametinib uz nivolumab) klinička je studija faze 2 kod bolesnika s metastatskim BRAF-mutiranim melanomom refraktornim na terapiju inhibitorima kontrolnih točaka, i kod bolesnika s asimptomatskim moždanim metastazama. Od 27 uključenih bolesnika, nakon medijana praćenja od 18 mjeseci, ORR iznosio je 92% (uz 3 kompletna odgovora, tj. 12%), medijan PFS-a iznosio je 8,5 mjeseci, a medijan trajanja odgovora 5,8 mjeseci. Približno 78% imalo je nuspojave terapije gradusa 3 ili 4. (14)

IMPemBra kliničko istraživanje primjenjivalo je intermitentnu/kratkotrajnu inhibiciju MAPK-signalnog puta dabrafenibom i trametinibom uz pembrolizumab s namjerom smanjenja toksičnosti bez negativnog učinka na učinkovitost liječenja. Nakon medijana praćenja od 17,4 mjeseci, medijan PFS-a u kontrolnoj grani (monoterapija pembrolizumabom) bio je 10,6 mjeseci naspram 27,0 mjeseci kod bolesnika liječenih pembrolizumabom i kratkotrajnom/intermitentnom primjenom dabrafeniba i trametiniba ($p = 0.13$). Istraživači su zaključili da je kombinacija pembrolizumaba uz intermitentnu primjenu dabrafeniba i trametiniba lakše izvodiva i bolje se podnosi nego kontinuirana trojna terapija. Potrebno je dodatno ispitivanje na većoj kohorti bolesnika kako bi se potvrdila jednaka učinkovitost ove intermitentne kratkotrajne kombinacijske terapije, možda u drugoj liniji liječenja. (16)

COMBI-I (dabrafenib+trametinib uz spartalizumab) randomizirana je, dvostruko slijepa, placebom kontrolirana klinička studija faze 3 koja uspoređuje kombinaciju anti-PD-1 lijeka, spartalizumaba uz dabrafenib i trametinib, naspram placeba uz dabrafenib i trametinib u prvolinijskom liječenju bolesnika s neresektabilnim/metastatskim BRAF V600 pozitivnim melanomom. Prema obnovljenim podacima nakon duljeg praćenja, ova studija nije postigla svoj primarni cilj (dobit u PFS-u procijenjena od strane istraživača). (19)

Unaprijed planirana podanaliza utvrdila je najveću dobit trojne terapije među bolesnicima s visokim razinama LDH, visokim tumorskim mutacijskim opterećenjem, s brojnijim metastatskim sijelima i većim obujmom metastatske bolesti. Nuspojave gradusa 3 bile su prisutne kod 54,7% bolesnika na trojnoj terapiji i 33,3% bolesnika u kontrolnoj skupini na dvojnoj terapiji. Posljedični prekid terapije uslijedio je kod 12,4% bolesnika na trojnoj, te 8,0% bolesnika na dvojnoj terapiji.

Trojnim kombinacijama namjeravaju se iskoristiti visoke stope terapijskog odgovora koje se postižu primjenom BRAF/MEK inhibitora i dugotrajnost odgovora anti-PD-1/L1 imunoterapije. Trojne kombinacije u liječenju melanoma značajno produljuju trajanje odgovora. Navedeno ukazuje da dodatak blokade kontrolnih točaka imunološkog sustava ciljanoj terapiji postiže cilj – pretvaranje nekih kratkotrajnih odgovora u dugotrajne, aktivacijom imunološkog odgovora na melanom.

Trojne kombinacijske terapije inhibicijom PD-1/PD-L1, BRAF-a and MEK-a, postižu statistički značajnu i klinički vrijednu dobit u preživljenju u usporedbi s dvojnim kombinacijama ili monoterapijom.

Međutim, primjena trojne kombinacijske terapije povezana je s povećanom toksičnošću i dodatnim troškovima. Ciljana terapija u trojnim kombinacijama senzitizira bolesnikov imunološki sustav kako bi se poboljšala učinkovitost imunoterapije, a BRAF- i MEK-inhibicija kontrolira tumorski rast. Trojne kombinacije mogu imati dodatne dobrobiti kod bolesnika s BRAF V600 mutiranim uznapredovalim melanomom. Provođenje ciljane terapije BRAF- i MEK-inhibitorima prije započinjanja imunoterapije blokadom PD-1/PD-L1 može maksimalizirati učinak trojne kombinacije.

Međutim, unatoč obećavajućim rezultatima trojnih kombinacija, potrebno je dulje praćenje kako bi se jasno procijenila moguća terapijska dobit. Dodatno, potrebno je više kliničkih studija kako bi se utvrdilo koji bolesnici imaju najveću dobit od trojne kombinacijske terapije i kako bi se odredio optimalni redoslijed primjene i doze trojnih kombinacija.

Potencijalni kandidati za trojne kombinacije bolesnici su za koje se smatra da imaju samo jednu šansu za provođenje učinkovite terapije zbog prisutnosti različitih nepovoljnih čimbenika – brzoprogresivne bolesti, velikog tumorskog opterećenja, visokih razina LDH, metastaza lociranih u nekim kritičnim sijelima i slično. Međutim, kandidati za trojne kombinacije moraju biti pažljivo selektirani zbog više toksičnosti tih tzv. tripleta.

Zaključno, trojne kombinacije dodatkom PD-1/PD-L1-inhibitora BRAF- i MEK-inhibitorima trebale bi biti nova terapija izbora kod bolesnika s BRAF V600 mutiranim, neresektabilnim ili metastatskim melanomom kod kojih je planirano započinjanje liječenja kombinacijom BRAF- i MEK- inhibitora. (20)

Međutim, kako danas većina bolesnika započinje liječenje imunoterapijom, novi podaci sigurno neće još uvijek promijeniti paradigme liječenja. Da bi se to dogodilo, bit će potrebno dulje praćenje koje bi trebalo pokazati održano razdvajanje krivulja preživljenja bez progresije bolesti i „rep" krivulje ukupnog preživljenja sukladan onome koji je postignut primjenom dvojne blokade inhibitora imunoloških kontrolnih točaka.

## TRIPLE COMBINATION THERAPY WITH PD-1/PD-L1, BRAF AND MEK INHIBITOR CAN BE FUTURE THERAPEUTIC STANDARD FOR SOME PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA

DABELIĆ N.[1], Marić Brozić J.[1,2], Fröbe A.[3,1]

[1] University Hospital Center Sestre Milosrdnice
• *Department of Oncology and Nuclear Medicine*
[2] University of Zagreb
• *School of Medicine*
[3] University of Zagreb
• *School of Dental Medicine*
nina.dabelic@kbcsm.hr

Triple combinations of anti-PD-1/PD-L1 immunotherapy with anti-BRAF plus anti-MEK targeted therapy are a promising antitumor strategy and are increasingly used in clinical trials. In this overview we claim that before mentioned triple combinations can be future therapeutic standard for some patients with unresectable or metastatic melanoma.

Melanoma is the most aggressive form of skin cancer. It has one of the fastest growing incidence rate among all malignant tumors. Advanced unresectable/metastatic melanoma is the deadliest type of cutaneous cancer. Due to its high heterogeneity and capability to escape the immune system, melanoma cells often display a multidrug resistance phenotype and can be extremely difficult to treat.

Recently, new therapies for patients with advanced melanoma have emerged. Small molecule inhibitors are targeting B-Raf proto-oncogene serine/threonine-kinase (BRAF) and/or MAPK/ERK kinase (MEK), whereas immunotherapy drugs are targeting the programmed death-1/programmed death-ligand-1 (PD-1/PD-L1) or the cytotoxic T lymphocyte antigen-4 (CTLA-4). Targeted therapy comprising a BRAF inhibitor (vemurafenib, dabrafenib, or encorafenib), alone or, later on, in combination with a MEK inhibitor (trametinib, cobimetinib, binimetinib, or selumetinib) was the first-line therapy for metastatic or advanced BRAF V600-positive melanoma. With the development of cancer immunology and immunotherapy, CTLA-4 inhibitor ipilimumab, and

later on, PD-1/PD-L1 immune checkpoint inhibitors, ICI (primarily pembrolizumab and nivolumab, but also atezolizumab, and in clinical trials durvalumab, avelumab, or spartalizumab), also served as first-line therapy for advanced melanoma either alone or in combination.

Immunotherapy and targeted therapy both have considerable advantages and disadvantages. A strong benefit of targeted therapy over immunotherapy is the high objective response rate (ORR). However, the main disadvantage is often short-lived duration of response (DOR). A strong advantage of immunotherapy over targeted therapy is providing more durable responses with inhibitory effects on cancer growth which may be prolonged after cessation of immunotherapy. However, the biggest downside is lower response rate, with much smaller percentage of people that respond to immunotherapy. Subsequently, there is continuous need for new treatment strategies.

Taking into consideration that immunotherapy and targeted therapy are complementary in terms of advantages and disadvantages, combinations of immunotherapy and targeted therapy have been proposed and applied in clinical trials. Data show that BRAF and MEK inhibitors therapy increases both the number of T cells in the tumor microenvironment and CD8+ T cell infiltration (i.e. T cell ability to penetrate the tumor), downregulates immunosuppressive cytokines, and upregulates PD-1/PD-L1 expressions. This implies that adding targeted therapy to immunotherapy can enhance immune response.

Despite some promising results from the recent clinical trials, the question of whether triple combination therapy is superior to other sistemic therapy is still debatable.

Clinical trials in this setting include patients with stage III to IV metastatic melanoma treated with triple therapy of PD-1/PD-L1 inhibition, BRAF inhibition, and MEK inhibition versus two-drug combination or monotherapy as control group.

When closely looked-up, there are several main clinical trials to take into consideration with different trial results – IMSpire-150 (vemurafenib plus cobimetinib with atezolizumab, Gutzmer et al.), IMSpire-170 (cobimetinib with atezolizumab, Arance et al.), TRIdent (dabrafenib plus trametinib with nivolumab, Tawbi et al.; Burton et al.), Keynote-022 (dabrafenib plus trametinib with pembrolizumab, Ferrucci et al.), IMPemBra (dabrafenib plus trametinib with pembrolizumab, COMBI-i (dabrafenib plus trametinib with spartalizumab, Nathan et al.). In terms of patients' characteristics, all studies except one enrolled BRAF V600 mutation-positive patients in both triple and control treatment arm. Only the study by Ribas et al. enrolled BRAF V600 mutation-positive patients only in triple therapy arm, in contrast to BRAF-wild type patients and patients with other mutations in two-drug control arm. Besides that, only a study by Rozeman et al. used pembrolizumab monotherapy as the control arm, while IMSpire 150, Keynote-022, and COMBI-i studies all used BRAF inhibitor plus MEK inhibitor as control two-drug combination treatment and Ribas et al. study applied PD-L1 inhibitor and MEK inhibitor in the control arm.

The study with positive results that led to registration of triple combo treatment in this indication is IMSpire-150, using vemurafenib plus cobimetinib in combination with atezolizumab.

IMSpire-150 aimed to evaluate combination of BRAF plus MEK inhibitor and immune checkpoint inhibitor in first-line treatment of BRAF V600 mutation-positive advanced/metastatic melanoma.

It was a randomised, multicentric, double-blind, placebo-controlled phase 3 study. Patients with unresectable stage IIIC/IV, BRAF V600 mutation-positive melanoma were randomly assigned 1:1 to 28-day cycles of atezolizumab, vemurafenib, and cobimetinib (atezolizumab group) or atezolizumab placebo, vemurafenib, and cobimetinib (control group). In cycle 1, all patients received vemurafenib and cobimetinib only; atezolizumab or placebo was added from cycle 2 onward. Randomisation was stratified by lactate dehydrogenase (LDH) concentration and geographical region. The primary outcome was investigator-assessed progression-free survival (PFS). Patients (N=514) were enrolled and randomly assigned to the atezolizumab group (n=256) or control group (n=258). At a median follow-up of 18.9 months, PFS was significantly prolonged with atezolizumab versus control (15.1 vs 10.6 months; hazard ratio [HR] 0.78; 95% CI 0.63–0.97; p=0.025). The curves separated by 9 months and remained separate with 2 years follow-up. The median duration of response (DOR) also seemed longer with the triplet: 21.0 months vs 12.6 months.

Both arms experienced a notable amount of grade 3 or 4 toxicity: 79% with the triplet and 73% with the doublet. Common treatment-related adverse events (>30%) in the atezolizumab and control groups were blood creatinine phosphokinase (CPK) increased (51.3% vs 44.8%), diarrhoea (42.2% vs 46.6%), rash (40.9%, both groups), arthralgia (39.1% vs 28.1%), pyrexia (38.7% vs 26.0%), alanine aminotransferase (ALT) increased

(33.9% vs 22.8%), and lipase increased (32.2% vs 27.4%). Interestingly, more patients in the control group stopped all treatment because of adverse events (16%), than patients in the atezolizumab group (13%). Overall, 14 patients died from grade 5 toxicities, seven in the triplet arm and seven in the placebo arm.

The conclusion was that the addition of atezolizumab to targeted therapy with vemurafenib and cobimetinib was safe and tolerable and significantly increased PFS in patients with BRAF V600 mutation-positive advanced melanoma.

However, triple therapy did not increase the objective response rate. There was no difference between groups in the PFS curves for the first 6–8 months, which separated later on. As most patients were censored before 18 months, the tails of the PFS curves in both study groups require further follow-up. The triple combination therapy resulted in increased overall toxicities, but no change in the rate of discontinuation of study drugs owing to toxicities.

Based on these study results, on July 30, 2020, the Food and Drug Administration (FDA) approved atezolizumab in combination with cobimetinib and vemurafenib for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. However, it is not approved by European Medicines Agency (EMA).

Keynote-022 (dabrafenib+trametinib with pembrolizumab) did not meet its primary endpoint (improved median progression free survival, PFS), although a trend towards a longer PFS with addition of pembrolizumab (median PFS 16.0 months versus 10.3 months with placebo) was reported. An updated analysis of KEYNOTE 022 trial at 24-month follow-up showed the triplet combo as a potentially superior treatment option for patients with BRAF-mutant advanced melanoma. 24-month PFS rates were 41% with pembrolizumab compared to 16.3% with placebo. Median overall survival (mOS) was not reached with pembrolizumab vs 26.3 months with placebo (HR: 0.64; 95% CI: 0.38–1.06). Overall survival (OS) rates at 24 months were 63.3% with pembrolizumab compared to 51.7% with placebo, respectively (HR: 0.64). Median duration of response (mDOR) was 25.1 months in the pembrolizumab arm compared to 12.1 months in the placebo arm. G3–5 AEs occurred in 58.3% in the pembrolizumab arm, compared to 25% in the placebo arm. The most common G3–5 treatment related adverse effects (trAEs) were: pyrexia (10.0% vs 3.3%), increased aspartate aminotransferase (6.7% vs 3.3%), and increased γ-glutamyl transferase (6.7% vs 5.0%).

TRIdent (dabrafenib+trametinib with nivolumab) is a phase II trial in patients with metastatic melanoma with BRAF mutations, refractory to immune-checkpoint inhibitor (IC) therapy, and in patients with asymptomatic brain metastasis. Of the 27 patients, after a median follow-up of 18 months, ORR was 92% (3 CR, 12%), median PFS was 8.5 months, and mDOR was 5.8 months. Approximately 78% of patients experienced G3–4 trAEs.

IMPemBra clinical trial used intermittent/short-term dual MAPK-pathway inhibition with dabrafenib+ trametinib with pembrolizumab in order to diminish toxicity without compromising efficacy. After median follow-up of 17.4 months, the median PFS in the control arm (pembrolizumab monotherapy) was 10.6 months versus 27.0 months for patients treated with pembrolizumab and short-term/intermittent dabrafenib and trametinib ($p = 0.13$). Investigators concluded that the combination of pembrolizumab plus intermittent dabrafenib and trametinib seemed more feasible and tolerable than continuous triplet therapy. Futher investigation in larger patient cohort is needed to confirm equal effectivenes of this intermittent short-time combination therapy, possibly as second line treatment.

COMBI-I (dabrafenib+trametinib with spartalizumab) is a randomized, double-blind, placebo-controlled, phase III clinical trial comparing the combination of anti-PD-1 spartalizumab in combination with dabrafenib and trametinib in comparison to the combination of placebo with dabrafenib and trametinib, in the first line in patients with unresectable/metastatic BRAFV600-positive melanoma. According to the update, this trial failed to meet its primary endpoint (investigator-assessed PFS).

Conclusion: Triple combination therapy of PD-1/PD-L1, BRAF- and MEK- inhibition had significant survival benefit over two-drug combination or monotherapy and should be therefore considered a new preferred therapy for patients with stage III-IV advanced and metastatic melanoma. However, the use of triple combination therapy is associated with the increased toxicity and added costs. Use of the triple combination drugs sensitized the patients' immune system to improve the efficacy of immunotherapy and inhibition of BRAF and MEK to control tumor growth. Triple combination therapy can have added benefits for patients harboring the BRAF V600 mutation-positive advanced melanoma. Applying a period of BRAF and MEK targeted therapy prior to the commencement of PD-1/PD-L1 immunotherapy could maximize the benefits of triple combo therapy. However,

despite the promising results of triple combination therapy, longer follow-up is needed to see the possible benefit from the triple therapy. Additionally, more clinical trials are needed to establish which patients benefit the most from the triple combination therapy, and to find out the optimal sequence and dose of triple drug administration.

## LITERATURA


1. *Schadendorf D, van Akkooi ACJ, Berking C i sur.* Melanoma. Lancet. 2018;392(10151):971–84.
2. *Long GV, Stroyakovskiy D, Gogas H i sur.* Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877–88.
3. *Larkin J, Chiarion-Sileni V, Gonzalez R i sur.* Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(1):23–34.
4. *Robert C, Long GV, Brady B i sur.* Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320–30.
5. *Robert C, Ribas A, Schachter J i sur.* Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019;20(9):1239–51.
6. *Postow MA, Chesney J, Pavlick AC i sur.* Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372(21):2006–17.
7. *Hodi FS, O'Day SJ, McDermott DF i sur.* Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23.
8. *Kakadia S, Yarlagadda N, Awad R i sur.* Mechanisms of resistance to BRAF and MEK inhibitors and clinical update of US Food and Drug Administration-approved targeted therapy in advanced melanoma. Onco Targets Ther. 2018;11:7095–107.
9. *Giugliano F, Crimini E, Tarantino P i sur.* First line treatment of BRAF mutated advanced melanoma: Does one size fit all? Cancer Treat Rev. 2021;99:102253.
10. *Trojaniello C, Vitale MG, Ascierto PA.* Triplet combination of BRAF, MEK and PD-1/PD-L1 blockade in melanoma: the more the better? Curr Opin Oncol. 2021;33(2):133–8.
11. *Liu Y, Zhang X, Wang G, Cui X.* Triple Combination Therapy With PD-1/PD-L1, BRAF, and MEK Inhibitor for Stage III-IV Melanoma: A Systematic Review and Meta-Analysis. Front Oncol. 2021;11:693655.
12. *Wilmott JS, Long GV, Howle JR i sur.* Selective BRAF inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clin Cancer Res. 2012;18(5):1386–94.
13. *Gutzmer R SD, Gogas H, Robert C i sur.* Atezolizumab, Vemurafenib, and Cobimetinib as First-Line Treatment for Unresectable Advanced BRAF(V600) Mutation-Positive Melanoma (Imspire150): Primary Analysis of the Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. Lancet. 2020;395(10240):1835–44.
14. *Burton EM, Amaria RN, Glitza IC i sur.* Phase II Study of TRIplet combination Nivolumab (N) with Dabrafenib (D) and Trametinib (T) (TRIDeNT) in patients (pts) with PD-1 naïve or refractory BRAF-mutated metastatic melanoma (MM) with or without active brain metastases. J Clin Oncol. 2021;39(15_suppl):9520–.
15. *Ferrucci PF, Di Giacomo AM, Del Vecchio M i sur.* KEYNOTE-022 part 3: a randomized, double-blind, phase 2 study of pembrolizumab, dabrafenib, and trametinib in BRAF-mutant melanoma. J Immunother Cancer. 2020;8(2).
16. *Rozeman EA, Versluis JM, Sikorska K i sur.* The IMPemBra trial, a phase II study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in melanoma patients harboring the BRAFV600 mutation. J Clin Oncol. 2020;38(15_suppl):10021–.
17. *Dummer R, Arance Fernández AM, Hansson J i sur.* Preliminary findings from part 1 of COMBI-i: A phase III study of anti–PD-1 antibody PDR001 combined with dabrafenib (D) and trametinib (T) in previously untreated patients (pts) with advanced BRAF V600-mutant melanoma. J Clin Oncol. 2018;36(5_suppl):189–.
18. *Robert C LK, Ascierto PA i sur.* Effects of baseline lactate dehydrogenase, interferon gamma expression, and tumor mutational burden on treatment response to first-line atezolizumab + vemurafenib and cobimetinib in BRAF V600 mutation-positive advanced melanoma. ASCO Annual Meeting 2021.
19. *Nathan P DR, Long GV, Ascierto PA i sur.* Spartalizumab Plus Dabrafenib and Trametinib (Sparta-DabTram) in Patients (pts) With Previously Untreated BRAF V600–Mutant Unresectable or Metastatic Melanoma: Results From the Randomized Part 3 of the Phase III COMBI-I Trial. Ann Oncol. / ESMO. 2020;31.
20. *Ribas A.* Triple therapy for BRAF(V600)-mutated melanoma. Lancet. 2020;395(10240):1814–5.

## BUDUĆNOST LIJEČENJA UZNAPREDOVALOG MELANOMA BITI ĆE U SEKVENCIJSKOM LIJEČENJU

BLAŽIČEVIĆ K.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
kblazice@gmail.com

Već dulji niz godina standard u liječenju uznapredovalog melanoma uključuje imunoterapiju inhibitorima kontrolne točke te ciljanu terapiju BRAF i MEK inhibitorima. Premda sada već imamo dosta podataka iz kliničkih studija i iz svakodnevne kliničke prakse i dalje nemamo potpuno jednoznačan algoritam liječenja bolesnika s uznapredovalim melanomom. Pojavom novih terapija postigli smo to da je petogodišnje preživljenje oko 40% za one liječene imunoterapijom (čak preko 50% za liječene kombinacijskom imunoterapijom), a 1/3 liječenih BRAF i MEK inhibitorima preživi 5 godina.

Koliko god ovi podatci izgledaju fascinantno, pogotovo ako usporedimo s ranijim periodom kada je jedina opcija bila liječenje kemoterapijom, i dalje ostaje značajan udio bolesnika koji nemaju povoljne ishode što nas upućuje na potrebu za dodatnim studijama kako bi postigli što bolje ishode liječenja.

Na tom tragu rađeno je nekoliko studija koje nastoje odgovoriti kako najbolje odabrati prvolinijsko liječenje, odnosno kako najbolje sekvencionirati postojeće terapijske opcije.

Kod melanoma koji nemaju mutaciju u BRAF genu izbor prvolinijskog liječenje donekle je jednostavan te uključuje imunoterapiju inhibitorima kontrolne točke, bilo kao monoterapija (nivolumab, pembrolizumab) ili kao kombinacijska terapija (nivolumab+ipilimumab).

Puno kompleksnija situacija je kod BRAF mutiranih melanoma kod kojih u prvoj liniji moramo odabrati BRAF i MEK inhibitore ili imunoterapiju. Pa tako imamo studije koje su istraživale sekvencijski pristup liječenju, a koje su pokušale dati odgovor na pitanje koja bi terapijska opcija bila optimalnija u prvoj liniji liječenja. S druge strane, istraživan je i pristup u kojem se u prvoj liniji liječenja koriste istovremeno obje opcije – imunoterapija u kombinaciji s BRAF i MEK inhibitorima (trojna kombinacija).

Prednost u sekvencijskom pristupu liječenju očituje se u tome što imamo dokazano učinkovite terapije u prvoj liniji i pitanje je jeli potrebno koristiti trojne kombinacije ako nam je jedan lijek odnosno jedna terapijska opcija dovoljna za postizanje dobre stope odgovora, odnosno kontrole bolesti.

Nadalje, ako bi u prvoj liniji koristili trostruku kombinaciju, pitanje je što bi nakon progresije mogli ponuditi kao daljnju opciju liječenja.

I naposljetku, trojne kombinacije nose i znatno više nuspojava te znatno veće financijsko opterećenje.

S druge strane, postoje još neka otvorena pitanja u sekvencijskom pristupu liječenju. Nejasno je kada bi trebalo napraviti promjenu terapije, jeli to u trenutku progresije bolesti ili pak nakon određenog maksimalnog odgovora odnosno maksimalne redukcije tumora ili bi to trebalo biti nakon nekog točno određenog vremena ('run in' faza). Nejasno je i utječe li različito sekvencioniranje terapije na dugoročne ishode (poput ukupnog preživljenja). Potrebne su svakako dodatne studije, a i dodatni podaci iz stvarnog svijeta ('Real world data') koji bi nam potencijalno mogli dati odgovore na otvorena pitanja. Osim toga, definiranje biomarkera moglo bi biti od dodatne koristi, kao i neke nove tehnike kao što su, primjerice, tekućinska biopsija.

## SEQUENCING APPROACH WILL BE THE FUTURE OF TREATMENT OF ADVANCED MELANOMA

BLAŽIČEVIĆ K.[1]

[1] University Hospital Center Zagreb
• *Department of Oncology*
kblazice@gmail.com

For many years now, the standard treatment of advanced melanoma includes immunotherapy with checkpoint inhibitors and targeted therapy with BRAF and MEK inhibitors. Although we already have a lot of data from clinical studies and from everyday clinical practice, we still do not have a completely unambiguous algorithm for treating patients with advanced melanoma. With the advent of new therapies, we have achieved a five-

year survival of about 40% for those treated with immunotherapy (over 50% for those treated with combination immunotherapy), and about one third of patients treated with BRAF and MEK inhibitors survive 5 years.

As fascinating as these data may seem, especially when compared to the earlier period when chemotherapy was the only treatment option, a significant proportion of patients still do not have favorable outcomes, suggesting the need for additional studies to achieve better treatment outcomes.

On this track, several studies have been conducted that seek answer how to choose optimal first-line treatment, or how to choose best therapy sequence within existing therapeutic options.

In BRAF wild type melanoma, the choice of first-line treatment is somewhat simple and involves immunotherapy with checkpoint inhibitors, either as monotherapy (nivolumab, pembrolizumab) or as a combination therapy (nivolumab + ipilimumab).

A much more complex situation is with BRAF mutant melanomas where in the first line we have to choose between BRAF and MEK inhibitors or immunotherapy. Studies were conducted that explore sequential approach to treatment, and which have tried to answer the question of which therapeutic option would be optimal for the first-line treatment. On the other hand, we also have trials that explore both treatment options applied simultaneously in the first line of treatment – immunotherapy in combination with BRAF and MEK inhibitors (triplet combination).

The advantage of sequential approach to treatment is that we have proven effective therapies in the first line and the question is whether it is necessary to use triplet combinations if one drug or one therapeutic option is enough to achieve a good response rates and disease control.

Furthermore, if a triplet combination was used in the first line, the question is what could be offered as a further treatment option after disease progression.

Finally, triplet combinations carry significantly more side effects and have significantly higher financial burden.

On the other hand, there are still some open questions regarding sequential approach. It is still unclear when a change in therapy should be made, whether at the time of disease progression or after a certain maximum response or maximum tumor reduction, or whether it should be after a specific time period ('run in' phase). It is also unclear whether different sequencing of therapy affects long-term outcomes (such as overall survival). We definitely need additional studies, as well as additional real-world data that could potentially give us answers to open questions. In addition, defining biomarkers could be of additional benefit, as well as some new techniques such as, for example, liquid biopsy.

## U VREMENU DOSTUPNE ADJUVANTNE TERAPIJE ZA MELANOM KOJI SU BOLESNICI KANDIDATI ZA NEOADJUVANTNO LIJEČENJE?

SIMETIĆ L.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
luka.doc@gmail.com

**Cilj**: Adjuvantni ili neoadjuvantni pristup kod liječenja melanoma, kome, kada i kod kojeg stadija? Definitivni odgovor, gledajući rezultate adjuvantnih i neoadjuvantnih studija, još uvijek ne postoji. Brojne studije faze II i III ispitivale su adjuvantnu primjenu ciljane terapije i imunoterapije u kompletno reseciranom stadiju III (IIIA, IIIB, IIIC) i stadiju IV (anti PD-1 inhibitor nivolumab). Pokazale su jasan benefit u vremenu do povratka bolesti (PFS) i ukupnom preživljenju (OS). Također su sve brojnije studije s neoadjuvantnom aplikacijom navedenih lijekova i posljedično izvrsnim rezultatima.

**Metode**: U svrhu izrade rada pretražena je medicinska bibliografska baza PubMed® po pojmovima: neo/adjuvantna terapija u stadiju III i IV melanoma, ciljana terapija i imunoterapija uz orijentaciju na studije faze II-III te meta analize i sistematske preglede.

**Rezultati**: Adjuvantna terapija, i imunoterapija i ciljana BRAF I MEK terapija, kod kompletno reseciranog melanoma stadija III i stadija IV (samo anti PD-1 inh. nivolumab) postala je zlatni standard u liječenju. Studije s neadjuvantnom intencijom, donijele su zanimljivi koncept "uvida" u učinak imuno ili ciljane terapije nakon operativnog liječenja i PHD analize (patološki odgovor) i time mogućnosti procjene rizika od povrata bolesti i preživljenja. S druge strane uvidom u postoperativni nalaz postoji mogućnost " promjene" adjuvantne terapije.

**Zaključak**: opsežnija lokalna bolest (klinički palpabilni limfni čvorovi) odnosno viši podstadiji stadija III (IIIC, IIID) sugeriraju uporabu neoadjuvantnog pristupa, koji je trenutno još uvijek ekperimentalnog statusa. Navedeno nam omogućuje "downstaging" bolesti, lakšu kirurgiju ili čak potencijalno izbjegavanje kirurgije (u slučaju kompletnog patološkog odgovora). Uvidom u posterapijski/postoperativni nalaz (patološki odgovor) moći ćemo predvidjeti rizik od povrata biolesti i preživljenje. Adjuvantna terapija je svakako zlatni standard te će osim u visokorizičnim stadijima (IIIC I IIID) svoje definitivno mjesto imati u nižim podstadijima stadija III i prema friškim studijama s ESMO 2021. vjerojatno i u visokorizičnim stadijima II (IIC, IIB).

## WHO ARE THE CANDIDATES FOR NEOADJUVANT APPROACH IN THE ERA OF ADJUVANT THERAPIES OF MELANOMA?

SIMETIĆ L.[1]

[1] University Hospital Center Zagreb
• *Department of Oncology*
luka.doc@gmail.com

**Aim**: Adjuvant or neoadjuvant approach in stage III melanoma? Who are the best candidates and when to apply it? Many questions, but from a current oncological perspective without any definitive answer. A plethora of phase II/ phase III neo/adjuvant trials with immunotherapy or targeted therapy in completely resected stage III melanoma (IIIA, IIIB, IIIC adn IIID) are available. Adjuvant therapy showed promising results with statistically significant benefit in progression free survival (PFS) and overall survival (OS). Similar results are awaited from neoadjuvant trials

**Methods**: we searched PubMed to identify systematic reviews, meta analysis and phase II, phase III neo/adjuvant clinical trials with immunotherapy or targeted therapy in completely resected stage III melanoma.

**Results**: Immunotherapy and targeted therapy (BRAF and MEK inh.) are a standard of care in completely resected stage III (IIIA, IIIB, IIIC and IIID). With neoadjuvant approach and analysis of postoperative pathological response score we can predict some survival outcomes and even change the adjuvant arm (if needed) in case of inadequate pathological response.

**Conclusion**: patients with clinically palpable lymph nodes or high risk subgroups of stage III (IIIC and IIID) are suggested to be the best candidates for neoadjuvant approach. Neoadjuvant therapy is still designated as off label. With neoadjuvant approach we can reduce tumor mass and facilitate surgery or possibly avoid it (in case of complete pathological response). Postoperative pathological response score is a surrogate of progression free survival and OS respectively-results are awaited. From a current perspective, adjuvant therapy in stage III melanoma is a standard of care and neoadjuvant approach is still experimental. In near future, according to novel studies presented at ESMO 2021, adjuvant therapy will be also placed in high risk stage II (IIB and II C).

# SEKCIJA POTPORNO LIJEČENJE I PALIJATIVNA SKRB / SUPPORTIVE AND PALLIATIVE CARE SESSION

## KRITERIJI ZA UKLJUČIVANJE SUPORTIVNOG I PALIJATIVNOG LIJEČENJA KOD ONKOLOŠKIH BOLESNIKA – PREPOZNAVANJE PACIJENATA KOJIMA JE POTREBNA PALIJATIVNA SKRB

KUKEC I.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
ivana.kukec.md@gmail.com

Rano uključivanje palijativne skrbi kod pacijenata s rakom dokazano poboljšava stanje pacijenta, smanjuje simptome, poboljšava bolesnikovu kvalitetu života, poboljšava zadovoljstvo pacijenta i zdravstvenih djelatnika, podržava komunikaciju i promiče izbor pacijenta. Nadalje, pokazalo se da rana palijativna skrb smanjuje broj akutnih onkoloških prijema i broj dolazaka u hitne službe.

Istaknute organizacije poput Svjetske zdravstvene organizacije, ESMO-a, ASCO-a preporučuju da bi palijativna skrb trebala započeti rano, zajedno sa standardnom onkološkom skrbi.

Postoje prepreke za pravovremeno upućivanje bolesnika palijativnoj skrbi. Jedna od prepreka je što riječi ”palijativa” ili “palijativna skrb” imaju negativnu konotaciju među pacijentima. Radi navedenog ESMO odbor za suportivno i palijativno liječenje predlaže termin “Patient-centred-care” tj. skrb/njega usmjerena na bolesnika. Zatim, postoji manjak edukacije i percepcije kako među bolesnicima, tako i među zdravstvenim djelatnicima što suportivno i palijativno liječenje uključuje. Samim time odgađa se pravovremeno upućivanje i prihvaćanje palijativnih intervencija, pa palijativna skrb često započinje prekasno, kada je bolest u kritičnoj fazi.

U ovom radu istražuju se dvije skupine kriterija za uključivanje suportivnog i palijativnog liječenja kod ambulantnih onkoloških bolesnika.

Prvo su kriteriji za upućivanje onkološkog bolesnika palijativnoj skrbi tzv. Hui-evi kriteriji donešeni međunarodnim koncenzusom stručnjaka iz područja palijativne medicine (Delphi metodom). Radi se o alatu koji uključuje 11 kriterija. Drugi kriteriji su razvijeni u „Royal Marsden Hospital” (London, UK) tzv. “RM triggers tools”. Radi se o alatu koji uključuje 7 kriterija.

## TRIGGERS FOR REFERRAL TO PALLIATIVE CARE – IDENTIFYING PATIENTS IN NEED OF PALLIATIVE CARE

KUKEC I.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
ivana.kukec.md@gmail.com

Early involvement of palliative care for patients with cancer has been proven in studies to improve patient experience, reduce symptom burden, improves quality of life, improves the patient and caregiver satisfaction, support communication, and promote patient choice. Furthermore, early palliative care has been shown to reduce the use of acute care services including inpatient hospital admissions and emergency department attendances.

Prominent organisations such as The World Health Organisation, the European Society for Medical Oncology and the American Society of Clinical Oncology recommend that palliative care should be delivered early on, alongside standard oncology care.

There are several barriers to palliative care referral. Some of the obstacles are that the word “palliative” may have negative connotations for patients. The ESMO Supportive and Palliative Care Faculty therefore proposes the use of the term “patient-centered care”. Furthermore, there is a lack of education and awareness among patients and caregivers of what supportive and palliative care entails. This delays the palliative care referral and acceptance of palliative interventions, and palliative care is often initiated late in the course of a critical illness.

Two groups of criteria for referral (triggers) to supportive and palliative care among outpatient oncology patients are investigated in this paper.

First, of the criteria for referring an oncology patient to palliative care are the so-called Hui's criteria adopted by the international consensus of experts in the field of palliative medicine (Delphi method). It is a tool that includes 11 criteria. Other Palliative Care Referral criteria-"Trigger" Tool was developed at the Royal Marsden Hospital (London, UK) – "RM triggers tool". It is 7-point palliative care referral criteria.

## NOVOSTI U LIJEČENJU I PREVENCIJI EMEZE

GOLČIĆ M.[1]

[1] Klinički bolnički centar Rijeka
• *Klinika za radioterapiju i onkologiju*
marin.golcic@gmail.com

Prevencija mučnine i povraćanja jedna je od najvažnijih zadaća onkologa tijekom planiranja kemoterapije, s obzirom da su studije pokazale kako je strah od mučnine i povraćanja jedan od najvažnijih čimbenika za kvalitetu života pacijenata. Vodeće svjetske smjernice dijele kemoterapeutike ovisno o riziku za izazivanje mučnine, odnosno emeze u 4 kategorije: one s visokim (>90% šanse za emezu), umjerenim (30–90%), malim (10–30%) i minimalnim rizikom (<10%). Kao dugogodišnja baza za liječenje i prevenciju emeze koristili su se metoklopramid, prokinetik s dodatnim djelovanjem na serotoninske receptore, i deksamethason, dok je velik napredak postignut u 1980-im godinama s razvojem dodatnih serotoninskih antagonista poput ondanseetrona. Uz djelovanje na 5-HT sustav, važan pomak u liječenju emeze postignut je s razvojem NK1 antagonista poput aprepitanta teposebno u kombiniranju ove dvije skupine lijekova u jedan lijek. Stoga, za najemetogenije kemoterapeutike danas se prema smjernicama uvriježila kombinacija deksametazona uz 5-HT3 i NK1 receptor antagoniste. Međutim, čak ni ta kombinacija nije često dovoljna što je potaklo japanske kolege da dizajniraju studiju faze 3 (J-FORCE), u kojem je ispitivano korištenje olanzapina uz trostruku antiemetsku terapiju za bolesnike liječene cisplatinom. Rezultati pokazuju da je kompletan odgovor postignut u skoro 4/5 svih bolesnika (79%), značajno više u odnosu na bolesnike bez olanzapina (66%), p<0.0001. Od značajnijih nuspojava isticale su se sedacija i suhoća ustiju, no lijek se odlično podnosio jer su nuspojava bile gradusa 1 i 2. Navedena studija, obavljena u *The Lancetu* krajem 2019, postavila je novi standard prevencije emeze što su ubrzo i prihvatile i NCCN smjernice. No, kako se radi o starom lijeku koji je inicijalno korišten kao antipsihotik, a sada je dostupan u više generičkih formulacija, potrebno je osvijestiti i diskutirati o odličnim rezultatima olanzapina kako bi našim pacijentima mogli ponuditi najkvalitetniju moguću skrb.

## A NEW PARADIGM IN THE TREATMENT AND PREVENTION OF EMESIS

GOLČIĆ M.[1]

[1] University Hospital Centre Rijeka
• *Department of Radiotherapy and Oncology*
marin.golcic@gmail.com

Prevention of nausea and vomiting is one of the most important tasks of oncologists during chemotherapy planning, as studies have shown that fear of nausea/vomiting is one of the most important factors for patients' quality of life. Leading oncological guidelines divide chemotherapeutics depending on the risk of causing nausea or emesis into 4 categories: those with high (> 90% chance of emesis), moderate (30–90%), low (10–30%) and minimal risk (< 10%). Metoclopramide, a prokinetic with additional action on serotonin receptors, and dexamethasone have been used for an extended period of time as a basis for the treatment and prevention of emesis. Great progress was made in the 1980s with the development of additional serotonin antagonists such as ondansetron. In addition to targeting the 5-HT system, an important breakthrough in the treatment of emesis has been achieved with the development of NK1 antagonists such as aprepitant and in particular in the combination of these two groups of drugs into a single medication. Therefore, for the most emetogenic chemotherapeutics, the combination of dexamethasone with 5-HT3 and NK1 receptor antagonists has become a standard of care. Howe-

ver, even this combination is often insufficient, prompting Japanese colleagues to design a phase 3 (J-FORCE) study, which examined the use of olanzapine with triple antiemetic therapy for cisplatin-treated patients. The results show that a complete response was achieved in almost 4/5 of all patients (79%), significantly more than in patients without olanzapine (66%), p <0.0001. Although sedation and dry mouth were significantly more common in the olanzapine group, the drug was well tolerated because the majority of side effects were grades 1 and 2. The study, published in *The Lancet* in late 2019, set a new standard for emesis prevention and was accepted by the NCCN guidelines. However, as olanzapine is an old drug that was initially used as an antipsychotic and is now available in multiple generic formulations, we need to be aware of and discuss the excellent results of olanzapine in order to offer our patients the best possible care.

## ANALIZA BIOELEKTRIČNE IMPENDANCE U PROSUDBI NUTRITIVNOG STATUSA ONKOLOŠKIH BOLESIKA

VUČINIĆ D.[1], Dobrila-Dintinjana R.[1,2]

[1] Klinički bolnički centar Rijeka
• *Klinika za radioterapiju i onkologiju*
[2] Sveučilište u Rijeci
• *Medicinski fakultet*
damir.vucinic@gmail.com

Sindrom tumorske anoreksije-kaheksije (CACS) je sindrom karakteriziran gubitkom tjelesne težine s popratnim gubitkom mišićnog i masnog tkiva, oslabljenom imunološkom funkcijom i metaboličkim smetnjama koji je uzrokovan multifaktorijelnim čimbenicima (smanjen unos hrane, sustavna upala, abnormalni metabolizam). Razvoju sindroma CACS u velikoj mjeri pridonose i nuspojave liječenja onkološke bolesti (kirurgija/radioterapija/sistemna antitumorska terapija). CACS dovodi do slabljenja funkcionalnosti pacijenta i tjelesnih performansi te je povezan s lošim odgovorom na onkološku terapiju, lošom kvalitetom života i lošijim ishodom bolesti. Osim u malignih bolesti, gubitak mišića i slabost česti su i u mnogim drugim bolestima i stanjima, uključujući starenje.

Sarkopenija je sindrom koji označava gubitak mišićne mase uz gubitak snage i funkcije i u određenoj životnoj dobi je uobičajen nalaz. Dijagnoza sarkopenije temelji se na nalazu niske mišićne mase uz nisku mišićnu snagu ili niske tjelesne performanse. Kaheksija i sarkopenija imaju i neke zajedničke patološke mehanizme koji utječu na propadanje mišića (upala i oksidativni stres). Točne procjene sarkopenije dobivaju se radiološkim metodama: skeniranje kompjuterskom tomografijom (CT) sa slikama presjeka na razini trećeg lumbalnog kralješka (L3); snimanje magnetskom rezonancijom (MRI); skeniranje rentgenske apsorpciometrije s dvostrukom energijom (DXA). DXA se više koristi za analizu gustoće kostiju, ali također pruža točnu procjenu ostale tjelesne mase, osim za masu skeletnih mišića.

Prema smjernicama EU i više azijskih zemalja za objektivnu procjenu tjelesne građe potrebno je koristiti analizu bioelektrične impedancije (BIA). Tijekom pregleda, BIA analizatori unose električnu struju niske voltaže u tijelo ispitanika i mjere otpor ili impedanciju protoku struje. BIA tehnologija koristi različite električne frekvencije (1 do 1.000 kHz) za procjenu količine izvanstanične vode, unutarstanične vode, ukupne tjelesne vode, masne mase, mase bez masti, mišićne mase i faznog kuta. Phase Angle – PA odnosno fazni kut (omjer između rezistencije i reaktancije) smatra se pokazateljem integriteta stanične membrane i prediktorom ukupne tjelesne mase stanica. Nizak PA može ukazivati na oštećenje stanične membrane, što je u onkoloških bolesnika učestalo povezano sa smanjenim ukupnim preživljenjem. U literaturi se između ostalih, izdvaja čak devet studija s 1496 pacijenata koje su pokazale da je nizak PA bio povezan s lošijim indeksom tjelesne mase, nižom razinom albumina u serumu, transferinom i masom bez masti. Stoga su Grossberg i sur. zaključili da BIA daje točne procjene tjelesnog sastava kod pacijenata s rakom glave i vrata. Wladysiuk i sur. povezali su rizik od niskog ukupnog preživljavanja s PA i dokazali da je rizik bio statistički značajno veći u pacijenata s PA manjim od 4,733 stupnja u odnosu na druge pacijente.

Zaključno, BIA je pristupačna metoda, jednostavna za korištenje i dokazano učinkovita metoda za otkrivanje nutritivnog rizika kod odraslih osoba oboljelih od raka prije i tijekom onkološkog liječenja. Kaheksija i sarkopenija utvrđene BIA metodom mogu imati prognostičku vrijednost za više vrsta tumora.

# BIOELECTRICAL IMPEDANCE ANALYSIS IN THE ASSESSMENT OF NUTRITIONAL STATUS IN CANCER PATIENTS

**VUČINIĆ D.**[1], **Dobrila-Dintinjana R.**[1,2]

[1] University Hospital Centre Rijeka
• *Department of Radiotherapy and Oncology*
[2] University of Rijeka
• *School of medicine*
damir.vucinic@gmail.com

Tumor anorexia-cachexia syndrome (CACS) is a syndrome characterized by weight loss with concomitant loss of muscle and fat tissue, impaired immune function and metabolic disturbances caused by multifactorial factors (decreased food intake, systemic inflammation, abnormal metabolism). The side effects of cancer treatment (surgery / radiotherapy / systemic antitumor therapy) also contribute greatly to the development of CACS syndrome. CACS leads to impaired patient functionality and physical performance and is associated with poor response to oncology therapy, poor quality of life, and poorer disease outcome. In addition to malignant diseases, muscle loss and weakness are common in many other diseases and conditions, including aging.

Sarcopenia is a syndrome that means loss of muscle mass with loss of strength and function and is a common finding at a certain age. The diagnosis of sarcopenia is based on the finding of low muscle mass with low muscle strength or low physical performance. Cachexia and sarcopenia also have some common pathological mechanisms that affect muscle deterioration (inflammation and oxidative stress). Accurate estimates of sarcopenia are obtained by radiological methods: computed tomography (CT) scan with cross-sectional images at the level of the third lumbar spine (L3); magnetic resonance imaging (MRI); double energy X-ray absorptiometry scanning (DXA). DXA is used more for bone density analysis, but it also provides an accurate estimate of other body mass, except for skeletal muscle mass.

According to the guidelines of the EU and several Asian countries, it is necessary to use bioelectrical impedance analysis (BIA) for an objective assessment of body composition. During the examination, BIA analyzers introduce low voltage electric current into the subject's body and measure the resistance or impedance of the current flow. BIA technology uses different electrical frequencies (1 to 1,000 kHz) to estimate the amount of extracellular water, intracellular water, total body water, fat mass, fat-free mass, muscle mass, and Phase Angle (PA). PA (ratio between resistance and reactance) is considered an indicator of cell membrane integrity and a predictor of total cell mass. Low PA may indicate cell membrane damage, which is often associated with reduced overall survival in cancer patients. In the literature, as many as nine studies with 1496 patients stand out, among others, which showed that low PA was associated with poorer body mass index, lower serum albumin levels, transferrin and fat-free mass. Therefore, Grossberg et al. concluded that BIA provides accurate estimates of body composition in patients with head and neck cancer. Wladysiuk et al. they associated the risk of low overall survival with PA and demonstrated that the risk was statistically significantly higher in patients with PA less than 4,733 degrees compared to other patients.

In conclusion, BIA is an affordable method, easy to use, and a proven effective method for detecting nutritional risk in adults with cancer before and during cancer treatment. Cachexia and sarcopenia determined by the BIA method may have prognostic value for several types of tumors.

# POTENCIJALNE PET / CT POGREŠKE U DIJAGNOSTICI METASTAZA U VRIJEME EPIDEMIJE COVID-19

HORVATIĆ HERCEG G.[1]

[1] Klinički bolnički centar Zagreb
• *Klinički zavod za nuklearnu medicinu i zaštitu od zračenja*
ghherceg@gmail.com

Program cijepljenja protiv bolesti koronavirusa 2019 (COVID-19) započeo je u svijetu krajem 2020. godine, odnosno početkom 2021. godine u Hrvatskoj. Kako je ovo cijepljenje sve raširenije, raste broj pacijenata koji su upućeni na 18F FDG-PET/CT zbog onkoloških indikacija, a prethodno su bili cijepljeni protiv COVID-19. Premda PET/CT pokazuje visoku osjetljivost od 91% za limfne čvorove > 10 mm i 69% za manje čvorove, specifičnost je niža od (71%). Upalna reakcija limfnih čvorova jedan je od glavnih uzroka lažno pozitivnih nalaza PET/CT u onkoloških bolesnika. Nespecifičan nodalni uptake 18F-FDG-a može dovesti do lažne dijagnoze metastaza i do početka nepotrebnog liječenja.

Nakon cijepljenja protiv COVID-19 u deltoidni mišić, FDG uptake može se vidjeti u ipsilateralnim aksilarnim, supraklavikularnim i cervikalnim limfnim čvorovima. Intenzitet uptake-a FDG-a varira ovisno o vremenskoj blizini cijepljenja. Cijepljenje protiv COVID-19 može rezultirati osim FDG-avidnom limfadenopatijom i povećanim difuznim nakupljanjem FDG-a u slezeni. Što se tiče CT-a, limfni čvorovi mogu pokazivati varijabilnu morfologiju nakon cijepljenja. Premda su obično normalni ili pokazuju blago zadebljali korteks s očuvanim masnim hilusom, limfni čvorovi mogu pokazati abnormalnu morfologiju s gubitkom masnog hilusa, osobito ubrzo nakon cijepljenja. Čini se da oba mRNA cjepiva (Pfizer-BioNTech, Moderna) u većoj mjeri stimuliraju imunološku aktivnost nego cjepiva temeljena na tradicionalnim biotehnologijama (Astra Zeneca). Incidencija uptake-a FDG-a u limfne čvorove je viša za cjepivo Moderna od cjepiva Pfizer.

Dvije zanimljive kohortne studije iz Izraela pokazale su da je otkrivanje metabolički aktivnih aksilarnih limfnih čvorova na PET/CT-u prilično uobičajeno nakon cijepljenja protiv COVID-19, uglavnom nakon inokulacije druge doze cjepiva protiv COVID-19. Međutim, trenutačno nedostaju točni podaci koji izvještavaju o vremenu koje je potrebno nakon cijepljenja za rezoluciju uptake-a FDG-a na mjestima imunološkog odgovora povezanog s cjepivom. Nedavno objavljena publikacija iz Izraela s 426 cijepljenih pacijenata izvijestila je o povećanoj stopi FDG-avidnih aksilarnih limfnih čvorova u 46% bolesnika koji su podvrgnuti PET/CT-u nakon cijepljenja Pfizer-BioNTech-om. Nešto više od polovice imunokompetentnih pacijenata (53%) i trećina imunokompromitiranih pacijenata (33%) pokazalo je uptake FDG-a u aksilarne limfne čvorove. Multivarijantna logistička regresijska analiza otkrila je značajnu inverznu povezanost između pozitivnog unosa FDG-a u ipsilateralne limfne čvorove i dobi bolesnika i imunosupresivnog liječenja. Ove povezanosti impliciraju da bi visoka metabolička aktivnost u limfnim čvorovima mogla biti marker aktivacije imunološkog sustava izazvane cjepivom. Studija švicarskih autora na 140 bolesnika pokazala je FDG-avidne limfne čvorove ipsilateralno od injekcije cjepiva u 75/140 (54%) pacijenata s prosječnim SUVmax od 5,1 (raspon 2,0–17,3). FDG-avidni limfni čvorovi bili su češći u pacijenata cijepljenih s Modernom nego s Pfizer-BioNTech cjepivom (36/50 [72%] nasuprot 39/90 [43%] slučajeva, p <0,001). FDG-avidna aksilarna limfadenopatija najčešće se viđala nakon 1–7 dana nakon cijepljenja (71%bolesnika) i pokazala je negativnu korelaciju s vremenom nakon cijepljenja, međutim i nakon 28 dana i dulje, još uvijek je 38% pacijenata prezentirano s FDG-avidnim limfnim čvorovima.

Prepoznavanje metabolički aktivnih aksilarnih limfnih čvorova kao pokazatelja prethodnog cijepljenja spriječit će nepotrebno onkološko liječenje pacijenata. Dokumentiranje povijesti cijepljenja i mjesta ubrizgavanja cjepiva u vrijeme snimanja PET/CT-a iznimno je korisno za pravilnu interpretaciju PET/CT-a kako bi se izbjegli lažno pozitivni nalazi, daljnji dijagnostički pregledi i nepotrebne promjene u terapiji.

# POTENTIAL PET/ CT PITFALLS IN THE DIAGNOSIS OF METASTASES IN THE TIME OF 19-COVIDE EPIDEMIC

HORVATIĆ HERCEG G.[1]

[1] University Hospital Zagreb
• *Department of nuclear medicine and radiation protection*
ghherceg@gmail.com

Large-scale worldwide vaccination programs against the 2019 coronavirus diseases (COVID-19) are being rapidly deployed. As this vaccination is becoming more widespread, we are observing an increase of patients with previous vaccination against COVID-19 who underwent 18F-FDG PET/ CT for different indications. With regard to lymph node metastases, PET/CT shows sensitivity of 91% for nodes >10 mm and 69% for smaller nodes (with a similar specificity of 71%). The inflammatory reaction of the lymph nodes is one of the main causes of the false positive PET/CT findings in oncological patients. A non-specific nodal 18F-FDG uptake may lead to a false diagnosis of metastases and to the initiation of an unnecessary treatment. After deltoid vaccination, FDG uptake can be seen in the axillary levels 1, 2, and 3; supraclavicular; and cervical lymph nodes. The degree of FDG uptake varies with temporal proximity to the vaccination. COVID-19 vaccination can result in FDG-avid lymphadenopathy and increased splenic uptake on PET/CT; findings that can overlap with certain cancers. In addition, after vaccination, lymph nodes may show variable morphology on CT but are usually normal or show a mildly thickened cortex with maintained fatty hilum. However, particularly shortly after vaccine administration, lymph nodes may show abnormal morphology and can appear completely rounded with loss of fatty hila. Both mRNA vaccines appear to stimulate immune activity to a greater degree than do than vaccines based on traditional biotechnologies. The incidences of FDG uptake in lymph nodes were reported as higher for the Moderna vaccine than the Pfizer vaccine. Both in vitro and clinical data suggest that these two mRNA vaccines are inherently immunostimulatory and therefore more immunogenic compared with other traditional vaccine biotechnologies, potentially accounting for the lymphadenopathy observed on imaging.

Two interesting cohort studies from Israel demonstrated that the detection of hypermetabolic axillary lymph nodes at 18F-FDG PET/CT is quite common after vaccination against COVID-19, mainly after the inoculation of the second dose of COVID-19 vaccine. However, accurate data reporting the time required after COVID-19 vaccination to allow for resolution of 18F-FDG uptake in sites of vaccine-related immune response are currently lacking. A very recent publication from Israel with 426 vaccinated patients reported an increased rate of FDG-avid axillary lymph nodes in 46% of patients undergoing PET/CT after vaccination with Pfizer-BioNTech. A little over half of immunocompetent patients (53%) and a third of immunocompromised patients (33%) showed FDG axillary lymph node uptake. Multivariate logistic regression analysis revealed a strong inverse association between positive FDG uptake in ipsilateral lymph nodes and patients' age and immunosuppressive treatment. These associations imply that the high metabolic activity in the lymph nodes might be a marker of vaccine-induced immune system activation. The study of Swiss authors with 140 patients FDG PET/CT showed FDG-avid lymph nodes ipsilateral to the vaccine injection in 75/140 (54%) patients with a mean SUVmax of 5.1 (range 2.0 – 17.3). FDG-avid lymph nodes were more frequent in patients vaccinated with Moderna than Pfizer-BioNTech (36/50 [72%] vs. 39/90 [43%] cases, $p < 0.001$). FDG-avid axillary lymphadenopathy was most frequently seen on day 1–7 after vaccination (71% of patients) and showed a negative correlation with time after vaccination, but after 28 days and longer, still 38% of patients presented with FDG-avid lymph nodes.

Recognition of metabolically active axillary lymph nodes as an indicator of previous vaccination will prevent unnecessary oncological treatment of patients. Documenting vaccination history and vaccine injection location at the time of PET scan is extremely useful for PET reporters to avoid false interpretation, useless further diagnostic examinations and unnecessary changes in management.