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USPOREDBA UČESTALOSTI POJAVE VISOKOG OPTEREĆENJA TUMORA MUTACIJAMA U TUMORIMA S VISOKOM MIKROSATELITNOM NESTABILNOŠĆU I NEDOSTATNOŠĆU HOMOLOGNE REKOMBINACIJE

PRISELAC S.*[1], MEŽNARIĆ LJ.*[1], Prejac J.[2,3], Dedić Plavetić N.[1,2], Pleština S.[1,2]

[1] Sveučilište u Zagrebu
• *Medicinski fakultet*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[3] Sveučilište u Zagrebu
• *Stomatološki fakultet*
sara.priselac@gmail.com

Uvod: Opterećenje tumora mutacijama (TMB, eng. tumor mutation burden) opisuje količinu mutacija u genomu tumora. Izražava se kao broj mutacija po megabazi (mut/Mb). Veći TMB povezan je s boljim odgovorom na terapiju inhibitorima imunosnih nadzornih točaka u nekim tumorima, stoga je TMB klinički važan podatak. Mikrosatelitna nestabilnost (MSI, eng. microsatelite instability) i nedostatna homologna rekombinacija (HRD, eng. homologous recombination deficiency) su stanja koje podržavaju neispravno umnažanje DNA. Visoku MSI (MSI-H) i HRD dosadašnja su istraživanja povezala s višim TMB. Cilj našeg rada bio je odrediti postoji li razlika u učestalosti visokog TMB u grupi s MSI-H u odnosu na one s HRD u uzorcima malignih tumora analiziranih sekvencioniranjem nove generacije (NGS, eng. next generation sequencing).

Materijali i metode: NGS je metoda koja obuhvaća skup testova u kojima se uspoređuje DNA zdravih stanica i DNA izolirana iz tumora te se na taj način može uočiti mutacija specifična za tumor. Korišten je test FoundationOne®CDx (Roche, FMI Germany GmbH). Analizirani su uzorci malignih tumora različitih primarnih sijela. Kao visoki TMB uzeta je vrijednost ≥ 10 mut/Mb. Od gena čije mutacije dovode do HRD analizirali smo *ATM, BRCA1/2, CDK12, CHEK1/2, FANCA, FANCL, NBN, PALB2, RAD51* i *RAD51C*. Za statističku analizu je korišten chi kvadrat test, razina značajnosti uzeta je kao $p < 0.05$.

Rezultati: Analizirali smo rezultate 100 NGS testova. Izdvojili smo skupinu uzoraka s MSI-H i skupinu s HRD. Unutar svake skupine smo prebrojali uzorke s visokim TMB. U MSI-H skupini od ukupno 6 uzoraka visok TMB smo našli u njih 5 (5/6 = 83%). U HRD skupini od ukupno 20 uzoraka visok TMB ima njih 5 (5/20 = 25%). Učinjenim chi kvadrat testom ispitano je ima li statistički značajne razlike u učestalosti TMB između dvije skupine. Učestalost TMB u skupini MSI-H je statistički značajno veća nego u skupini HRD ($X2 = 6,6354$, $p = 0,01$).

Zaključak: Prema navedenim rezultatima postoji statistički značajna razlika između učestalosti visokog TMB u skupinama uzoraka sa MSI-H i HRD. Visok TMB bolje korelira s MSI-H, nego s alteracijama gena za HRD. Ograničenje ovog istraživanja je malen broj uzoraka te će se buduće analize napraviti na većem broju.

*Ovi autori su jednako pridonijeli radu.

A COMPARISON OF HIGH TUMOR MUTATION BURDEN INCIDENCE IN TUMORS WITH HIGH MICROSATELITE INSTABILITY AND HOMOLOGOUS RECOMBINATION DEFICIENCY

PRISELAC S.*[1], MEŽNARIĆ LJ.*[1], Prejac J.[2,3], Dedić Plavetić N.[1,2], Pleština S.[1,2]

[1] University of Zagrebu
• *School of medicine*
[2] University Hospital Centre Zagreb
• *Department of Oncology*
[3] University of Zagreb
• *School of Dental Medicine*

Introduction: Tumor mutation burden (TMB) measures the number of mutations in a tumor's genome. It is expressed as a number of mutations per megabase (mut/Mb). High TMB correlates with a better response to immune checkpoint inhibition therapy in some tumors, hence it is a clinically important parametar. Microsatelite instability (MSI) and homologous recombination deficiency (HRD) are conditions which support imperfect DNA replication. High MSI (MSI-H) and HRD have been shown by previous studies to correlate with a high TMB. The aim of this study was to examine malignant tumor samples analized with next generation sequencing (NGS) and determine if there is a difference in proportion of samples with high TMB in the group with MSI-H in comparison to the group with HRD.

Materials and methods: NGS is a method covering various tests which compare the DNA of healthy cells to the DNA isolated from tumor cells and find mutations which are tumor specific. The test used was FoundationOne®CDx (Roche, FMI Germany GmbH). Analized samples originated from malignant tumors of various primary sites. The value of ≥ 10 mut/Mb was used as the cut-off for high TMB. Mutations in *ATM, BRCA1/2, CDK12, CHEK1/2, FANCA, FANCL, NBN, PALB2, RAD51* and *RAD51C* were regarded as causing HRD. The chi-squared test was used for statistical analysis. The level of significance was set to $p < 0.05$.

Results: The results of 100 NGS tests were analized. Samples were split into a group with MSI-H and a group with HRD. Each group was counted for the number of samples with high TMB. The MSI-H group of 6 samples in total had 5 with a high TMB (5/6 = 83%). The HRD group of 20 samples in total had 5 with a high TMB (5/20 = 25%). The chi-squared test examined if there is a statistically significant difference in the proportion of samples with a high TMB between the two groups. The proportion of samples with a high TMB was larger in the group with MSI-H than in the group with HRD ($X2 = 6.6354$, $p = 0.01$).

Conclusion: According to the results, there is a statistically significant difference in the incidence of samples with a high TMB in the MSI-H and HRD groups. A high TMB correlates better with MSI-H than with alterations in genes for HRD. The limitation of this study was a small number of samples. Future studies will be done on a larger cohort.

*These two authors contributed equally to this work.

INCIDENCIJA I ISHODI VENSKIH TROMBOEMBOLIJSKIH DOGAĐAJA U KOHORTI AMBULANTNIH BOLESNIKA S METASTATSKIM KOLOREKTALNIM KARCINOMOM S DOKAZANIM MUTACIJAMA U RAS I BRAF GENU: RETROSPEKTIVNO-PROSPEKTIVNA MULTICENTRIČNA STUDIJA

JOVIĆ ZLATOVIĆ J.[1], Bevanda M.[2], Skelin M.[3,4], Grubišić-Čabo F.[1], Krečak I.[1], Marijanović I.[5], Telesmanić Dobrić V.[6], Curić Z.[7], Omrčen T.[8]

[1] Opća bolnica Šibenik
• *Odjel za onkologiju, hematologiju i kliničku onkologiju*
[2] Sveučilišna klinička bolnica Mostar
• *Klinika za unutarnje bolesti*
[3] Opća bolnica Šibenik
• *Odjel bolničke ljekarne*
[4] Sveučilište u Rijeci
• *Medicinski fakultet*
[5] Sveučilišna klinička bolnica Mostar
• *Klinika za onkologiju*
[6] Opća bolnica Zadar
• *Odjel za onkologiju i nuklearnu medicinu*
[7] Opća bolnica Dubrovnik
• *Odjel za onkologiju*
[8] Klinički bolnički centar Split
• *Klinika za onkologiju i radioterapiju*
josipa_jovic@yahoo.com

Uvod: Venske tromboembolije (VTE) su česti uzrok morbiditeta i mortaliteta u bolesnika s metastatskim kolorektalnim karcinomom (mKRK). Mutacije onkogena KRAS i BRAF povezane su s povećanim rizikom od VTE. Cilj ove studije bio je ispitati incidenciju i preživljenje u kohorti bolesnika s mKRK koji su nositelji KRAS/NRAS/BRAF mutacija.

Metode: Ovo je retrospektivo-prospektivna analiza 134 ambulantna bolesnika s mKRK i dokazanim KRAS/NRAS/BRAF mutacijama koji su liječeni u tri hrvatska onkološka centra (Opća bolnica Šibensko-kninske županije, Opća bolnica Zadar i Opća bolnica Dubrovnik) od lipnja 2013. do ožujka 2020. Minimalno praćenje bolesnika je bilo godinu dana. VTE je bila definirana kao duboka venska tromboza (DVT) i/ili plućna embolija (PE) koja je nastala 6 mjeseci prije ili u bilo koje vrijeme nakon dijagnoze mKRK. Primarni cilj istraživanja bila je incidencija VTE i preživljenje bolesnika s KRAS/NRAS/BRAF mutiranim mKRK s obzirom na primarnu lokalizaciju tumora (lijevo/desni). Karakteristike bolesnika prikazane su kao medijan s interkvartalnim rasponom (IQR) za kontinuirane varijable, ili u obliku apsolutnih vrijednosti s postocima za kategoričke varijable. Multivarijatna logistička regresijska analiza korištena je za istraživanje prediktora povezanih s VTE za kategoričke varijable. Kaplan-Meirova analiza s log-rank testom korištena je za testiranje preživljenja između skupina. Svi testovi su bili dvostrani. Razina statističke značajnosti postavljena je na Alfa=0.05.

Rezultati: Medijan dobi iznosio je 68 godina (IQR 61–75). Od 134 bolesnika s mKRK i RAS/BRAF mutacijom 67% su bili muškarci, dobrog općeg stanja (ECOG PS 0–1) bilo je njih 95%. Mutacije KRAS/NRAS i BRAF gena dokazane su u 92% i 8% bolesnika. Karcinomi desne strane debelog crijeva dijagnosticirani su u 33% bolesnika. Nakon medijana praćenja od 21 mjesec (IQR 13–33) kod 33 bolesnika (24, 6%) dijagnosticiran jeVTE. Rezultati multivarijatne logističke regresije nakon prilagodbe za nezavisne prediktore VTE uključujući komorbiditete, varikozitete, bevacizumab, kemoterapiju, onkogene mutacije i primarnu lokalizaciju tumora potvrdili su da tumori desne strane debelog crijeva predstavljaju značajno veći rizik za nastanak VTE u bolesnika s RAS/BRAF mutacijama (OR = 5.75; 95% CI:1.68 –19.72, p=0,005) u usporedbi s tumorima koji su se nalazili na lijevoj strani. Nije bilo razlike u ukupnom preživljenju između promatranih skupina budući da je medijan ukupnog preživljenja (mOS) iznosio 26 mjeseca za bolesnike s tumorima lijeve strane, te 23 mjeseca za tumore desne strane debelog crijeva (HR = 1.35, 95% CI:0.84–2.16, p=0,21). Nije primjećena statistički značajna razlika u mOS između bolesnika sa ili bez VTE kojima je primarna lokalizaciju tumora bila desno (HR = 0.61, 95% CI:0.29–1.26, p=0,18) u odnosu na bolesnike s lijevo lokaliziranim tumorima (HR = 1.11, 95% CI:0.52–2.34, p=0.79).

Zaključak: Tumori desne strane debelog crijeva bili su statistički značajno povezani s većim rizikom za nastanak VTE u skupini bolesnika s mutiranim KRAS/NRAS/BRAF mKRK u odnosu na istu skupinu u kojoj se

navedeni tumor nalazio na lijevoj strani. Nije bilo razlike u preživljenu u promatranim skupinama (lijevo/desno) bolesnika s mKRK s RAS/BRAF mutacijama. Potrebna su daljnja istraživanja s nezavisnim uzorcima koja bi potvrdila ili opovrgnula rezultate ovog istraživanja.

Ključne riječi: Kolorektalni karcinom, KRAS, BRAF, Venska tromboembolija, Desna strana, Lijeva strana, Lokalizacija tumora

INCIDENCE AND OUTCOMES OF VENOUS TROMBOEMBOLISM IN A COHORT OF AMBULATORY PATIENTS WITH METASTATIC COLORECTAL CANCER WITH RAS AND BRAF GENES MUTATION. A RETROSPECTIVE-PROSPECTIVE MULTICENTER STUDY

JOVIĆ ZLATOVIĆ J.[1], Bevanda M.[2], Skelin M.[3,4], Grubišić-Čabo F.[1], Krečak I.[1], Marijanović I.[5], Telesmanić Dobrić V.[6], Curić Z.[7], Omrčen T.[8]

[1] General Hospital Šibenik
• *Department of Oncology, Hematology and Clinical Immunology*
[2] University Clinical Hospital Mostar, Mostar
• *Department of Internal Medicine*
[3] General Hospital Šibenik
• *Department of Pharmacy*
[4] University of Rijeka
• *School of medicine*
[5] Univerity Clinical Hospital Mostar
• *Department of Oncology*
[6] General Hospital Zadar
• *Department of Oncology and Nuclear medicine*
[7] General Hospital Dubrovnik
• *Department of Oncology*
[8] Clinical Hospital Centre Split
• *Department of Oncology and Radiotherapy*

Introduction: Venous thromboembolism (VTE) is a frequent cause of morbidity and mortality in patients with metastatic colorectal cancer (mCRC)[1]. The mutation of the KRAS and BRAF oncogenes have been associated with increased risk of VTE[2]. The aim of this study was to describe incidence of VTE and survival in a cohort of patient with KRAS/NRAS/BRAF-mutated mCRC.

Methods: This is a retrospective-prospective analysis of 134 ambulatory patients with KRAS/NRAS/BRAF-mutated mCRC who were treated in three Croatian oncologic centers (General Hospital of Šibenik-Knin County, General Hospital Zadar and General Hospital Dubrovnik) from June 2013. to March 2020. Minimum follow-up was 1 year. VTE was defined as deep venous thrombosis (DVT) and/or pulmonary embolism (PE) occured 6 months before or at any time after the diagnosis of mCRC. The primary endpoint was incidence of VTE and survival regarding the localization of tumor for patients with KRAS/NRAS/BRAF-mutated mCRC. Characteristics of patients were presented as median with interquartile range (IQR) for continuous variables, or as absolute values with percentages for categorical variables. Multivariate logistic regression analysis were used for exploring predictors associated with VTE for categorical variables. Kaplan-Meier analysis with log-rank test was used to test survival between groups. All tests were two-sided. The significance level was set to Alpha = 0.05.

Results: Median age was 68 years (IQR61-75). Of 134 included patients with RAS/BRAF mutated mCRC, 67% were men and 95% had a good perfomance status (ECOG PS 0-1). KRAS/NRAS and BRAF mutations were detected in 92% and 8% of patients, respectively. Right-sided colon cancers were diagnosed in 33% of patients. With a median follow-up time of 21 months (IQR 13–33) thirty three patients (24.6%) developed of VTE. The results of multivariate stepwise logistic regression analysis after adjustment for independent baseline predictors of VTE including varicosis, comorbidity, bevacizumab, chemotherapy, oncogene mutations and tumor sidedness confirmed that right-sided tumors were significant predictors of VTE in RAS/BRAF-mutated patients (OR = 5.75; 95% CI:1.68 – 19.72 p=0.005) compared to the left-sided localization of tumor. Median overall survival (mOS) was 26 months for patients with left-sided and 23 months for right-sided RAS/BRAF-mutated tumors (HR= 1.35, 95% CI:0.84–2.16, p=0,21). No statistically significant mOS was observed between patients with or without VTE according to right-sided tumors (HR = 0.61, 95% CI:0.29–1.26, p=0,18), and left-sided tumors (HR = 1.11, 95% CI:0.52–2.34, p=0.79).

Conclusion: Right-sided tumor location was significantly associated with a increased risk of VTE compared to the left-sided localized tumores in a cohort of patients with KRAS/NRAS/BRAF-mutated mCRC. There was not statistical significant difference regarding OS in both cohort of patients. Independent sample in a larger study is necessary to confirim these findings.

Keywords: Colorectal cancer, KRAS, BRAF, Venous thromboembolism, Right, Left, Tumor location

LITERATURA/LITERATURE:

1. *Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH.* Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost. 2007;5:632–4.
2. *Ades S, Kumar S, Alam M, Goodwin A, Weckstein D, et al.* Tumor oncogene (KRAS) status and risk of venous thrombosis in patients with metastatic colorectal cancer. J Thromb Haemost. 2015;13:998–1003.

INICIJALNA ISKUSTVA S PERKUTANOM CT-OM VOĐENOM KRIOABLACIJOM ZA TERAPIJU TUMORA BUBREGA, KOSTI I PLUĆA

NOVOSEL L.[1], Ivica Sjekavica I.[1], Bolanča Čulo K.[1]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinički zavod za dijagnostičku i intervencijsku radiologiju*
novosel0701@gmail.com

Uvod: Perkutana krioablacija predstavlja minimalno invazivnu perkutanu opciju liječenja malignih bolesti bubrega, pluća i kosti, koja se primjenjuje u svijetu više od 20 godina. Zbog svojih karakteristika niske invazivnosti, preciznosti i smanjenog rizika komplikacija prema kirurškim i ostalim ablacijskim tehnikama, preporuča se kao opcija liječenja kod karcinoma bubrega stadija T1a, metastatskih lezija pluća dimenzije do 3 cm i litičnih metastaza kosti. Iako inicijalno namijenjena prvenstveno pacijentima starije dobi s komorbiditetima i kontraindikacijama za kirurško liječenje, noviji rezultati pokazuju da ablacijske metode postižu onkološke ishode usporedive s kirurgijom te da se mogu koristiti kod većine pacijenata s lokaliziranom onkološkom bolesti. Primjenom kriosondi, koje se pod kontrolom CT navode u tumor, postiže se kroz dva ciklusa zaleđivanja u leziji temperature do –140 C, primjenom plina Argona, što uzrokuje destrukciju tumorskih stanica uz minimalno oštećenje okolnog parenhima tretiranog organa kao i okolnih vitalnih struktura.

Materijali i metode: Kod 6 pacijenata (3 žene i 3 muškarca) dobi od 56 do 75 godina se u razdoblju od 7–9. mj. 2022. prvi put u našoj ustanovi izvela metoda perkutane krioablacije pod kontrolom CT-a. Primjenom IceFX krioablacijskog sustava liječeni su: 3 pacijenta sa svjetlostaničnim RCC bubrega stadija T1a (dimenzije veće od 3 cm, koje su lokacijom u parenhimu bubrega, u blizini kanalnog sustava bili pod povišenim rizikom komplikacija), 2 pacijenta s litičnim metastazama u kostima od karcinoma dojke i karcinoma kolona (u torakalnoj kralježnici i zdjelici) i 1 pacijentica s metastatskim karcinomom kolona u pluća dimenzije 15 mm. Procedura se izvela u općoj anesteziji ili sedaciji, a svi pacijenti su otpušteni idući dan nakon zahvata. Korištene su do 3 kriosonde po zahvatu, ovisno o dimenziji tumora. Pacijenti se prate mjesec dana nakon zahvata kontrolnim CT ili MR pregledom te svakih 6 mjeseci po daljnjem protokolu praćenja.

Rezultati: Kod svih pacijenata krioablacija se pokazala sigurnom metodom minimalno invazivnog liječenja, bez zabilježenih značajnih komplikacija. Kod jedne pacijentice s karcinomom bubrega dimenzije 4 cm zabilježena je postproceduralno perirenalna hemoragija, koja nije zahtijevala daljnje liječenje niti nadoknadu krvi. Kod pacijenta s krioablacijom pluća nije zabilježen pneumotoraks niti druge komplikacije. Kod koštanih metastaza nije zabilježena pojava ozljeda neuralnih struktura kod pacijenta s promjenama u torakalnoj kralježnici. Na kontrolnim snimkama nakon mjesec dana kod svih pacijenata nisu pronađeni znakovi lokalnog recidiva ili rezidue tumorskih lezija.

Zaključak: Krioablacija zbog izostanka dostupnosti tehnologije nije bila do sada primjenjivana kao metoda minimalnog invazivnog liječenja onkoloških pacijenata u Hrvatskoj. Inicijalna institucionalna iskustva iz KBC Sestre Milosrdnice pokazuju da se radi o sigurnoj i provjerenoj metodi liječenja, koja se najčešće koristi u liječenju primarnih karcinoma bubrega te metastaza u plućima te litičnih metastaza koštanog sustava, prvenstveno kod radiorezistentnih tumora.

INITIAL EXPERIENCE WITH PERCUTANEOUS CT GUIDED CRYOABLATION THERAPY FOR KIDNEY, BONE AND LUNG TUMORS

NOVOSEL L.[1], Ivica Sjekavica I.[1], Bolanča Čulo K.[1]

[1] University Hospital Centre Sestre milosrdnice
• *Department of Diagnostic and interventional Radiology*

Introduction: Percutaneous crioablation presents a minimally invasive treatment option of malignant disease in the kidney, lungs and bones, which is used worldwide for more than 20 years. Due to the characteristics of being minimally invasive, precise and with reduced complication rates compared to surgical resection and even other ablation techniques, it is recommended as a treatment option for T1a stage of kidney RCC, metastatic lesions of the lungs up to 3 cm in diameter and bone osteolytic lesions. It was initially intended for older patients with comorbidities and contraindications for surgery, recent studies show oncological outcomes of ablation to be comparable to surgery and that it can be used in the majority of patients with localized oncological disease. With the use of crioprobes, which are placed inside the lesion under CT guidance, freezing with temperatures as low as minus 140C is achieved through 2 cycles of ablation. This causes the destruction of tumor cells with minimal damage to the surrounding parenchyma and vital structures.

Materials and methods: Six patients (3 female and 3 male) age 56 to75 were treated for the first time using CT guided percutaneous crioablation from July to September 2022 at our institution. IceFX crioablation system was used to treat: 3 patients with T1a renal carcinoma (size greater than 3 cm, located in the renal parenchyma, near the collecting system with higher risk of procedural complications), 2 patients with lytic bone metastasis (from breast and colon cancer located in the thoracic spine and pelvis) and 1 patient with lung metastasis from colon cancer (15 mm in diameter). All procedures were performed under general anesthesia or sedation and all patients were discharged the next day. Up to three cryoprobes were used per procedure, depending on the size of the lesion. Patient are followed-up with CT or MRI scan after one month and every 6 months after that.

Results: In all patients, cryoablation proved to be a safe method of minimally invasive treatment, with no significant complications recorded. In one patient with kidney cancer measuring 4 cm, postprocedural perirenal hemorrhage was noted, which did not require further treatment or blood replacement. No pneumothorax or other complications were seen in the patient after lung cryoablation. In the case of bone metastases, no injuries to neural structures were observed. No signs of local recurrence or residual tumor lesions were found on the one month follow-up scans in all patients.

Conclusion: Cryoablation, due to the lack of availability of this technology, has not been used as a method of minimally invasive treatment of oncological patients in Croatia until now. Initial institutional experience from KBC Sestre Milosrdnice show that it is a safe and effective method of treatment, which is most often used in the treatment of primary kidney cancer and metastases in the lungs and lytic metastases of the scelet primarily in radioresistant tumors.

UTJECAJ DOBA DANA PRIMJENE PEMBROLIZUMABA NA PREŽIVLJENJE U PACIJENATA S METASTATSKIM MELANOMOM

GOLČIĆ M.[1], Jerković I.[1], Skočilić I.[1], Zahirović D.[1], Marušić J.[1], Špondreht M.[1], Beg A.[1], Polić N.[1], Golčić G.[1], Dobrila-Dintinjana R.[1], Mikolašević I.[1]

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

Uvod: Metastatski melanom je proširena maligna bolest podrijetla melanocita, za koju je zadnjih desetak godina postignut revolucionaran napredak u liječenju. Najnovija istraživanja o bolesnicima liječenim imunoterapijom govore da u gotovo trećine bolesnika nema znakova bolesti u 6.5 godina praćenja. Međutim i dalje nema dovoljno podataka o čimbenicima koji utječu na uspjeh imunoterapije, iako se unos vlakana, antibiotika, probiotika i mikrobiom spominju kao neki od važnijih faktora. Novija istraživanja naglašavaju i važnost doba dana kada se primjenjuje imunoterapija, jer je prema studiji MEMOIR pokazano kako pacijenti koji su imali barem 20% infuzija iza 16:30h imaju značajno lošije ukupno preživljenje (HR 2.04). S obzirom da se u KBC-u Rijeka

zbog organizacije posla veliki broj imunoterapija aplicira u popodnevnim satima, istražili smo povezanost aplikacija imunoterapija u određeno doba dana u odnosu na preživljenje i stopu odgovora.

Materijali i metode: Ukupno smo analizirali 25 pacijenata s metastatskim melanomom koji su primali pembrolizumab između 2017–2021 i imali barem jednu kontrolnu radiološku obradu. Pacijente smo podijelili, radi ravnomjernosti skupina, ovisno jesu li više od 50% imunoterapija primili u popodnevnim satima (P) ili manje (U)

Rezultati: Većina pacijenata su bili muškog spola (N=15, 60%), prosječne dobi 65.4 godine (±12.9). Najčešće sijelo primarnog tumora bilo je na trupu (N=10, 40%), a najčešća sijela metastaza bila su limfni čvorovi (N=13, 52%) i pluća (N=8, 32%). Za većinu bolesnika, pembrolizumab je bio prva linija liječenja (N=18, 72%). Ukupno preživljenje iznosilo je 33.9 mjeseci (±19.9), dok je 11 pacijenata (44%) preminulo do ovog trenutka. Nije bilo razlike u ukupnom preživljenju između U i P (36.0 vs 32.3 mj., log rank p=0.86). Stopa radiološkog odgovora iznosila je 40%, bez statističke razlike U vs. P (27.3% vs. 50%, p>0.05).

Zaključak: Stopa odgovora u registracijskoj studiji za pembrolizumab iznosila je oko 40%, uz prosječno preživljenje od 38 mjeseci. Rezultati stope odgovora i preživljenja pacijenata liječenih u KBC-u Rijeka su u skladu s navedenim rezultatima, a pacijenti koji su imali više od 50% infuzija u popodnevnim satima nemaju kraće preživljenje niti manju stopu odgovora od pacijenata s dominantno jutarnjim aplikacijama. Ipak, zbog malog broja pacijenata su potrebna dodatna istraživanja.

INFLUENCE OF THE TIME OF DAY OF PEMBROLIZUMAB APPLICATION ON SURVIVAL IN PATIENTS WITH METASTATIC MELANOMA

GOLČIĆ M.[1], Jerković I.[1], Skočilić I.[1], Zahirović D.[1], Marušić J.[1], Špondreht M.[1], Beg A.[1], Polić N.[1], Golčić G.[1], Dobrila-Dintinjana R.[1], Mikolašević I.[1]

[1] University Hospital Centre Rijeka
• *Department of Radiotherapy and Oncology*

Introduction: Metastatic melanoma is a malignant disease derived from melanocytes, which has experienced dramatic progress in treatment over the last ten years. The latest research on patients treated with immunotherapy shows that in almost a third of patients, there are no signs of the disease in the 6.5 years of follow-up. However, there is still not enough data on the factors that influence the success of immunotherapy, although the intake of fiber, antibiotics, probiotics, and the microbiome are mentioned as some of the more important factors. Newer research also emphasizes the importance of the time of day when immunotherapy is administered because, according to the MEMOIR study, it was shown that patients who had at least 20% of infusions after 4:30 pm had significantly worse overall survival (HR 2.04). Considering that at KBC Rijeka, due to the organization of the outpatient clinic, a large number of immunotherapies are applied in the afternoon, we investigated the association between the time of the immunotherapy application with survival and response rate.

Materials and methods: In total, we analyzed 25 patients with metastatic melanoma who received pembrolizumab between 2017–2021 and had at least one radiological follow-up. We divided the patients due to the balance between groups, whether more than 50% of the immunotherapy was received in the afternoon (P) or less (U).

Results: The majority of patients were male (N=15, 60%), with an average age of 65.4 years (±12.9). The most common site of the primary tumor was on the trunk (N=10, 40%), and the most common sites of metastasis were lymph nodes (N=13, 52%) and lungs (N=8, 32%). For the majority of patients, pembrolizumab was the first-line treatment (N=18, 72%). Overall survival was 33.9 months (±19.9), while 11 patients (44%) had died during the follow-up. There was no difference in overall survival between U and P (36.0 vs 32.3 months, log-rank p=0.86). The radiological response rate was 40%, with no statistical difference between U vs. P (27.3% vs. 50%, p>0.05).

Conclusion: The response rate in the registration study for pembrolizumab was about 40%, with a median survival of 38 months. The results of the response rate and survival of patients treated at KBC Rijeka are in accordance with the stated results, and patients who had more than 50% of infusions in the afternoon did not have a shorter survival or a lower response rate than patients with predominantly morning applications. However, additional research is needed due to the small number of patients.

UTJECAJ COVID-19 PANDEMIJE NA BOLESNIKE S NOVOOTKRIVENIM KOLOREKTALNIM RAKOM U OPĆIM BOLNICAMA (OB) ZADAR, ŠIBENIK I DUBROVNIK.

DILBER I.[1], Jović Zlatović J.[2], Curić Z.[3], Nalbani M.[3], Bilić Knežević S.[1]

[1] Opća bolnica Zadar
• *Odjel za onkologiju i nuklearnu medicinu*
[2] Opća bolnica Šibenik
• *Odjel za onkologiju, hematologiju i kliničku onkologiju*
[3] Opća bolnica Dubrovnik
• *Odjel za onkologiju*
ivodilber81@gmail.com

Uvod: Kolorektalni rak je najučestalija zloćudna bolest u Republici Hrvatskoj. Godišnje prosječno oboli oko 3600 osoba, od čega 60% muškaraca. Po smrtnosti od zloćudnih bolesti kolorektalni rak je na drugom mjestu, iza raka pluća. Stoga je iznimno važno dijagnosticirati kolorektalni rak u što ranijem stadiju bolesti radi boljeg ishoda liječenja. Za vrijeme Covid-19 pandemije zabilježen je smanjen broj obavljenih kolonoskopija i odaziv na program ranog otkrivanja raka debelog crijeva.

Materijali i metode: Cilj ovog istraživanja je retrospektivno evaluirati utjecaj COVID-19 pandemije na bolesnike s novootkrivenim kolorektalnim rakom u periodu od 01.04.2020. do 30.09.2021. (za vrijeme Covid-19 pandemije) u odnosu na period od 01.04.2018. do 30.09.2019. (vrijeme prije COVID-19 pandemije) u tri županijske bolnice.

Istraživanje je uključilo 542 bolesnika kojima je kolorektalni rak dijagnosticiran u OB Zadar, OB Šibenik i OB Dubrovnik. Podaci su skupljeni pretragom bolničkog informatičkog sustava. Uspoređivali smo broj i opće stanje bolesnika, dob, stadij bolesti, te vrstu operacije primarnog tumora (elektivno vrs hitno).

Od analiziranih 542 bolesnika, 271 bolesnik u periodu prije Covid-19 pandemije, te 271 bolesnik za vrijeme Covid-19 pandemije.

Rezultati: Statistički nije bilo značajne razlike u dobi, spolu, performance statusu i stadiju bolesti prije i za vrijeme Covid-19 pandemije, ali je zabilježena statistički značajna razlika u broju hitnih operacija u odnosu na elektivne zahvate za vrijeme Covid-19 pandemije u usporedbi s vremenom prije pandemije (23% i 77% vrs 15.7% i 84.3%; P=0.045).

Zaključak: Odgađanje ili otkazivanje preventivnih pregleda može dovesti do odgode liječenja i dijagnosticiranja zloćudne bolesti u višim stadijima bolesti. Ovo istraživanje je pokazalo da je COVID-19 pandemija imala značajan utjecaj na vrstu operativnog zahvata što se može povezati sa smanjenim brojem preventivnih pregleda u sekundarnim zdravstvenim ustanovama, odnosno smanjenim odazivom na program za rano otkrivanje raka debelog crijeva.

IMPACT OF THE COVID-19 PANDEMIC ON PATIENTS WITH NEWLY DIAGNOSED COLORECTAL CANCER IN THE GENERAL HOSPITALS (GH) OF ZADAR, SIBENIK AND DUBROVNIK

DILBER I.[1], Jović Zlatović J.[2], Curić Z.[3], Nalbani M.[3], Bilić Knežević S.[1]

[1] General Hospital Zadar
• *Department of Oncology and Nuclear medicine*
[2] General Hospital Šibenik
• *Department of Oncology, Hematology and Clinical Immunology*
[3] General Hospital Dubrovnik
• *Department of Oncology*

Introduction: Colorectal cancer is the most common malignant disease in Croatia. An average incidence is 3,600 people, of which 60% are men. In terms of mortality from malignant diseases, colorectal cancer is on the second place, after lung cancer. Therefore, it is extremely important to diagnose colorectal cancer at the earliest stage of the disease for a better treatment outcome. The Covid-19 pandemic caused screening tests (colonoscopy) to be halted and delayed.

Materials and methods: The aim of this research is to retrospectively evaluate the impact of the COVID-19 pandemic on patients with newly diagnosed colorectal cancer in the period from April 1, 2020. until 30.09.2021. (during the Covid-19 pandemic) compared to the period from April 1, 2018. until 30.09.2019. (time before the COVID-19 pandemic) in three county hospitals.The research included 542 patients who were diagnosed with colorectal cancer in GH Zadar, GH Šibenik and GH Dubrovnik. The data were optained from electronical hospital data base. We compared the number and general condition of patients, age, the stage of the disease, and the type of primary tumor surgery (elective vs urgent).Of the analyzed 542 patients, 271 patients were in the period before the Covid-19 pandemic, and 271 patients were during the Covid-19 pandemic.

Results: There was no statistically significant difference in age, sex, performance status and disease stage before and during the Covid-19 pandemic, but a statistically significant difference was found in the number of emergency operations compared to elective procedures during the Covid-19 pandemic compared to time before the pandemic (23% and 77% vs. 15.7% and 84.3%; P=0.045).

Conclusion: Postponement or cancellation of preventive examinations can lead to delay in treatment and diagnosis of malignant disease in higher stages of the disease. This research showed that the COVID-19 pandemic had a significant impact on the type of surgery, which can be associated with a reduced number of preventive examinations in secondary healthcare institutions, i.e. a reduced response to the program for the early detection of colon cancer.

KLINIČKA VRIJEDNOST ODREĐIVANJA KINETIKE OMJERA NEUTROFILA I LIMFOCITA (NLR) KAO BIOMARKERA ODGOVORA I TOKSIČNOSTI NA IMUNOTERAPIJU U BOLESNIKA S UZNAPREDOVALIM UROTELNIM KARCINOMOM: ANALIZA JEDNOG CENTRA

MILETIĆ M.[1], Brčić H.[1], Franceschi D.[1], Prgomet Sečan A.[1], Murgić J.[1], Jazvić M.[1], Fröbe A.[1,2]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za onkologiju i nuklearnu medicinu*
[2] Sveučilište u Zagrebu
• *Stomatološki fakultet*
mmileti90@gmail.com

Uvod: Omjer neutrofila i limfocita (NLR) prepoznat je kao mogući biomarker odgovora na imunoterapiju (IO), ali malobrojne studije su istraživale kinetiku NLR-a tijekom IO liječenja. Naš cilj je bio istražiti kinetiku NLR-a i ispitati njegovu povezanost s ishodima liječenja u kohorti bolesnika s uznapredovalim urotelnim karcinomom (aUC) liječenih IO.

Materijali i metode: Retrospektivno smo analizirali podatke bolesnika s aUC koji su liječeni IO. Odredili smo NLR prije početka liječenja IO i prije svakog ciklusa IO te smo, uz ostale karakteristike bolesnika, analizirali njihovu povezanost s ukupnim preživljenjem (OS). Korištena je univarijatna i multivarijatna Coxova regresijska statistička analiza. Medijan NLR na početku je proizvoljno uzet kao prag za analize preživljenja.

Rezultati: Ukupno smo uključili 43 bolesnika, 44% je imalo 1 Bellmunt rizični faktor, 14% bolesnika 2, a 2% je imalo 3 Bellmunt rizična faktora. Medijan NLR-a prije početka IO iznosio je 2.7, a 57% bolesnika su imali povišen NLR. Vrijednost NLR-a bila je veća u bolesnika s većim stadijem bolesti, miješanom histologijom i većim brojem Bellmunt rizičnih faktora ($p<0.01$). Medijan OS-a iznosio je 3 mjeseca za bolesnike s NLR>2.7, a 9 mjeseci za one s nižim NLR-om (HR 2.6, $p=0.01$). Nadalje, povišen NLR bio je značajno povezan s lošijim OS-om u svim procijenjenim vremenskim točkama ($p<0,05$). Osim NLR-a, broj Bellmunt faktora rizika i prethodna operacija bili su također povezani s lošijim OS-om u univarijantoj analizi, međutim, multivarijatnom analizom NLR nije uspio zadržati značajnu povezanost s OS-om (HR 1.9, $p=0,07$). Longitudinalnom analizom, NLR je korelirao s odgovorom na IO, NLR se povećao za 0.03 ($p<0,01$) po ciklusu u bolesnika koji su doživjeli progresiju bolesti (67%); bio je stabilan u onih koji su postigli potpuni odgovor (2%), djelomični odgovor (11%) ili stabilnu bolest (18%), svi $p>0,1$ za nagib krivulje. Dvanaest pacijenata razvilo je imunološki uvjetovane nuspojave (Gr≥3), međutim, NLR nije bio u korelaciji s imunološkom toksičnošću ($p=0.3$).

Zaključak: Kinetika NLR-a određivana na početku i tijekom IO kod bolesnika s aUC koristan klinički biomarker. U bolesnika koji su nisu postigli odgovor na IO, NLR će se vjerojatno povećati, dok ima tendenciju ostati stabilan u bolesnika koji postignu kliničku korist od IO. Potrebna su daljnja istraživanja kako bi se potvrdila ova zapažanja i procijenila moguća uloga NLR dinamike kao novog biomarkera učinkovitosti IO.

UTILITY OF NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) KINETICS AS A BIOMARKER OF CLINICAL BENEFIT AND TOXICITY OF IMMUNE CHECKPOINT INHIBITOR THERAPY IN PATIENTS WITH ADVANCED UROTHELIAL CANCER: A SINGLE INSTITUTION EXPLORATORY ANALYSIS

MILETIĆ M.[1], Brčić H.[1], Franceschi D.[1], Prgomet Sečan A.[1], Murgić J.[1], Jazvić M.[1], Fröbe A.[1,2]

[1] University Hospital Centre Sestre milosrdnice
• *Department of Oncology and Nuclear medicine*
[2] University of Zagreb
• *School of Dental Medicine*

Introduction: Neutrophil-to-lymphocyte ratio (NLR) is considered biologically associated with immune checkpoint inhibitors (ICI) but has generally been evaluated as a single threshold value. We assessed NLR kinetics and examined its association with treatment outcomes in cohort of patients with advanced urothelial cancer (aUC) treated with ICI.

Materials and methods: We performed a retrospective study of patients with aUC treated with ICI. Baseline NLR and NLR at every cycle of ICI therapy were calculated and, along with other characteristics, correlated with overall survival (OS) in univariate and multivariate analyses. Longitudinal analysis of NLR dynamics was performed using mixed-effect regression model.

Results: A total of 43 patients were included; 44%, 14%, 2% had 1, 2, and 3 Bellmunt risk factors, respectively. Median NLR at baseline was 2.7; 57% of patients had high NLR. Patients with more advanced stage at baseline, variant histology, and increasing number of Bellmunt risk factors were more likely to have high NLR ($p<0.01$). Median OS was 3 months for patients with high NLR and 9 months for patients with low NLR (HR 2.6, $p=0.01$). Furthermore, high NLR was significantly associated with poor OS at all assessed time points during ICI therapy ($p<0.05$). Beside NLR, the number of Bellmunt risk factors and previous radical surgery were associate with OS on univariate analysis, however, on multivariate analysis, NLR failed to retain significant association with OS (HR 1.9, $p=0.07$). Longitudinally, NLR correlated with response: NLR increased by 0.03 ($p<0.01$) per cycle in patients who experienced progression disease (67%); NLR was stable in patients who achieved complete response (2%), partial response (11%) or stable disease (18%), all $p>0.1$ for slope. Twelve patients experience grade≥3 immunological-related side-effects, however, NLR was not correlated with immune toxicity ($p=0.3$).

Conclusion: NLR determined at baseline and during the course of ICI therapy is prognostic of clinical outcome. In patients who are not responding to ICI therapy, NLR is likely to increase, while it tends to remain stable in patients who derive clinical benefit from ICI therapy. More research is needed to confirm these observations.

ULOGA 3D KONFORMALNE RADIOTERAPIJE U PALIJATIVNOJ TERAPIJI BOLNIH KOŠTANIH METASTAZA

RADOJČIĆ M.[1], Smilović Radojčić Đ.[2,3], Skočilić I.[1], Špondreht M.[1], Polić N.[1]

[1] Klinički bolnički centar Rijeka
• *Klinika za radioterapiju i onkologiju*
[2] Klinički bolnički centar Rijeka
• *Zavod za medicinsku fiziku i zaštitu od zračenja*
[3] Sveučilište u Rijeci
• *Medicinski fakultet*
milan.radojcic@kbc-rijeka.hr

Uvod: Palijativna radioterapija ima važnu ulogu u liječenju onkoloških bolesnika. Njena je osnova poboljšanje kvalitete života bolesnika. Sekundarizmi u kosti najčešće su sijelo udaljenih presadnica (50–80%). Cilj ovog istraživanja je utvrđivanje razlike u raspodjeli apsorbirane doze dobivene trodimenzionalnom konformalnom tehnikom (3DCRT) u odnosu na konvencionalnu dvodimenzionalnu tehniku (2DRT) usporedbom dozimetrijskih parametara.

Materijali i metode: Konvencionalna 2DRT koristi jedno stražnje (PA) ili dva nasuprotna, (AP/PA) polja. Ovakve tehnike su jednostavne, ali ne pružaju mogućnost poštede okolnih zdravih struktura od utjecaja ionizi-

rajućeg zračenja visokih energija. 3DCRT omogućuje predaju propisane apsorbirane doze uz bolju doznu pokrivenost tumorskih volumena i, istovremeno, poštedu okolnog zdravog tkiva. U ovom istraživanju je provedena retrospektivna analiza raspodjela apsorbirane doze dobivene 2DRT tehnikom u odnosu na 3DCRT tehniku na 16 bolesnika sa sekundarizmima grudnih kralježaka. Propisana doza je svim bolesnicima predana 3DCRT tehnikom, a u svrhu ovog istraživanja su raspodjele apsorbirane doze izračunate za 2DRT. S ciljem usporedbe utjecaja svake od tehnika na raspodjelu apsorbirane doze analizirani su parametri vezani uz planirane tumorske volumene (PTV) i organe rizika (srce i pluća).

Rezultati: Rezultati analize parametara vezanih za doznu pokrivenost PTV-a, pokazali su da je 100% pokrivenost kod svih bolesnika statistički značajno bolja korištenjem 3DCRT (Tablici 1). Analizom parametara vezanih uz organe rizika pokazano je da je pošteda srca statistički također značajno bolja kod korištenja 3DCRT u odnosu na AP/PA tehniku 2DRT. Nije utvrđena statistički značajna razlika u raspodjeli doze kod pluća, a maksimalna vrijednost apsorbirane doze na okolne strukture kod svih bolesnika je veća kod korištenja AP/PA 2DRT tehnike, a najveća je kod PA 2DRT tehnike (Tablica 1.).

Tablica 1. Srednje vrijednosti s pripadajućim standardnim devijacijama analiziranih parametara za PTV, srce, pluća i maksimalne vrijednosti apsorbirane doze predane pacijentu, uz pripadajuće p-vrijednosti izračunate usporedbom 2DRT i 3DCRT.

		3DCRT	AP/PA	PA	3DCRT vs AP/PA	3DCRT vs PA
Strukture	**Parametar**	**Srednja vrijednost (SD)**	**Srednja vrijednost (SD)**	**Srednja vrijednost (SD)**	**p-vrijednost**	**p-vrijednost**
PTV	V_{100}(%)	88,89 (2,87)	75,41 (1,37)	71,12 (3,97)	**0,000018**	**0,000001**
	V_{95}(%)	99,46 (0,37)	89,45 (3,43)	82,14 (3,12)	0,172412	**0,000001**
srce	V_{80}(%)	11,39 (3,27)	40,65 (6,78)	4,66 (1,89)	**0,000035**	0,358035
pluća	V_{50}(%)	8,75 (4,69)	8,63 (5,17)	8,73 (5,66)	0,799701	0,761643
maksimalna doza	D_{max}(%)	109,21 (0,57)	111,23 (4,74)	126,19 (5,41)	**0,000001**	**0,000001**

podebljane p-vrijednosti su statistički značajne

Zaključak: U planiranju palijativne radioterapije bolnih koštanih sekuundarizama grudnih kralježaka, jednostavnije izvedbe 3D konformalne radioterapije nude značajno smanjenje apsorbirane doze na zdrave organe te pružaju mogućnost bolje pokrivenosti ciljnih volumena. Posebnu korist primjene 3DCRT imaju bolesnici s boljom prognozom bolesti i oni kod kojih postoji potreba za ponovnim zračenjem.

ROLE OF 3D CONFORMAL RADIATION THERAPY IN PALLIATIVE TREATMENT OF THE PATIENT WITH THORACIC BONE METASTASES

RADOJČIĆ M.[1], Smilović Radojčić Đ.[2,3], Skočilić I.[1], Špondreht M.[1], Polić N.[1]

[1] University Hospital Centre Rijeka
• *Department of Radiotherapy and Oncology*
[2] University Hospital Centre Rijeka
• *Medical Physics and Radiation Protection Department*
[3] University of Rijeka
• *School of Medicine*

Introduction: Palliative irradiation is an important part of radiation oncology. The purpose of palliative irradiation is to improve the patient's quality of life. Bone metastases are the most common site of distant metastases (50–80%). This research has been performed with purpose of investigating the dosimetric advantages of threeu2011dimensional conformal radiation therapy (3DCRT) for thoracic spine metastases over conventional twou2011dimensional (2D) approach.

Materials and methods: Conventional 2D techniques for spine metastases utilize a single posteroanterior (PA) field or anteroposterior/posteroanterior (AP/PA) parallelu2011opposed fields. These techniques are straightforward but with limited possibility of sparing adjacent healthy tissues from the harmful effects of high

energy ionizing radiation. 3DCRT provides highly conformal and accurate irradiation, permitting an increased target dose while reducing the unnecessary irradiation of normal structures. Retrospective analysis of dose distributions calculated using 3DCRT and 2D techniques for 16 patients with thoracic spine metastases was performed in this study. Prescribed dose for all patients was delivered using 3DCRT, and for the purpose of this research, dose distributions were readjusted to 2D technique. To determine the influence of treatment delivery technique on absorbed dose distribution, parameters related to target volumes (PTV) and organs-at-risk (heart and lung) were analysed.

Results: By analysing parameters related to PTV, 100% absorbed dose coverage using 3DCRT was statistically significant higher for all involved patients. (Table 1.) Comparing the effect to organs-at-risk, the sparing for heart is statistically significantly better for 3DCRT technique in comparison with AP/PA technique. No statistically significant difference was found when comparing absorbed dose to the lung. Maximum dose in the patient increased when using AP/PA and PA as compared to 3DCRT is shown in Table 1.

Table 1. Mean values of relevant parameters with corresponding standard deviation for PTV, heart, lung and the maximum dose to the patient, accompanied with p-values determined by comparison of 2DRT with 3DCRT.

		3DCRT	AP/PA	PA	3DCRT vs AP/PA	3DCRT vs PA
Structure	**Parameter**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p-Value**	**p-Value**
PTV	V_{100}(%)	88,89 (2,87)	75,41 (1,37)	71,12 (3,97)	**0,000018**	**0,000001**
	V_{95}(%)	99,46 (0,37)	89,45 (3,43)	82,14 (3,12)	0,172412	**0,000001**
heart	V_{80}(%)	11,39 (3,27)	40,65 (6,78)	4,66 (1,89)	**0,000035**	0,358035
lung	V_{50}(%)	8,75 (4,69)	8,63 (5,17)	8,73 (5,66)	0,799701	0,761643
maximum dose	D_{max}(%)	109,21 (0,57)	111,23 (4,74)	126,19 (5,41)	**0,000001**	**0,000001**

p-Value in bold are statistically significant

Conclusion: In palliative treatment planning of radiation treatment of spinal metastases, simple variants of 3DCRT techniques can offer a significant dose reduction to the organs at risk, while providing a better absorbed dose coverage of the target volume. Especially patients with favourable life expectancy and potential need for re-irradiation might benefit from such 3DCRT approaches.

DUGOTRAJNO PRAĆENJE PACIJENTA KOMPLETNE REMISIJE PACIJENTA S HEPATOCELULARNIM KARCINOMOM LIJEČENIM SORAFENIBOM – PRIKAZ SLUČAJA

ADŽIĆ G.[1], Tomek Hamzić D.[1], Kekez D.[1,2], Librenjak N.[1], Goršić I.[1], Prejac J.[1,2], Pleština S.[1,3]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Sveučilište u Zagrebu
• *Stomatološki fakultet*
[3] Sveučilište u Zagrebu
• *Medicinski fakultet*
gordan.adzic@gmail.com

Uvod: Hepatocelularni karcinom (HCC) izaziva oko 90% primarnih karcinoma jetre. Može biti uzrokovan raznim rizičnim faktorima koji uključuju infekciju s hepatitis B i C virusom, ekscesivnom konzumacijom alkohola i metaboličkim sindromom. Prognoza pacijenata s ovom bolešću je loša s medijanom preživljenja od godinu dana za pacijente s uznapredovalom bolesti. Sorafenib je oralni inhibitor tirozin kinaza koji inhibira Raf kinazu te vaskularni endotelijalni receptor čimbenika rasta. SHARP studija je afirmirala sorafenib kao lijek izbora u prvoj liniji za sustavno liječenje HCC-a, iako je ukupna stopa odgovora bila niska te nijedan slučaj kompletnog odgovora nije bio detektiran.

Prikaz slučaja: U srpnju 2020., 73-godišnjak je obrađen u našoj ustanovi zbog bolova u abdomenu. Inicijalnim CT-om je verificirana tromboza portalne, splenične i gornje mezenterične vene s tumorskim trombom

neodvojivim od nepravilnog lobusa caudatusa. MR abdominalnih organa je potvrdio dijagnozu HCC-a. Pacijent nije imao poznate faktore rizika za razvoj HCC-a. Jetrena funkcija je bila očuvana (Child-Pugh skor A6) te je pacijent bio dobrog općeg stanja (ECOG 0). U laboratorijskim nalazima se pratio blaže povišen AFP (17.3 µg/L). Učinjena je atipična resekcija lobusa caudatusa te se prema PHD-u radilo o HCC-u gr. III. Postoperativno, vrijednosti AFP-a su se normalizirale dok je MR ukazao na postojanje kolekcije u području reseciranog lobusa caudatusa, novonastalu metastazu u VI segmentu jetre te progresiju tromboze portalne vene. U 10/2020. započeto je liječenje sorafenibom u dozi od 800 mg dnevno. Nakon 2 mjeseca, reevaluacijski CTom je verificirana parcijalna regresija postoperativne kolekcije i tromboze te potpuna regresija metastaze u VI segmentu. Zbog blažeg oblika "hand-foot" sindroma, doza sorafeniba je deeskalirana na 400 mg dnevno. Pacijent je potom evaluiran svaka 2 mjeseca sve do 9/2022. te je prema nalazima MSCT-a bez znakova vijabilnog tumora.

Zaključak: Prezentirali smo rijedak slučaj pacijenta koji je postigao kompletan odgovor na sorafenib u liječenju uznapredovalog HCC-a. Daljnje studije koje će rasvijetliti mehanizme i preditivne faktore koje uzrokuju kompletni odgovor su nužne zbog pozicioniranja sorafeniba u kontekstu dolaska novih, učinkovitijih terapija.

LONG-TERM FOLLOW-UP OF COMPLETE REMISSION IN A PATIENT WITH ADVANCED HEPATOCELLULAR CARCINOMA TREATED WITH SORAFENIB: A CASE REPORT

ADŽIĆ G.[1], Tomek Hamzić D.[1], Kekez D.[1,2], Librenjak N.[1], Goršić I.[1], Prejac J.[1,2], Pleština S.[1,3]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] University of Zagreb
• *School of Dental medicine,*
[3] University of Zagreb
• *School of Medicine*

Introduction: Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancer. It can be caused by a variety of risk factors which include infection with hepatitis B and C viruses, alcohol intake and metabolic syndrome. The overall prognosis remains poor with a median survival of 1 year for advanced-stage cases. Sorafenib, is a multitargeted oral tyrosine-kinase inhibitor which inhibits Raf kinase and vascular endothelial growth factor receptor. SHARP trial established sorafenib as a first line agent in systemic treatment of HCC, however, ORR was low, and there was no established cases of complete response (CR).

Case report: In 7/2020, a 73-year old male presented at our institution with abdominal pain. Initial CT scan showed thrombosis of portal, splenic and superior mesenteric vein with a probable tumor thrombus which was inseparable from an irregular caudate lobe. MRI of abdominal organs confirmed the diagnosis of HCC. Patient had no known risk factors for developing HCC. Liver function was well retained (Child Pugh score A6), and the patient was in good clinical condition (ECOG 0) with mildly elevated AFP of 17.3 u03bcg/L (nv

Conclusion: We present a rare case of a patient who demonstrated complete response to sorafenib treatment in advanced HCC. Further studies which aim to clear mechanisms and predictive factors leading to CR are warranted to correctly position the use of sorafenib, especially in the context of arising of more effective therapies.

IMPLEMENTACIJA NEANTRACIKLINSKIH PROTOKOLA U NEOADJUVANTNO LIJEČENJE HER2 POZITIVNOG RAKA DOJKE

GUDELJ D.[1], Čular K.[1], Toula L.[1], Vičić I.[1], Dedić Plavetić N.[2], Popović M.[1], Križić M.[1], Pleština S.[1], Silovski T.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Sveučilište u Zagrebu
• *Medicinski fakultet*
dora.gudelj1@gmail.com

Uvod: Standard u liječenju HER2 pozitivnog raka dojke većeg od 2 cm i/ili s pozitivnim limfnim čvorovima pazuha je neoadjuvantna primjena kombinacije kemoterapije (antraciklinski ili neantraciklinski protokoli) i dualne antiHER2 terapije (trastuzumab + pertuzumab). Cilj ovog istraživanja bio je usporediti ishod – stopu

kompletnog patološkog odgovora na neoadjuvantnu primjenu antraciklinskih i neantraciklinskih protokola u liječenju ranog HER2 pozitivnog raka dojke.

Materijali i metode: Provedeno je retrospektivno istraživanje koje je uključilo ukupno 83 bolesnika s HER2 pozitivnim rakom dojke koji su od 1.1.2020. do 31.12.2021. bili liječeni neoadjuvantnom terapijom u KBC Zagreb.

Bolesnici su bili podijeljeni u dvije skupine ovisno o apliciranom protokolu:

1) antraciklinska skupina: 4 ciklusa AC – doksorubicin + ciklofosfamid (svaka 3 ili 2 tjedna), potom 12 ciklusa tjednog paklitaksela uz trastuzumab i pertuzumab svaka 3 tjedna
2) ne-antraciklinska skupina: TCPH (6 ciklusa docetaksel, karboplatin, pertuzumab, trastuzumab, svaka 3 tjedna) ili protokol po TRAIN2 studiji (9 ciklusa paklitaksel 1. i 8. dan, karboplatin, pertuzumab, trastuzumab 1. dan, svaka 3 tjedna)

Rezultati: Od ukupno 83 bolesnika, njih 87% (72/83) je bilo liječeno antraciklinskim, a 13% (11/83) neantraciklinskim protokolom. Ukupno 95% (79/83) bolesnika je završilo neoadjuvantno liječenje: 96% (69/72) u antraciklinskoj i 91% (10/11) u neantraciklinskoj skupini. U dvije bolesnice u antraciklinskoj skupini je zabilježena progresija bolesti tijekom neoadjuvantnog liječenja, a jedna bolesnica u neantraciklinskoj skupini nije završila liječenje uslijed nepodnošenja kemoterapije (polineuropatija). Kompletni patološki odgovor (pCR) je postignut u ukupno 61% bolesnika: 58% (40/69) u antraciklinskoj i 80% (8/10) u neantraciklinskoj skupini.

Zaključak: Iako je ovo istraživanje provedeno na relativno malom broju bolesnika, stopa kompletnog patološkog odgovora postignuta primjenom neantraciklinskih protokola usporediva je stopi postignutoj primjenom antraciklinskih protokola. Potrebno je daljnje praćenje kako bi se procijenila učinkovitost i utjecaj primijenjenih protokola na odgođenu kardijalnu i drugu toksičnost.

THE IMPLEMENTATION OF NON-ANTHRACYCLINE BASED REGIMENS IN NEOADJUVANT TREATMENT OF HER2-POSITIVE BREAST CANCER

GUDELJ D.[1], Čular K.[1], Toula L.[1], Vičić I.[1], Dedić Plavetić N.[2], Popović M.[1], Križić M.[1], Pleština S.[1], Silovski T.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] University of Zagreb
• *School of Medicine*

Introduction: Neoadjuvant chemotherapy (anthracycline or non-anthracycline based protocols) in combination with dual antiHER2 therapy (trastuzumab + pertuzumab) has become the standard of care for HER2-positive breast cancer larger than 2 cm and/or with positive axillary lymph nodes. This study aimed to compare outcome – complete pathologic response (pCR) rate, of anthracycline-based regimens to the non-anthracycline ones in neoadjuvant treatment of HER2-positive early breast cancer.

Materials and methods: This retrospective study included 83 patients with HER2-positive breast cancer who received neoadjuvant chemobiotherapy (NACT) between January 2020 and December 2021 at the University Hospital Centre Zagreb.Patients were divided into two groups based on the regimen which they received: anthracycline group: 4 cycles of AC – doxorubicin + cyclophosphamide (every 2 or 3 weeks) followed by 12 weekly cycles of paclitaxel with three-weekly cycles of trastuzumab and pertuzumab concomitantly.non-anthracycline group: TCPH (6 cycles of docetaxel, carboplatin, pertuzumab, trastuzumab, every 3 weeks) or TRAIN2 study-based regimen (9 cycles of paclitaxel – day 1 and 8, carboplatin, pertuzumab, trastuzumab – day 1, every 3 weeks)

Results: Of all patients, 87% (72/83) were treated with an anthracycline-based regimen and 13% (11/83) with a non-anthracycline one. Altogether 95% (79/83) patients completed neoadjuvant treatment, 69 out of 72 patients (96%) in the anthracycline group and 10 out of 11 patients (91%) in the non-anthracycline group. Disease progression was recorded in 2 patients during neoadjuvant treatment in the anthracycline group, and in the non-anthracycline group one patient did not complete the treatment due to polyneuropathy.A pathological complete response (pCR) was achieved in 61% of cases: 40 out of 69 patients in the anthracycline group (58%) and 8 out of 10 patients in the non-anthracycline group (80%).

Conclusion: Although this research included only modest number of patients, the rate of pCR achieved with the use of non-anthracycline-based protocols is comparable to the one achieved using anthracycline-based ones. Further follow-up is necessary to compare efficacy as well as cardiac toxicity and other adverse events between investigated treatment regimens.

IZAZOVI U LIJEČENJU DEZMOIDNIH TUMORA – PRIKAZ SLUČAJA

JERKOVIĆ I.[1], Golčić M.[1], Dobrila-Dintinjana R.[1,2], Zahirović D.[1], Skočilić I.[1], Mikolašević I.[1,2], Špondreht M.[1], Beg A.[1], Bešvir Džubur A.[1], Polić N.[1], Simetić L.[3], Herceg D.[3]

[1] Klinički bolnički centar Rijeka
• *Klinika za radioterapiju i onkologiju*
[2] Sveučilište u Rijeci
• *Medicinski fakultet*
[3] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
ivona.jerkovic051@gmail.com

Uvod: Dezmoidni tumori su novotvorine vezivnog tkiva bez metastatskog potencijala, ali koje zbog svoje lokalne agresivnosti mogu dovesti do značajnog morbiditeta i mortaliteta. Zbog nepredvidivog kliničkog tijeka, relativno rijetke učestalosti te malog broja kliničkih studija, liječenje dezmoida predstavlja izazov u modernoj onkologiji.

Prikaz slučaja: Našoj 58-godišnjoj bolesnici je u kolovozu 2019. pronađena lezija uz desnu karotidnu arteriju, veličine 32x23x43 mm, koja je potiskivala jugularnu venu i zajedničku karotidnu arteriju. Inicijalno je postavljena dijagnoza nodularnog fascitisa, no zbog progresije u veličini tumora u siječnju 2020. učinjena je proširena radikalna disekcija desne strane vrata kojom se potvrdila dijagnoza dezmoidnog tumora. Postoperativno je liječena adjuvantnom radioterapijom, a zatim je nastavljeno praćenje do listopada 2021. godine kada je utvrđen lokalni recidiv bolesti, veličine 30x30x66 mm. S obzirom na kritičnu lokalizaciju, inoperabilnost recidiva i potrebu za brzim kliničkim odgovorom, u prosincu 2021. započeto je liječenje peroralnim tirozin kinaznim inhibitorom sorafenibom u dozi od 400 mg. Tijekom prvih 12 tjedana liječenja kod bolesnice smo na tjednoj bazi pratili i utjecaj terapije na kvalitetu života upitnikom EORTC QLQ-C30, te pokazali da se pozitivan učinak sorafeniba na opću kvalitetu života i bol primjetio već nakon 7 dana uzimanja terapije, dok je učinak na umor i fizikalno funkcioniranje bio izraženiji nakon 4 tjedna uzimanja lijeka. Bolesnica je sorafenib uzimala gotovo 9 mjeseci bez većih nuspojava, a na dvije radiološke kontrole pratila se regresivna dinamika bolesti. Pred kontrolnu obradu u kolovozu 2022. bolesnica je hospitalizirana na Kardiologiji zbog progresivne zaduhe te se učinjenom obradom i isključivanjem drugih uzroka postavila dijagnoza toksične kardiomiopatije najvjerovatnije uzrokovane sorafenibom te je lijek isključen iz terapije.

Zaključak: Iako je aktivno praćenje primarna terapijska opcija za većinu dezmoidnih tumora, za progresivnu ili simptomatsku bolest preporuča se kirurško liječenje, ili kada to nije moguće, sistemska terapija. Liječenje sorafenibom je preferirana opcija sistemskog liječenja, no važan je individualni pristup pacijentu uz evaluaciju multidisciplinarnog tima s obzirom na nepredvidiv klinički tok bolesti te moguće rizike i nuspojave same terapije.

CHALLENGES IN DESMOID TUMOR MANAGEMENT – CASE REPORT

JERKOVIĆ I.[1], Golčić M.[1], Dobrila-Dintinjana R.[1,2], Zahirović D.[1], Skočilić I.[1], Mikolašević I.[1,2], Špondreht M.[1], Beg A.[1], Bešvir Džubur A.[1], Polić N.[1], Simetić L.[3], Herceg D.[3]

[1] University Hospital Centre Rijeka
• *Department of Radiotherapy and Oncology*
[2] University of Rijeka
• *School of Medicine*
[3] University Hospital Centre Zagreb
• *Department of Oncology*

Introduction: Desmoid tumors are mesenchymal neoplasms that usually do not metastasize but can cause significant functional morbidity and mortality due to local invasion. As it is a relatively rare disease with an unpredictable clinical course and only a handful of clinical trials evaluating treatment options, the treatment of desmoid tumors is a challenge in modern oncology.

Case report: We present a 58-years-old patient who presented with a lesion localized, 32x23x43 mm in size, adjacent to the right carotid artery, causing the compression of the right jugular vein and common carotid artery in August 2019. Initially, a diagnosis of nodular fasciitis was made, but due to tumor size progression, extended neck dissection was performed in January 2020, and a histology report revealed a desmoid tumor. The patient

was treated with adjuvant radiotherapy, and a follow-up was continued until October 2021, when a local recurrence, 30x30x66 mm in size, was detected. Due to the critical anatomical location of the lesion, which was deemed inoperable, and a need for a rapid clinical response, the treatment with the oral tyrosine kinase inhibitor sorafenib at a dose of 400 mg daily was started in December 2021. During the first 12 weeks of the patient's treatment, we also evaluated the impact of the treatment on quality of life using the EORTC QLQ-C30 questionnaire weekly. Results showed a positive effect of sorafenib on global health quality of life, and pain reduction after only 7 days of treatment, while the effect related to physical functioning and fatigue was more noticeable after 4 weeks. The patient took sorafenib for almost 9 months without significant side effects, and the regressive dynamics of the disease was reported at two subsequent radiological assessments. However, before the follow-up in August 2022, the patient was hospitalized at the Cardiology department due to progressive shortness of breath. After extensive workup and exclusion of other causes, a diagnosis of toxic cardiomyopathy was made, most likely caused by sorafenib, so the drug was excluded from the therapy.

Conclusion: Although active surveillance is now considered the primary therapeutic option in most patients, surgery is still the preferred option for patients with progressive or symptomatic disease. When surgery is not an option, medical therapy should be administered. While TKI sorafenib is the recommended systemic therapy option, the treatment decision should be individualized and managed by a multidisciplinary team considering the unpredictable clinical course and possible treatment-related adverse events.

JETRENA TOKSIČNOST POVEZANA S INHIBITORIMA KINAZA OVISNIH O CIKLINIMA (CDK4/6I) – ISKUSTVO JEDNE INSTITUCIJE

JAKŠIĆ P.[1], Vazdar LJ.[1], Linarić P.[1], Trajbar M.[1], Mirčevski K.[1], Popović J.[1], Tečić Vuger A.[1], Pavlović Mavić M.[1], Šeparović R.[1,2]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za internističku onkologiju*
[2] Sveučilište J.J. Strossmayera u Osijeku
• *Medicinski fakultet*
petra.lepetic@gmail.com

Uvod: Endokrina rezistencija je prepoznata kao važan klinički problem u liječenju hormon receptor pozitivnog, HER-2 negativnog uznapredovalog raka dojke. Da bi se to premostilo, razvijeni su inhibitori kinaza ovisnih o ciklinima (CDK 4/6i) kao dodatak antihormonskoj terapiji. Registracijske studije faze III za abemaciklib, palbociklib i riboclklib, u kombinaciji s antihormonskom terapijom, pokazale su poboljšanje ishoda liječenja i tako promijenile standard liječenja ovog najčešćeg podtipa raka dojke. Sigurnosni profil ovih lijekova je sličan, razliku definira selektivnost lijeka za određenu ciklin ovisnu kinazu 4/6. Porast transaminaza zabilježena je uz liječenje sa sva tri lijeka. Prema sažetcima opisa svojstava lijeka od strane proizvođača (SmPC), odstupanja u nalazima testova funkcije jetre je svrstana u vrlo česte nuspojave. Isto je potvrđeno u sustavnom preglednom članku Jahna i suradnika; učestalost porasta vrijednosti ALT gradusa 3/4 je 4.1% u skupini CDK4/6i, 0.8% u kontrolnoj skupini, dok je učestalost porasta vrijednosti AST gradusa 3/4 2.9% u ispitivanoj skupini i 0.9% u kontrolnoj skupini.

Materijali i metode: Ovim istraživanjem smo obuhvatili 295 oboljelih od HR-pozitivnog, HER2 negativnog uznapredovalog raka dojke, liječenih na Zavodu za internističku onkologiju Klinike za tumore abemaciklibom, palbocilibom ili riboclklibom u kombinaciji s antihormonskom terapijom u razdoblju od 08/2018 do 8/2022. Uključeni su oni kod kojih je proveden barem jedan cjeloviti četverotjedni ciklus liječenja. Određivanje gradusa porasta transaminaza (AST i ALT) je bilo u skladu sa Common Terminology Criteria for Adverse Events verzija 4.0.

Rezultati: U otprilike 7% promatranih zabilježen je porast AST/ALT gradusa 3 ili 4. Kod tri bolesnice je obustavljeno liječenje zbog ove nuspojave, dok se kod njih četiri liječenje nastavilo drugim CDK4/6i. Nije zabilježen niti jedan smrtni ishod uslijed jetrenog oštećenja.

Zaključak: Ova analiza kliničkog iskustva naše institucije je potvrdila kako CDK4/6i uzrokuju porast transaminaza u određenog broja liječenih što je u skladu s dosadašnjim spoznajama. U zaključku, spoznaja i razumijevanje toksičnog profila antineoplastičnih lijekova vodi do ranog prepoznavanja te posljedičnog ranog liječenja eventualniih neželjenih učinaka.

Ključne riječi: rak dojke, CDK 4/6 inhibitori, jetrena toksičnost, porast transaminaza

HEPATOTOXICITY ASSOCIATED WITH CYCLIN-DEPENDENT KINASE 4/6 INHIBITORS (CDK4/6I) – SINGLE INSTITUTION EXPERIENCE

JAKŠIĆ P.[1], Vazdar LJ.[1], Linarić P.[1], Trajbar M.[1], Mirčevski K.[1], Popović J.[1], Tečić Vuger A.[1], Pavlović Mavić M.[1], Šeparović R.[1,2]

[1] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department Medical Oncology*
[2] University of J.J.Strossmayer Osijek
• *School of medicine*

Introduction: Cyclin-dependent kinase inhibitors (CDK 4/6i) are developed as an addition to endocrine therapy since endocrine resistance has been recognized as a clinical problem in the treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer. Based on pivotal randomized phase III trials, abemaciclib, palbociclib, and ribociclib, in combination with endocrine therapy, have improved treatment outcomes. Therefore, they changed the treatment landscape of this most frequent breast cancer subtype. The safety profile of this targeted therapy is quite related, and the distinction defines selectivity for cyclin-dependent kinase 4/6. Transaminase elevations have been reported with the use of all three CDK 4/6i. According to a summary of product characteristics (SmPC) of all three drugs, an abnormal liver function test is a very common adverse event. This is following the systematic review and meta-analysis of phase 3 randomized controlled trials by Jahan and all; the incidence of grade 3/4 ALT elevation was 4.1% in the CDK4/6i arm and 0.8% in the control arm, while the incidence of grade 3/4 AST elevation was 2.9% in the CDK4/6i arm and 0.9% in the control arm.

Materials and methods: We obtained data from 295 patients with HR-positive Her-2 negative breast cancer treated at the Division for Medical Oncology, University Hospital for Tumors Zagreb, with abemaciclib, palbociclib, or ribociclib in combination with endocrine therapy, in the period from 08/2018 to 8/2022. Patients had completed at least one four-week cycle of therapy. Grading of transaminases elevation (ALT or AST) was performed according to Common Terminology Criteria for Adverse Events version 4.0.

Results: In the observed population, around 7% had grade 3/4 AST or ALT elevation. Discontinuation in treatment was in three patients, while four patientscontinued treatment with another CDK 4/6i. None of the patients had fatal outcomes due to hepatotoxicity.

Conclusion: This analysis from clinical practice implied that treatment with CDK4/6i is associated with the elevation of transaminases. This is in concordance with available publications. In conclusion, comprehension of the safety profile of antineoplastic drugs leads to early recognition hence early management of side effects.

Keywords: breast cancer, CDK 4/6 inhibitors, hepatotoxicity, transaminases elevation

KAKO POSTAVITI GRANICU ZA PRIMJENU KEMOTERAPIJE KOD STARIJIH BOLESNIKA?

REDŽOVIĆ A.[1], Marušić J.[1], Jerković I.[1], Beg A.[1]

[1] Klinički bolnički centar Rijeka
• *Klinika za radioterapiju i onkologiju*
arnelar@uniri.hr

Uvod: Dob je izrazito važan čimbenik kada se donosi odluka primjeniti ili ne onkološko liječenje. Gerijatrijska onkologija dijeli bolesnike starije životne dobi (iznad 65 godina) ili izrazito stare (iznad 80 godina). S obzirom na starenje europskog stanovništva povećana je pojavnost karcinoma a s time i broj starijih bolesnika. Primjena sistemne terapije kod stariijh onkoloških bolesnika razlikuje se je u odnosu na mlađe zbog smanjene farmakodinamike i farmakovigilancije lijekova. Stoga dozu treba prilagoditi s ciljem manje toksičnosti i nuspojava i imati na umu brojne komorbiditete starijih osoba i polifarmacije istih (pet i više lijekova). Kliničke studije uglavnom obuhvaćaju mlađe bolesnike no recentne istraživanja Cancer and Aging Research Group (CARG) s više od 500 bolesnika da više od 50% bolesnika starije životne dobi ima nuspojave liječenja unutar 3 mjeseca a na temelju mjerenja s „geriatric assessment (GA)“. Nuspojave povećavaju hospitalizacije, morbiditet, mortalitet i financijski opterećuju zdravstveni sustav. EMA je dala preporuke o pravilnom utrvđivanja nuspojava kod krhkijih starijih bolesnika. „The Geriatric-8 (G8)“ i „Vulnerable Elders Survey-13 (VES-13)“ alati imaju također cilj određivanja bolesnika kojima terapija donosi dobrobit, a smanjuje rizik lošeg ishoda. Ponekad je davanje terapije

milosrdni čin, te pružanje "lažne nade" starijim, usamljenim i prestrašenim starijim bolesnicima. Stoga su za neke karcinome u smjernicama postavili „očekivano vrijeme života" kao čimbenik prosudbe liječiti ili ne starije bolesnike. Mora se također naglasiti da nekad mlađe ljude pretretiramo s nadom i željom izliječenja dok starije bolesnike „pratimo" te na taj način zasigurno doprinosimo smanjenju preživljenja onkoloških bolesnika.

Prikaz slučaja: Bolesniku 80 godina starom u lipnju 2021 se postavi dijagnoza metastatskog karcinoma gušterače. Započelo se liječenje kemoterapijom nabpaklitaksel i gemcitabinom. Nakon 2 ciklusa dolazi do pojave generaliziranog makulopapuloznog osipa te se postavi sumnja na alergiju na gemcitabin. Stoga se na Konziliju odluči nastaviti liječenje prema FOLFOX protokolu u prilagođenim dozama. Do sada je primio 7 ciklusa bez tegoba s nekoliko odgoda ciklusa radi trombocitopenije gradusa II. Bolest je stabilna bez znakova progresije, a bolesnik je odličnog općeg stanja kao i na početku liječenja.

Zaključak: Bolesnici starije životne dobi svakako moraju biti prikazani na multidisciplinarnim timovima, a radi razmatranja najboljeg modaliteta liječenja –adjuvantno ili palijativno. Potrebno je svakako voditi se osnovnim etičkim načelom „ne naškoditi" bolesniku uz često kliničko procjenjivanje, praćenje djelovanja terapije i ranim otkrivanjem nuspojavama s premisom, pruduljenja kvalitetnog života.

HOW TO DECIDE WHEN OLDER ADULTS SHOULD RECIEVE CHEMOTHERAPY?

REDŽOVIĆ A.[1], Marušić J.[1], Jerković I.[1], Beg A.[1]

[1] University Hospital Centre Rijeka
• *Department of Radiotherapy and Oncology*

Introduction: As age is the most significant risk factor for cancer, and with the aging of the population, there is a vast increase in the number of older cancer patients. Geriatric oncology is the clinical field of cancer treatment in older adults (above 65 years) and in the oldest-old (above 80 years). Importantly, the pharmacology of anticancer drugs might differ between younger and older people because of reduced pharmacodynamics. These age-related pharmacological differences might require dose adaptations for anticancer drugs with a narrow therapeutic window to maximise efficacy and minimise toxic effects, especially for patients with concomitant diseases and polypharmacy (five or more drugs). There has been also a marked under-representation of older patients in key oncology trials. Several studies, including a Cancer and Aging Research Group (CARG) study in 500 patients, have demonstrated that 50% of older patients have severe toxicity from chemotherapy within 3 months of treatment initiation and that measures within a geriatric assessment (GA), a validated approach to assessing health status in older persons, can predict severe chemotherapy toxicities. Side effects increase hospitalizations, morbidity, mortality and there is no cost – effectivness. The EMA produced guidelines for the appropriate evaluation of side-effects according to frailty status in older patients. The Geriatric-8 (G8) and the Vulnerable Elders Survey-13 (VES-13) were the most frequently evaluated screening tools. Unfortunatelly, lonely, scared, depressed older adults are given a hope by chemotherapy treatment. More recently, research has advocated using life expectancy, which incorporates not only age but also an individual's health and functional status, to inform screening decision. Otherwise, we usually overtreat younger age and undertreatment was related with increasing age and possible reduction of clinical outcome.

Case report: An 80-year-old patient was diagnosed with metastatic pancreatic cancer in June 2021. Chemotherapy treatment was started with nabpaclitaxel and gemcitabine. After 2 cycles, a generalized maculopapular rash appeared, and an allergy to gemcitabine was suspected. Therefore, at the Council, it was decided to continue the treatment according to the FOLFOX protocol in adjusted doses. So far, he has received 7 cycles with few delays of therapy due to thrombocytopenia grade II. The disease is stable with no signs of progression, and the patient is in excellent general condition as at the beginning of the treatment.

Conclusion: Thus, each older patient being considered for definitive treatment must be discussed in a multidisciplinary tumor board and thew the most important first step is to define treatment intent – cure or palliation. It is important that our main principal guidance is 'primum non nocere' with frequent clinical monitoring, flexibility in administration drugs. Our goal is prolongation of survival and quality of life.

KARAKTERISTIKE BOLESNIKA S METASTATSKIM KARCINOMIMA BILIJARNOG SUSTAVA LIJEČENIH U KLINIČKOM BOLNIČKOM CENTRU ZAGREB

TOMEK HAMZIĆ D.[1], Adžić G.[1], Goršić I.[1], Kekez D.[1,2], Librenjak N.[1], Prejac J.[1,2], Pleština S.[1,3]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Sveučilište u Zagrebu
• *Stomatološki fakultet*
[3] Sveučilište u Zagrebu
• *Medicinski fakultet*
doratomek@icloud.com

Uvod: Karcinomi bilijarnog sustava uključuju intrahepatalni i ekstrahepatalni kolangiokarcinom te karcinom žučnog mjehura. Relativno su rijetka skupinu tumora, ali s nepovoljnom prognozom. Samo operacija omogućuje definitivno izlječenje, no nažalost, većina pacijenata u vrijeme dijagnoze ima već lokalno uznapredovalu ili metastatsku bolest.[1] Standard liječenja prve linije uznapredovale bolesti je kombinacija gemcitabina i cisplatine (GC), što je potvrdila i studija ABC-02 (faza III).[2] Trenutno još ne postoji standard liječenja u drugoj liniji. Cilj našeg rada bio je procijeniti stopu preživljenja i ishode liječenja bolesnika s metastatskim karcinomima bilijarnog sustava u Kliničkom bolničkom centru (KBC) Zagreb

Materijali i metode: Prikupljena je i retrospektivno pregledana medicinska dokumentacija 188 pacijenata s dijagnozom karcinoma bilijarnog sustava liječenih od početka 2017. godine u KBC-u Zagreb. Statistički podaci analizirani su korištenjem IBM SPSS 24.

Rezultati: Od 188 pacijenata, 116 je razvilo metastatsku bolesti, od čega 56 muškaraca i 60 žena. Prosječna dob dijagnoze bila je 67 godina. Bolesnici su stratificirani prema lokalizaciji bolesti (intrahepatalni, ekstrahepatalni ili rak žučnog mjehura). Medijan ukupnog preživljenja (OS) u svim skupinama s metastatskom bolešću bio je 8,4 mjeseca. Medijan OS-a za intrahepatalni kolangiokarcinom je bio 14,8 mjeseci, za ekstrahepatalni 8,2 mjeseca, a za rak žučnog mjehura 6,6 mjeseci. Sedamdeset i osam pacijenata liječeno je kemoterapijom, u prvoj liniji je većina primila terapiju na bazi platine i gemcitabina. Medijan preživljenja bez progresije (PFS) bio je 2,9 mjeseci u svim skupinama. Za intrahepatalni karcinom i rak žučnog mjehura medijan PFS-a je bio 2,6 mjeseci, a ze ekstrahepatalni karcinom 3,7 mjeseci.

Zaključak: Naša studija pokazuje rezultate liječenja iz kliničke prakse u jednoj akademskoj instituciji, ali nedostatak joj je retrospektivni dizajn. Kolangiokarcinom je jedan od najslabije poznatih karcinoma GI trakta s lošom prognozom i ograničenim mogućnostima liječenja u metastatskom okruženju. Za bolje razumijevanje i učinkovitije liječenje ovih agresivnih karcinoma potrebna su daljnja istraživanja.

METASTATIC BILIARY TRACT CANCER PATIENT CHARACTERISTICS IN UNIVERSITY HOSPITAL CENTRE ZAGREB

TOMEK HAMZIĆ D.[1], Adžić G.[1], Goršić I.[1], Kekez D.[1,2], Librenjak N.[1], Prejac J.[1,2], Pleština S.[1,3]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] University of Zagrebu
• *School of medicine*
[3] University of Zagrebu
• *School of Dental Medicine*

Introduction: Biliary tract cancers (BTC) refers to a spectrum of invasive adenocarcinomas, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder carcinoma. They represent a rare group of tumors with unfavorable prognosis.1 Surgery is the cornerstone of cure, but unfortunately most patients present with locally advanced or metastatic disease. For the first-line treatment of advanced disease, Phase III ABC-02 trial confirmed combination of gemcitabine and cisplatin (GC) as standard of care, whereas there is no currently defined standard-of-care regimen in the second-line setting.2 The goal of our paper was to evaluate survival rate and clinical outcome of patients with metastatic BTC in University Hospital Centre Zagreb (UHC Zagreb).

Materials and methods: Medical records of 188 patients diagnosed with BTC since the beginning of 2017 at UHC Zagreb were collected and retrospectively reviewed. Statistical data were analyzed using IBM SPSS 24.

Results: Out of 188 patients, 116 reached the metastatic stage of disease, of which 56 were men and 60 were women. Median age of diagnosis was 67 years. Patients were stratified according to localization of disease (intrahepatic, extrahepatic or gallbladder cancer). Median overall survival (OS) across all groups with metastatic disease was 8.4 months. Median OS for intrahepatic, extrahepatic, and gallbladder cancer were 14.8, 8.2, and 6.6 months, respectively. Seventy-eight patients were treated with chemotherapy, mostly based on cisplatin and gemcitabine in the first line. Median progression free survival (PFS) was 2.9 months across all groups with median PFS of 2.6 months for intrahepatic and gallbladder cancer, and 3.7 months for extrahepatic cancer.

Conclusion: Although limited by retrospective nature, our study represents real world data of BTC treatment outcomes at a single academic institution. Cholangiocarcinoma remains one of the most poorly understood GI tract cancers with poor prognosis and limited treatment options in metastatic setting. Further research is warranted for better understanding and more efficient treatment of these aggressive cancers.

LITERATURA / LITERATURE:

1. *Valle J, Kelley R, Nervi B, Oh D, Zhu A*. Biliary tract cancer. The Lancet. 2021;397(10272):428–44.
2. *Valle J, Wasan H, Palmer D, Cunningham D, Anthoney A, Maraveyas A et al.* Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. New England Journal of Medicine. 2010;362(14):1273–81.

KIRURŠKO LIJEČENJE JETRENIH METASTAZA KOLOREKTALNOG KARCINOMA U KBC-U ZAGREB

MAVREK J.[1], Grbavac D.[1], Tomić M.[1], Kolak J.[1], Romić I.[1], Silovski H.[1,2]

[1] Klinički bolnički centar Zagreb
• *Klinika za kirurgiju*
[2] Sveučilište u Zagreb
• *Medicinski fakultet*
josip.mavrek@gmail.com

Uvod: Cilj ove retrospektivne opservacijske studije provedene na Klinici za kirurgiju KBC-a Zagreb bio je istražiti ishode kirurškog liječenja pacijenata s jetrenim metastazama kolorektalnog karcinoma (CRC-a).

Materijali i metode: Podaci su preuzeti iz medicinske dokumentacije pacijenata koji su u razdoblju od 01.01. do 31.08.2022. operirani na Zavodu za hepatobilijarnu kirurgiju pod dijagnozom CRC-a. Od 66 pacijenata njih 25 je imalo metastaze u jetri. Oni su dalje kategorizirani u odnosu na vrijeme otkrivanja metastaza (sinkrone i metakrone), njihov broj, postojanje ekstrahepatalnih metastaza, vrstu učinjene operacije i neoadjuvantno kemoterapijsko liječenje.

Rezultati: Sinkrone metastaze (N=19) bile su češće nego metakrone (N=6). Kirurška resekcija jetrenih metastaza učinjena je kod 60% (N=15) promatranih pacijenata dok je kod 40% (N=10) uklonjen samo primarni tumor. Isključujući faktori za jetrenu resekciju su bili multiple (≥5) metastaze u jetri (50%, N=5) i ekstrahepatalne metastaze (10%, N=1). 40% (N=4) operiranih pacijenata imalo je oba faktora. Metastazektomija je učinjena kod 52,6% (N=10) pacijenata sa sinkronim i 83,3% (N=5) pacijenata sa metakronim metastazama. 15,8% (N=3) pacijenata sa sinkronim metastazama je primilo neoadjuvantnu kemoterapiju, dok je isto primilo 33,3% (N=2) pacijenata s metakronim metastazama. Kod svih (N=5) pacijenata koji su primili neoadjuvantnu kemoterapiju učinjena je metastazektomija. Resekcija je u 53,3% (N=8) slučajeva bila neanatomska (parenchymal sparing resection, PSR) a u 40% (N=6) anatomska (segmentektomija ili hepatektomija). Kod jednog pacijenta (6,7%) učinjene su istovremeno anatomska i neanatomska resekcija.

Zaključak: Rezultati naše studije usporedivi su sa suvremenim smjernicama za kirurško liječenje jetrenih metastaza CRC-a i pokazuju pozitivan učinak neoadjuvantne kemoterapije u liječenju pacijenata s uznapredovalom bolesti.

SURGICAL TREATMENT OF COLORECTAL CANCER LIVER METASTASES AT UHC ZAGREB

MAVREK J.[1], Grbavac D.[1], Tomić M.[1], Kolak J.[1], Romić I.[1], Silovski H.[1,2]

[1] University Hospital Center Zagreb
• *Department of Surgery,*
[2] University of Zagreb
• *School of medicine*

Introduction: Aim of this retrospective opservational study conducted in UHC Zagreb, Department of _ Surgery was to investigate the outcomes of surgical treatment of patients with colorectal cancer (CRC) liver metastases.

Materials and methods: Data was taken from medical records of patients that were operated in Department of hepatobiliary surgery from 01.01. to 31.08.2022. under the diagnosis of CRC. From 66 such patients 25 had liver metastases. They were further categorized depending on time when metastases were discovered (synchronous and metachronous), their number, existence of extrahepatal metastases, type of surgery performed and use of neoadjuvant chemotherapy.

Results: Synchronous metastases (N=19) were more common than metachronous (N=6). Surgical resection of liver metastases was performed on 60% (N=15) of patients and other 40% only had primary tumor removed. Excluding factors for liver resection were multiple (≥5) metastases (50%, N=5) and extrahepatic metastases (10%, N=1). 40% of operated patients had both factors. Metastasectomy was performed on 52,6% (N=10) of patients with synchronous and 83,3% (N=5) of patients with metachronous metastases. 15,8% (N=3) of patients with synchronous metastases underwent neoadjuvant chemotherapy while that number was 33,3% (N=2) for patients with metachronous metastases. Metastasectomy was performed on all (N=5) patients who underwent neoadjuvant chemotherapy. In 53,3% (N=8) of cases, resection was nonanatomic, parenchymal-sparing resection (PSR) while in 40% (N=6) it was anatomic (segmentectomy or hepatectomy). On one patient (6,7%) both anatomic and nonanatomic resection were performed simultaneously.

Conclusion: Results of our study are comparable to contemporary guidelines for surgical treatment of colorectal cancer liver metastases and show positive impact of neoadjuvant chemotherapy in treatment of patients with advanced disease.

KORELACIJA PERCIPIRANE SOCIJALNE PODRŠKE I EMOCIONALNOG DISTRESA KOD ONKOLOŠKIH BOLESNIKA.

SALAMUN A.[1], Kocić L.[1], Kopić B.[1], Trivanović D.[1], Dembić M.[1], Budisavljević A.[1]

[1] Opća bolnica Pula
• *Odjel za internističku onkologiju s hematologijom*
salamun.antonija@gmail.com

Uvod: Onkološki bolesnici, uslijed postavljanja dijagnoze maligne bolesti i kompleksnih načina liječenja, iskazuju povećane razine emocionalnih teškoća u odnosu na opću populaciju. Istraživanja pokazuju kako 30–50% onkoloških bolesnika pokazuje određenu razinu distresa. Potencijalni zaštitni mehanizam od distresa je adekvatna socijalna podrška. Cilj istraživanja je ispitati postoji li povezanost percipirane socijalne podrške i emocionalnog distresa kod onkoloških bolesnika.

Materijali i metode: Provedena je presječna studija od veljače do kolovoza 2022.g. na ukupno 94 onkoloških bolesnika u onkološkoj Dnevnoj bolnici OB Pula. Osim demografskih podataka, sudionici su ispunili Multidimenzionalnu skalu percipirane socijalne podrške (MSPSS) i emocionalni termometar (ET) koji se sastoji od 5 vizualno-analognih skala 0–10 (Uznemirenost, Tjeskoba, Depresivnost, Ljutnja i Potreba za pomoći). Za ET cut-off uzeta je vrijednost >3.

Rezultati: U uzorku (N=94) je 74% žena, prosječne dobi od 60±10,88 godina, 50% je SSS. Umirovljeno je 47%, zaposleno 39%, a nezaposleno 14%. Sudionici su podijeljeni u 3 dobne skupine (<35; 36–59; >60 godina). Dobiveno je da 80–90% bolesnika ima percepciju visoke socijalne podrške (ukupan rezultat i pojedini elementi skale). Analizom ET nađena je uznemirenost kod 39% sudionika, tjeskoba kod 33%, depresivnost kod 25%, ljutnja kod 27%, a potrebu za pomoći ima 16% sudionika. Samo 19% dobiva pomoć, a tek 9% njih smatra da treba dodatnu pomoć za

ove probleme. Uspoređujući s dosadašnjim istraživanjima, u ovom je uzorku manje onih sa značajno izraženim emocionalnim distresom. Dobivena je značajna korelacija između dobi i dobivanja pomoći (r=–0,32) i dobi i socijalne podrške od strane prijatelja (r=–0,23), pri čemu je veća socijalna podrška i dobivanje pomoći kod mlađih.

Zaključak: U ovoj pilot studiji dobivene su niže razine distresa nego u drugim studijama, s manje od 20% sudionika kojima je potrebna pomoć. Mlađi su bolesnici oni koji imaju veću percepciju pomoći i podrške od prijatelja, dok druge varijable nisu povezane (demografski podaci i ET). Ipak, preko 80% sudionika navelo je visoku razinu socijalne podrške. Rezultati potvrđuju važnost socijalne podrške kao zaštitnog faktora za onkološke bolesnike, no potrebno je uključiti veći broj sudionika za opravdanu generalizaciju.

THE CORRELATION BETWEEN PERCEIVED SOCIAL SUPPORT AND EMOTIONAL DISTRESS AMONG CANCER PATIENTS.

SALAMUN A.[1], Kocić L.[1], Kopić B.[1], Trivanović D.[1], Dembić M.[1], Budisavljević A.[1]

[1] General Hospital Pula
• *Department of Medical Oncology and Hematology*

Introduction: Due to the diagnosis of cancer, as well as complex treatments, cancer patients show greater levels of emotional difficulties compared to general population. Studies indicate that 30–50% of cancer patients show certain levels of distress. Adequate social support can be a potential protective mechanism. The purpose of this research is to investigate if there is a correlation between perceived social support and emotional distress among cancer patients.

Materials and methods: A cross-sectional study was performed from February to August of 2022, on 94 cancer patients in Day hospital of oncology department of General hospital Pula. The participants answered questions regarding demographics, Multidimensional Scale of Perceived Social Support (MSPSS), and Emotion Thermometer (ET), consisting of 5 visual analogue scales 0–10 (Distress, Anxiety, Depression, Anger, Need help). The ET cut-off for ET was >3.

Results: In the sample of 94, 74% were women, average age of 60±10.88, 50% had high school diploma. 47% of participants were retired, 39% employed, and 14% unemployed. The participants were divided in 3 age groups (<35, 36–59, >60). The results show that 80–90% of the participants have high perceived social support (total result and individual elements of the MSPSS). ET analysis showed distress in 39%, anxiety in 33%, depression in 25%, anger in 27% of the participants, and 16% of them confirm they need help. 19% gets help, and only 9% of the participants think they need additional help. Comparing to studies performed, these results show lower emotional distress levels. There is a significant correlation between age and getting help (r=–0.32), and age and social support gotten from friends (r=–0.23); younger ones get more help and social support.

Conclusion: This pilot study has shown lower distress levels than in other studies performed, with less than 20% of the participants that need help. Younger patients are those who get more help, and higher social support from friends, while other variables (demographic characteristics and ET) are not connected. Over 80% of the participants experience high social support. These results confirm the importance of social support as a protective mechanism for cancer patients, but greater number of participants need to be included to get more consistent information.

LIJEČENJE BOLESNICE SA SINKRONIM ADENOKARCINOMIMA REKTUMA I PLUĆA – PRIKAZ SLUČAJA

GORŠIĆ I.[1], Prejac J.[1], Librenjak N.[1], Kekez D.[1], Pleština S.[1]

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

Uvod: Karcinom debelog crijeva i pluća pripadaju među najčešće novodijagnosticirane karcinome. Jednako tako, to su karcinomi s najvećim mortalitetom. Istodobna pojava oba karcinoma je velika rijetkost. Izuzev okolišnih i genetskih faktora koji mogu povećati pojavnost svakog od njih zasebno do sada nije poznata etiologija koja bi mogla dovesti do istodobne pojave oba karcinoma.

Prikaz slučaja: 56 godina staroj bolesnici je u ožujku 2017. g. endoskopski potvrđen adenokarcinom rektuma (6–11 cm od anokutane granice). Prema inicijalnoj slikovnoj obradi postavljena je sumnja i na karcinom pluća lijevostano, neodvojiv od lijevog hilusa veličine 5x2,3cm. Obiteljska anamneza je negativna na maligne bolesti. G. 1989. učinjena je konizacija zbog karcinoma grlića maternice. Od komorbiditeta prisutna hipertenzija i hiperlipidemija. ECOG PS 0, normalne konstitucije, pušač. Karcinom rektuma operiran je u svibnju 2017.g., patohistološki- pT3N2b, G2, LVI+, PNI-, TD-. Postoperativno u dva navrata učinjena bronhoskopija urednog morfološkog nalaza, citološki bez malignih stanica. Obiteljska anamneza je negativna na maligne bolesti. G. 1989. učinjena je konizacija zbog karcinoma grlića maternice. Od komorbiditeta prisutna hipertenzija i hiperlipidemija. ECOG PS 0, normalne konstitucije, pušač. Karcinom rektuma operiran je u svibnju 2017.g., patohistološki pT3N2b, G2, LVI+, PNI-, TD-. Postoperativno u dva navrata učinjena bronhoskopija urednog morfološkog nalaza, citološki bez malignih stanica.

Rezultati: U srpnju 2017. g. započelo se s adjuvantnim liječenjem za karcinom rektuma (radiokemoterapija uz CapOx protokol). Kontrolni MSCT pokazuje tvorbu pluća u blagoj regresiji veličinom uz stacionarnu veličinu satelitskog nodusa i regresiju limfnog čvora (l.č.) uz lijevi glavni bronh s 1,3 cm na 1 cm. Prema nalazu PET-CT-a lezija je umjereno metabolički aktivna (SUVmax 4) bez drugih patoloških supstrata. U svibnju 2018. učinjena je lijevostrana torakotomija i gornja lobektomija. PHD govori za adenokarcinom pluća (G2), promjera 5 cm, R0 resekcije, pT2aN0Mx (0/34 l.č.) uz infiltraciju lamine elastike interne visceralne pleure (PL1), bez angioinvazije i zahvaćanja l. č. (3 pregledana), medijastinalni l. č. bez tumora. PDL1 status < 1% pozitivnih tumorskih stanica. Provedena su 4 ciklusa adjuvantnog liječenja pemetreksedom i cisplatinom do kolovoza 2018. Od tada je bolesnica u pažljivome praćenju, bez znakova povrata ijednog malignoma.

Zaključak: Unatoč rijetkoj pojavnosti, potrebna su daljnja istraživanja kako bi se utvrdilo eventulano postojanje rizičnih čimbenika koji bi mogli dovesti do pojave sinkronih karcinoma. U koliko se radi o metastatskim karcinomima izazov postaje još veći zbog potrebe optimizacije terapije.

TREATMENT OF A PATIENT WITH SYNCHRONOUS ADENOCARCINOMAS OF THE RECTUM AND LUNGS – CASE REPORT

GORŠIĆ I.[1], Prejac J.[1], Librenjak N.[1], Kekez D.[1], Pleština S.[1]

[1] University Hospital Centre Zagreb
• *Department of Oncology*

Introduction: Colon and lung cancer are the most common newly diagnosed cancers. Furthermore, these are the cancers with the highest mortality rate. Synchronous occurrence of both cancers is extremely rare. Except for environmental and genetic factors that can increase the development of each of them separately, etiology that could lead to the synchronous occurrence of both cancers remains unknown.

Materials and methods: In March 2017. 56-year-old woman was endoscopically confirmed to have adenocarcinoma of the rectum (6–11 cm above the anal verge). According to the initial staging, a left-sided lung cancer, inseparable from the left hilus, measuring 5x2.3cm, was also suspected. The family history of the patient is negative for malignant diseases. The patient's comorbidities include hypertension and hyperlipidemia. In 1989. conization was performed due to cervical carcinoma. The patient is ECOG PS 0, of normal constitution, smoker. Resection of rectal cancer was performed in May 2017. It was classified as pT3N2b, G2, LVI+, PNI-, TD-. Postoperatively, bronchoscopy was performed on two occasions with normal morphological findings, cytologically without malignant cells.

Results: In July 2017. began adjuvant treatment for rectal cancer (radiochemotherapy and CapOx protocol). Afterwards, MSCT showed lung neoplasm in slight regression in size with stationary size of the satellite node and regression of the lymph node (l.n.) next to the left main bronchus from 1.3 cm to 1 cm. According to the PET-CT scan the lesion is moderately metabolically active (SUVmax 4) without other pathological substrates in the body. In May 2018., a left thoracotomy and upper lobectomy was performed. Patohistological finding was lung adenocarcinoma (G2), 5 cm in diameter, R0 resection, pT2aN0Mx, +0/34 l.n. with infiltration of the lamina elastica of the internal visceral pleura (PL1), without angioinvasion and involvement of l.n. (3 examined), mediastinal l.n. without tumor. PDL1 status < 1% of positive tumor cells. The patient recieved 4 cycles of adjuvant treatment (pemetrexed and cisplatin) until August 2018. Since then, the patient has been under surveillance, with no signs of recurrence of any of the malignancy.

Conclusion: Despite its rare occurrence, further research is needed to determine the potential existence of risk factors that could lead to the development of theese synchronous cancers. In the metastatic setting, the challenge becomes even greater due to the need to optimize therapy for theese patients.

METASTAZA HEPATOCELULARNOG KARCINOMA U REKTUM – PRIKAZ SLUČAJA

JERKOVIĆ I.[1], Prejac J.[2], Golčić M.[1], Marušić J.[1], Dobrila-Dintinjana R.[1,3], Mikolašević I.[1,3], Polić N.[1]

[1] Klinički bolnički centar Rijeka
• *Klinika za radioterapiju i onkologiju*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[3] Sveučilište u Rijeci
• *Medicinski fakultet*
ivona.jerkovic051@gmail.com

Uvod: Hepatocelularni karcinom (HCC) je primarni tumor jetre s visokim mortalitetom. Ekstrahepatalne metastaze HCC-a su rjeđe nego intrahepatalne. Najčešća ekstrahepatalna sijela metastaza su pluća, abdominalni limfni čvorovi, kosti i nadbubrežne žlijezde. Metastaziranje HCC-a u gastrointestinalnom traktu vrlo je rijetko, najčešće u želucu i dvanaestniku dok se pojava metastaza u debelom crijevu svodi na opis pojedinačnih slučajeva.

Prikaz slučaja: Naša 44-godišnja bolesnica započinje obradu u siječnju 2022. godine zbog mikrocitne anemije, proljeva i subfebriliteta. U sklopu obrade učinjena je kolonoskopija kojom se na 5 cm od anokutane granice vizualizira tumorski proces u duljini od 10 cm dok se na CT-u toraksa i abdomena prikazuju politopne lezije jetre i regionalna lifadenopatija, no bez znakova ciroze jetre. Patohistološki nalaz morfološki i imunohistokemijski odgovara metastazi HCC-a. Isti morfološki izgled i imunohistokemijski profil potvrdi se na uzorku promjene u jetri. Osim dugogodišnjeg kompliciranog dijabetesa tipa 1 bolesnica boluje i od nealkoholne masne bolesti jetre (NAFLD) bez histoloških znakova ciroze. Hepatitis markeri su negativni. Nakon potvrde dijagnoze bolesnica je započela liječenje atezolizumabom i bevacizumabom te se na prvoj kontrolnoj obradi u srpnju 2022. prati stabilna bolest te je bolesnica još uvijek u tijeku prvolinijskog liječenja.

Zaključak: Iako su rektalne metastaze HCC-a izrazito rijetke, diferencijalno dijagnostički je važno razmatrati i takvu mogućnost, kako bi se pravovremeno započelo liječenje kombinacijom imunoterapije i bioterapije. Unatoč atipičnoj i agresivnoj biologiji tumora te velikom volumenu bolesti, već se na prvoj obradi prati stabilna bolest. NAFLD postaje vodeći uzrok HCC-a u necirotičnoj jetri.

RECTAL METASTASIS FROM HEPATOCELLULAR CARCINOMA: A CASE REPORT

JERKOVIĆ I.[1], Prejac J.[2], Golčić M.[1], Marušić J.[1], Dobrila-Dintinjana R.[1,3], Mikolašević I.[1,3], Polić N.[1]

[1] University Hospital Centre Rijeka
• *Department of Radiotherapy and Oncology*
[2] University Hospital Centre Zagreb
• *Department of Oncology*
[3] University of Rijeka
• *School of medicine*

Introduction: Hepatocellular carcinoma (HCC) is a primary liver tumor with high mortality. Extrahepatic metastases of HCC are rarer than intrahepatic. The most common extrahepatic sites of metastases are the lungs, abdominal lymph nodes, bones, and adrenal glands. Metastasis of HCC in the gastrointestinal tract is very rare, most often in the stomach and duodenum, while the occurrence of metastases in the colon is limited to rare individual cases.

Case report: Our 44-year-old patient started work-up in January 2022 due to microcytic anemia, diarrhea, and subfebrile temperature. As part of the work-up, a colonoscopy was performed and a 10 cm long tumor process 5 cm from the anocutaneous line was visualized. The CT scan of the thorax and abdomen showed polytopic liver lesions and regional lymphadenopathy, but without signs of liver cirrhosis. The pathohistological findings morphologically and immunohistochemically correspond to HCC metastasis. The same morphological and

immunohistochemical profile was confirmed on the sample of liver lesions. In addition to long-standing complicated type 1 diabetes, the patient also suffers from non-alcoholic fatty liver disease (NAFLD) without histological signs of cirrhosis. Hepatitis markers are negative. After confirming the diagnosis, the patient started treatment with atezolizumab and bevacizumab. At the first follow-up in July 2022, stable disease was observed, and the patient is still undergoing first-line treatment.

Conclusion: Although rectal metastases of HCC are extremely rare, it is important to consider such a possibility in the differential diagnosis in order to start timely treatment with a combination of immunotherapy and biotherapy. Despite the atypical and aggressive biology of the tumor and the large volume of the disease, stable disease is observed after the first follow-up. NAFLD is becoming the leading cause of HCC in the non-cirrhotic liver.

MULTIDISCIPLINARNI PRISTUP LIJEČENJU BOLESNICE S HR POZITIVNIM HER2 NEGATIVNIM KARCINOMOM DOJKE

ZUBČIĆ KRIŠTO S.[1], Bilić Knežević S.[1], Radovčić Gauta I.[1], Tokić M.[1], Telesmanić Dobrić V.[1]

[1] Opća bolnica Zadar
• *Odjel za onkologiju i nuklearnu medicinu*
zubcic.slavica@gmail.com

Uvod: Liječenje metastatskog karcinoma dojke danas temelji se na sistemskoj terapiji, izbor terapije definira biološki podtip tumora. Lokalno ablativne terapije kao kirurško i radioterapijsko liječenje obično se primjenjuju kao palijativno liječenje. Bolesnice s HR pozitivnom HER2 negativnom bolesti liječe se endokrinom terapijom u kombinaciji s CDK 4/6 inhibitorima. Podatci iz kliničkih studija kao i iz stvarne kliničke prakse govore o značajnom broju bolesnica s djelomičnim odgovorom na navedenu terapiju, kod nekih bolesnica nakon terapije ostaje mali broj rezistentnih lezija. EORTC predlaže klasifikaciju oligometastatske bolesti koja uključuje ovu skupinu bolesnica(bolesnice koje su dobro reagirale na terapiju-inducirana oligometastatska bolest).Iako ne postoje smjernice za liječenje ove skupine bolesnica studije sugeriraju da bolesnice s bolesti malog volumena mogu očekivati dulju remisiju bolesti ; produljenje PFS-a ako se uz učinkovitu sistemsku terapiju primjenjuje lokalna ablativna terapiju.

Prikaz slučaja: Ovdje prikazujemo slučaj bolesnice liječene prije navedenim pristupom. U 6/2020 50-godišnja postmenopauzalna žena, do sada zdrava upućena je u našu bolnicu zbog ultrazvukom detektirane tvorbe lijeve dojke, GMK 1 x 2,5 cm. Bolesnica je upućena na MR dojke, MSCT toraksa, abdomomena i zdjelice, „core" biopsiju dojke, PET-CT. Dijagnosticiran je karcinom lijeve dojke dojke (ER/PR pozitivan, HER-2 negativan, Ki 67 60%) s metastazama u limfne čvorove lijevo aksilarno,retropektoralno i supraklavikularno. Solitarni sekundarizam jetre. Ordinirana je terapija ribociklibom uz AI. Bolesnica dobro podnosi lijek, redovito učinjeni lab nalazi kao i EKG ne pokazuju odstupanja od referentnih vrijednosti.Nakon prva 3 mjeseca liječenja MSCT toraksa, abdomena i zdjelice limfni čvorovi u lijevoj aksili te retropektoralno, supraklavikularno pokazuju regresiju u veličini, tvorba lijeve dojke u medijalnom dijelu također pokazuje regresiju u veličini, lezija u jetri stacionarna. Bolesnica nastavlja liječenje ribociklibom uz radiološku kontrolu gdje se na svakoj od učinjenih pretraga prati daljnja regresija veličine patološki promijenjenih limfnih čvorova i tvorbe lijeve dojke. Lezija jetre stacionarna. U 6/2022. učinjen PET/CT koji pokazuje potpunu metaboličku i i morfološku regresija limfnih čvorova lijevo aksilarno, supraklavikularno i retropektoralno kao i potpunu metaboličku regresiju nalaza u ostatnoj i značajno i manjoj leziji GMK lijeve dojke (4x 3 mm). Metabolički aktivna fokalna lezija parenhima jetre (IVseg. uz žučnjak 15 mm) bez bitnije dinamike u kontrolnom intervalu – suspektan metabolički aktivan sekundarizam.

Bolesnica je upućena na SBRT, u 9/2022 provedeno je radiokirurško liječenje metabolički aktivne presadnice u jetri. Planira se nastavak sistemske terapije ribociklibom, kontrolna radiološka obrada za 3 mjeseca.

Zaključak: Karcinom dojke je heterogena bolest koja se liječi terapijom određenom karakteristikama samog tumora i multidisciplinarnom pristupom. Sistemska terapija temeljna je okosnica liječenja još uvijek. Integracija SBRT a sa sistemskom terapijom pokazuje obećavajuće rezultate u liječenju oligometastatskog karcinoma dojke. Ciljana eradikacija rezistentnih klonova koji se prezentiraju kao oligometastaze može produžiti ukupno preživljenje u bolesnica s karcinomom dojke. Raste broj kliničkih studija koje podupiru ulogu SBRT-a u ovoj indikaciji. Nove studije pokazuju da je ovaj način liječenje siguran u učinkovit. Nažalost još uvijek ne znamo koja vrste bolesti/bolesnika će imati naviše koristi od ovog načina liječenja. Korištenje bioloških i genskih markera moglo

bi nam pomoći u toj odluci, to bi predstavljalo korak prema individualiziranom pristupu bolesnicama s oligometastatskom bolesti. Idealno vrijeme SBRT-a u odnosu na sistemskom terapijom također nije poznato, kao ni postoji li mogućnost deeskalacije sistemske terapije poslije SBRT-a.

Za odgovore na ova pitanja, dodatno razjašnjenje prave uloge SBRT-a kao i za jasne smjernice za korištenje ovog modaliteta liječenja potrebno je pričekati rezultate brojnih kliničkih studija koje su u tijeku.

MULTIDISCIPLINARY APPROACH TO PATIENT WITH HR POSITIVE HER2 NEGATIVE METASTATIC BREAST CANCER

ZUBČIĆ KRIŠTO S.[1], Bilić Knežević S.[1], Radovčić Gauta I.[1], Tokić M.[1], Telesmanić Dobrić V.[1]

[1] General Hospital Zadar
• *Department of Oncology and Nuclear Medicine*

Introduction: Current standard treatment of metastatic breast cancer is predominanatly reliant upon systemic therapies, with choice of therapy directed by specific biological subtype. LATs (Local ablative therapy) as surgery and radiotherapy are usually reserved for use in paliative setting to alleviate symptoms. Patients with HR postitive and HER2 negative disease are typically treated with endocrine therapy in combination with CDK 4/6 inhibitor. Clinical trials an real-world data report significant number of patients with partial response, some of them with very low number and volume of resistant lesions after therapy. EORTC proposed classification system of different oligometstatatic states includes these patients who have responded well to systemic therapy (induces oligometastatic state). Althow threre are no clear guidance how to approach these patiets studies have suggested that patients with low volume could expect long term disease remission af experience improvement in PFS if thall the tumor cells can be removed of treated effictively. Here we present patinet treated according to these concept.

Case report: 50-year-old postmenopausal woman ECOG 0 with no medical history was referred in June 2020 to our hospital because od ultrasonography showed tumorous mass in left breast UIQ 1x 2,5 cm After obtaining history, clinical examination, magnetic resonance imaging and CT scan, CNB, PET-CT she was found to have metastatic breast cancer (ER/PR positive, HER-2 negative, Ki-67 60%) :primary malignant proces of left breast, metastases in left axillary, retropectoral an supraclavicular lymph nodes. solitary liver metastases. Systemic therapy with AI and ribociclib was ordinated.After first 3 months of systemic therapy reassesssement was done; MSCT showed reduction in size of metastatic lymph nodes (left axillar, supraclavicular,retropectoral). Breast lesion also showed reduction in size, liver lesion stationary.Patients continues with same treatment, radiologic assesessmet showed further regression in size of left breast lesion and malignant lymph nodes.

In June of 2022 PET/CT showed complete morphologic and metabolic regression in lymph nodes, complete metabolic regression in lesion in left breast. Metabolically active lesion in 4. hepatic segment. Patient was reffered to Centre for radiosurgery, in September of 2022 SBRT on metabolically active liver lesion was performed. Systemic therapy with AI and ribociclib was continued.

Conclusion: Breast cancer is recognized as heterogeneus disease which is best treated with a tailored and multidisciplinary approach.Systemic therapies remain the mainstay of treatment, wider acceptance of the biological diversity between breast cancer types is making way for a broader range of managment strategies.Integrated SBRT with systemic therapies has shown a lot of promise in treatment of OMBC.Targeted eradication of groups of resistent subclones, presenting as oligimetasases can lead to increased OS in breast cancer. There is a growing body of evidence to suport SBRT in this setting. Recent studies demonstrate it as safe and effective with possibility of offering cure when treating OMBC. Despite a small number of promising studies,we don t know yet which type of patient would benift the most of thos combined approach. Utilisation of biological and genomic classifiers as a strategy to predict which patients will benifit most from SBRT could be another another step towards individalised managment of OMBC. Ideal timing of SBRT in relation to systemic therapies is also unknown, as well as possibility of deescalation of systemic treatment after SBRT.

We are waiting the result of active studies to further claryfay the precise role of SBRT in advanced OMBC and clear guideliness to be established.

LITERATURA/ LITERATURE:

1. *Milano MT, et al.* Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. Int J Radiat Oncol Biol Phys. 2012;83(3):878–886

2. *Alomran R, et al.* Stereotactic radiotherapy for oligoprogressive ER-positive breast cancer (AVATAR) BMC Cancer. 2021;21(1):303.
3. *Tjong MC, et al.* Local ablative therapies in oligometastatic NSCLC-upfront or outback?—a narrative review. Transl Lung Cancer Res. 2021 0(0): pp. 0–0.
4. *Stewart R, White M, Tan J, Siva S, Karroum L, David S.* SABR in oligometastatic breast cancer: Current status and future directions. Breast. 2021 Dec;60:223–229. doi: 10.1016/j.breast.2021.10.009

NUSPOJAVE SUSTAVNE KEMOBIOLOŠKE TERAPIJE U LIJEČENJU PROŠIRENOG HER2-POZITIVNOG RAKA DOJKE: REZULTATI IZ STVARNE KLINIČKE PRAKSE

LINARIĆ P.[1], Mirčevski K.[1], Vazdar LJ.[1], Jakšić P.[1], Popović J.[1], Trajbar M.[1], Pavlović Mavić M.[1], Tečić Vuger A.[1], Šeparović R.[1,2]

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

Uvod: Osnova liječenja HER2-pozitivnog proširenog raka dojke je kombinacija HER2 blokade i kemoterapije. U metastatskom okruženju, osim učinkovitosti, od primarne su važnosti nuspojave liječenja i kvaliteta života (eng. QoL) bolesnika. U prvolinijskom liječenju, temeljem rezultata CLEOPATRA ispitivanja (docetaksel + trastuzumab + pertuzumab), najčešće nuspojave taksanske monokemoterapije u kombinaciji s pertuzumabom i trastuzumabom bile su proljev, alopecija i neutropenija (najučestalija nuspojava najvišeg gradusa). U drugolinijskom liječenju, temeljem EMILIA ispitivanja, nuspojave trastuzumab emtanzina (T-DM1) su najčešće bile asimptomatske promjene laboratorijskih parametara – trombocitopenija i povišene vrijednosti aminotransferaza. U sljedećoj liniji liječenja, kombinaciji kapecitabina i lapatiniba, najzastupljenije su nuspojave proljev i palmoplantarna eritrodizestezija. Rezultati svakodnevne kliničke prakse često se razlikuju od studijskih. Cilj naše studije bio je pokazati profil toksičnosti kombinacijske terapije u bolesnica sa proširenim HER2 pozitivnim rakom dojke koje su započele prvolinijsko liječenje u našoj ustanovi u periodu od siječnja 2015. do siječnja 2020.

Materijali i metode: Ispitivanje je obuhvatilo ukupno 100 bolesnica. Toksičnosti su utvrđivane na temelju medicinske dokumentacije i podijeljene su u skupine: hematološka, gastrointestinalna, mukozitisi, alopecija, neuropatija, kardiotoksičnost i ostalo. Kod svake bolesnice i svake linije terapijskog liječenja utvrdila se najznačajnija toksičnost te stupanj iste prema CTCAE kriterijima.

Rezultati: Ukupno 99 bolesnica (99%) liječenje je započelo dvostrukom HER2 blokadom uz dodatak taksana. Najčešće nuspojave bile su gastrointestinalne (70%), potom neuropatija (28%), mukozitis (21%), hematološke nuspojave (15%), a kardiotoksičnost (6%) i alopecija (2%) su bile značajno rjeđe. Sve nuspojave stupnja IV bile su hematološke, a najučestalije nuspojave stupnja III gastrointestinalne. Drugolinijsko liječenje su započele 53 bolesnice (53%), a njih 86% je dobivalo trastuzumab emtanzin (TDM-1). Najčešće nuspojave su bile gastrointestinalne (20%), zatim hematološke (17%) i kardiološke (1,8%), a preostale nuspojave (mukozitis, alopecija i neuropatija) nisu bile zabilježene. Nuspojava stupnja IV nije bilo, a najčešće nuspojave stupnja III bile su hematološke i kardiološke. Trećelinijsko liječenje je započeto u 20 žena (20%), a njih 65% je pritom liječeno kapecitabinom uz lapatinib. U 30% bolesnica javile su se gastrointestinalne nuspojave, hematološke nuspojave i mukozitis svaka u 10%, alopecija u jedne bolesnice, a neuropatija nije bila među prijavljenim nuspojavama. Zbog kardioloških nuspojava stupnja III kod jedne je bolesnice obustavljeno liječenje.

Zaključak: Sve se veća pažnja usmjerava na ispitivanje terapijske toksičnosti putem upitnika za samoprocjenu (eng. PROs – patient-reported outcomes) zbog njihove potencijalne prognostičke primjene, posebice u smislu ranijeg prepoznavanja težih oblika toksičnosti i potencijalne povezanosti s ukupnim preživljenjem. Rezultati dobiveni ovom analizom većinski odgovaraju rezultatima velikih randomiziranih ispitivanja, a zanimljivo je istaknuti kako su kod naših bolesnica hematološke nuspojave prvolinijskog liječenja bile rjeđe (15%) nego što je prijavljeno u CLEOPATRA ispitivanju (49% neutropenija). Naglašavamo kako su u našoj analizi nuspojave grupirane prema zahvaćenosti organskog sustava i obuhvaćaju širi spektar tegoba, dok su u randomiziranim ispitivanjima tegobe analizirane pojedinačno, što može objasniti blaža odstupanja u rezultatima. Zaključno, u cilju poboljšanja kvalitete života bolesnika u tijeku liječenja proširene maligne bolesti, potrebna su daljnja strukturirana istraživanja terapijske toksičnosti i nuspojava, posebno putem upitnika za samoprocjenu.

ANTICANCER TREATMENT SIDE EFFECTS IN ADVANCED HER2-POSITIVE BREAST CANCER – REAL LIFE CLINICAL PRACTICE RESULTS

LINARIĆ P.[1], Mirčevski K.[1], Vazdar LJ.[1], Jakšić P.[1], Popović J.[1], Trajbar M.[1], Pavlović Mavić M.[1], Tečić Vuger A.[1], Šeparović R.[1,2]

[1] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors Zagreb, Department of Medical Oncology*
[2] University of J.J.Strossmayer Osijek
• *School of Medicine*

Introduction: The basis of treatment for HER2-positive advanced breast cancer is a combination of HER2 blockade and chemotherapy. In the metastatic setting, in addition to efficiency, therapy side effects and patient's quality of life (QoL) are of primary importance. In the first-line treatment, based on the results of the CLEOPATRA trial (docetaxel + trastuzumab + pertuzumab), the most common side effects of taxane monochemotherapy combined with pertuzumab and trastuzumab were diarrhoea, alopecia, and neutropenia (which was the most common high grade side effect). In the second-line treatment, based on the EMILIA trial, the most common side effects of trastuzumab emtansine (T-DM1) were asymptomatic changes in laboratory parameters – thrombocytopenia and elevated aminotransferase values. In the next line of treatment, the combination of capecitabine and lapatinib, the most frequent side effects were diarrhoea and palmoplantar erythrodysesthesia. Results obtained in everyday clinical practice often differ from study results. The aim of our study was to show the toxicity profile of therapy used in patients with advanced HER2-positive breast cancer, who started first-line treatment in our institution between January 2015 and January 2020.

Materials and methods: A total of 100 patients were included. Toxicities were determined based on medical documentation and were divided into groups: hematological, gastrointestinal, mucositis, alopecia, neuropathy, cardiotoxicity and others. The most significant toxicity was determined and graded according to CTCAE criteria in each patient with each line of therapy.

Results: A total of 99 patients (99%) started treatment with double HER2 blockade with the addition of a taxane. The most common side effects were gastrointestinal (70%), followed by neuropathy (28%), mucositis (21%) and hematological side effects (15%). Other side effects such as cardiotoxicity (6%) and alopecia (2%) were less common. All grade IV side effects were hematological, and the most frequent grade III side effects were gastrointestinal. Total of 53 patients (53%) started second-line treatment, and 86% of them received trastuzumab emtansine (TDM-1). The most common side effects were gastrointestinal (20%), followed by hematological (17%) and cardiac (1.8%). Other side effects (mucositis, alopecia and neuropathy) were not reported. There were no grade IV side effects, and the most common grade III side effects were hematological and cardiological. Third-line treatment was used in 20 women (20%) and 65% of them were treated with capecitabine and lapatinib combination. Gastrointestinal side effects occured in 30% of patients, hematological side effects and mucositis each in 10%, alopecia in one patient and neuropathy was not reported. Treatment was discontinued in one patient due to grade III cardiac side effects.

Conclusion: Assessment of treatment toxicities through self-assessment questionnaires (PROs – patient-reported outcomes) is attracting increased attention because of their possible prognostic value, especially in terms of earlier recognition of more severe forms of toxicity and potential impact on overall survival. The results obtained from this analysis mostly correspond to the results of large randomized trials. It is interesting to note that in our patients hematological side effects of first-line treatment were less frequent (15%) than ones reported in the CLEOPATRA trial (neutropenia in 49%). We emphasize that in our analysis side effects were grouped according to the organ system involvement and cover a wider spectrum of complaints, while in randomized trials side effects were analyzed individually, which may explain milder deviations in the overall results. In conclusion, in order to improve patients quality of life during the treatment of metastatic disease, further structured studies of therapeutic toxicity and side effects are needed, especially through self-assessment questionnaires.

ODGOVOR RAKA DOJKE SA SLABO IZRAŽENIM HER2 NA NEOADJUVANTNU KEMOTERAPIJU

RAMIĆ S.[1], Puhalo A.[1], Cesarec Augustinović S.[1], Karačić E.[1], Marušić M.[2], Bubanović S.[1], Perić Balja M.[1]

[1] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Zavod za patologiju i citologiju Ljudevit Jurak*
[2] Klinički bolnički centar Sestre milosrdnice
• *Klinika za tumore, Odjel za dijagnostičku i intervencijsku radiologiju*
snjezana.ramic@gmail.com

Uvod: HER2 receptor je pozitivan (IHC 3+ ili 2+ s amplifikacijom gena) u 15–20% karcinoma dojke, što je važno za liječenje ciljanom anti-HER2 terapijom. Međutim, većina karcinoma dojke ima negativan status HER2 i ili uopće ne izražavaju receptor HER2 (IHC 0) ili pokazuju slabu/nisku izraženost receptora na membrani stanica karcinoma (IHC 1+ ili 2+ bez amplifikacije gena). Obzirom da karcinomi dojke s niskim HER2 ipak izražavaju nešto HER2 proteina, FDA je odobrila ciljanu anti-HER2 terapiju za adjuvantno liječenje karcinoma dojke sa slabo izraženim HER2. Ipak, neoadjuvantna anti-HER2 terapija (NAT) koja je u primjeni kod većine HER2-pozitivnih karcinoma dojke značajno poboljšava klinički tijek bolesti i smanjuje rizik od recidiva. U ovom radu predstavljamo podatke Klinike za tumore (KZT) KBC Sestre milosrdnice o odgovoru karcinoma dojke sa slabo izraženim HER2 na neoadjuvantnu terapiju (NAT).

Materijali i metode: Rad obuhvaća retrospektivno prikupljene podatke 161 bolesnice s karcinomom dojke sa slabo izraženim HER2 koje su primile NAT (123 slučaja s IHC 1+ i 38 slučajeva s IHC 2+ bez amplifikacije). Prosječna dob bolesnica u vrijeme uzimanja iglene biopsije bila je 54,3±11,4 godina.

Rezultati: Potpuni patološki odgovor (pCR) karcinoma dojke sa slabo izraženim HER2 na NAT postignut je u 15,5% bolesnica, dok je loš odgovor na NAT s RCB grupom III zabilježen u 34,2% slučajeva. Ovi podaci odgovaraju podacima skupine Luminal B, koja uopće ne izražava HER2 (IHC 0). Također, 11,7% ovih bolesnica doživjelo je progresiju bolesti, što je nešto više od onih s HER2 0 (8,3%). Promatrajući prema izraženosti HER2, karcinomi dojke s HER2 izraženosti 1+ postigli su pCR u 10,3% slučajeva, dok su u slučaju izraženosti 2+ pCR postigli u 22,2% slučajeva ($\chi2=3,33$; $P=0,068$). Međutim, karcinomi s intenzitetom izraženosti HER2 2+ imali su RCB III nakon NAT-a u 50% slučajeva u usporedbi s 30,8% karcinoma dojke čija je izraženost HER2 bila 1+ ($\chi2=8,01$; $P=0,005$). Bolesnice s HER2 2+ karcinomima imale su progresiju bolesti u 13,9% slučajeva, što je nešto češće od onih s HER2 1+ (10,3%) ($\chi2=1,58$; $P=0,208$). TNBC koji izražavaju određenu razinu receptora HER2 postigli su pCR u 32% slučajeva, a RCB III je zabilježen u 22,2% slučajeva. Ovi podaci u potpunosti odgovaraju ukupnoj skupini TNBC.

Zaključak: Uočili smo da bolesnice čiji karcinomi dojke slabije izražavaju receptor HER2 (IHC 2+ bez dokazane amplifikacije) imaju slabiji odgovor na NAT i nešto češću progresiju bolesti. Možda bi uvođenje ciljane anti-HER2 terapije na karcinome sa slabo izraženim HER2 u neoadjuvantnom okruženju poboljšalo ishod liječenja ovih bolesnica.

RESPONSE OF HER2-LOW BREAST CANCER TO NEOADJUVANT CHEMOTHERAPY

RAMIĆ S.[1], Puhalo A.[1], Cesarec Augustinović S.[1], Karačić E.[1], Marušić M.[2], Bubanović S.[1], Perić Balja M.[1]

[1] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors, Ljudevit Jurak University Department of Pathology*
[2] University Hospital Centre Sestre milosrdnice
• *University Hospital for Tumors, Department of Diagnostics and Interventional Radiology*

Introduction: The HER2 receptor is positive (IHC score 3+ or 2+ with gene amplification) in 15–20% of breast cancers (BCs), which is important in treatment with targeted anti-HER2 therapy. However, most BCs have negative HER2 receptor status and either do not express the HER2 receptor at all (IHC 0) or show low-level expression of the receptor (IHC score 1+ or 2+ without gene amplification). Given that HER2-low BCs express some HER2 protein, the FDA has approved specific anti-HER2 therapy in the adjuvant setting to target HER2-low BCs. Nevertheless, neoadjuvant anti-HER2 therapy (NAT), which is used in most HER2-positive BCs, significantly improves the clinical course of the disease and reduces the risk of recurrence. In this paper, we present

data from the University Hospital for Tumors, University Hospital Center Sestre milosrdnice Zagreb, on the response of HER2-low BCs to neoadjuvant therapy (NAT).

Materials and methods: This work includes retrospectively collected data on 161 patients with HER2-low BC who received NAT (123 cases with 1+ expression, and 38 cases with 2+ without amplification). The average age of patients at the time of biopsy was 54.3±11.4 years.

Results: Overall, pathological complete response (pCR) to NAT was achieved in 15.5% of cases, while poor response to NAT with RCB group III was recorded in 34.2% of HER2-low BCs. These data correspond to those of the Luminal B group, which does not express HER2 at all (IHC 0). Also, 11.7% of these patients experienced disease progression, slightly more than those with HER2 0 (8.3%). Comparing HER2 status, breast cancers with HER2 1+ expression achieved pCR in 10.3% of cases, while those with HER2 2+ expression achieved pCR in 22.2% of cases ($\chi 2=3.33$; P=0.068). However, HER2 2+ cancers had RCB III after NAT in 50% of cases compared to 30.8% of breast cancers with HER2 1+ ($\chi 2=8.01$; P=0.005). Patients with HER2 2+ BCs had disease progression in 13.9%, which is slightly more often than those with HER2 1+ (10.3%) ($\chi 2=1.58$; P=0.208). TNBC expressing some level of HER2 receptor achieved pCR in 32% of cases, and RCB III was recorded in 22.2% of cases. These data fully correspond to the total group of TNBC.

Conclusion: We noticed that patients with HER2-low BCs with IHC 2+ have a weaker response to NAT and somewhat more frequent disease progression. Perhaps the introduction of anti-HER2-low therapy in the neoadjuvant setting would improve the treatment outcome of these patients.

POJAVNOST DRUGIH TUMORA KOD BOLESNIKA S NEUROENDOKRINIM TUMORIMA

RACETIN A.[1], Adžić G.[2], Belev B.[2]

[1] Sveučilište u Zagrebu
• *Medicinski fakultet*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
andrearacetin1996@gmail.com

Uvod: Povećana učestalost drugih primarnih tumora kod bolesnika s NET-om, fenomen je kojeg prati sve veći interes. Predloženo je više teorija, međutim nije definiran zajednički nazivnik njihovog nastanka, barem ne u smislu genetske osnove. Cilj ovog rada bio je utvrditi učestalost drugih tumora kod bolesnika s NET-om te napraviti usporedbu s objavljenim podacima u literaturi.

Materijali i metode: Retrospektivno smo analizirali podatke bolničkog informatičkog sustava za 201 bolesnika s dijagnozom NET-a. Prosječno vrijeme praćenja bolesnika iznosi 6.73 godine (s rasponom od 1 mjesec do 21 godinu). Također, zabilježeni su podaci o pojavnosti drugih tumora, koji su potom podijeljeni u skupine sinkronih i metakronih. Bolesnici s dijagnozom MEN-1 i VHL sindroma isključeni su, budući da se kod njih zbog genske osnove i specifičnih mutacija očekuje po definiciji povećana učestalost pojave drugih tumora.

Rezultati: Dijagnoza NET-a potvrđena je histološki kod 201 bolesnika, (111 muškaraca i 90 žena). Prosječna dob bolesnika iznosila je 57.3 godine (19 – 84). Najčešće sijelo bila je gušterača u 76 slučajeva (37.8%), a potom tanko crijevo s 40 slučajeva (19.9%). Kod 17.9% bolesnika pronađeni su drugi primarni tumori uz NET. Ukupno su pronađena 41 dodatna tumora kod 37 bolesnika s NET-om. Kod 4 bolesnika pronađene su 2 dodatne neoplazme uz NET. Od ukupno 41 neoplazme, njih 12 (29.3%) dijagnosticirano je istovremeno ili u razmaku < 6 mjeseci u odnosu na NET (sinkrono). Ostalih 29 neoplazmi (70.7%) dijagnosticirane su > 6 mjeseci prije ili poslije NET-a (metakrono). Najzastupljenije su bile neoplazme probavnog sustava (21 slučaj, 51.2%), s najvećom učestalošću tumora kolona i rektuma (12 slučajeva). Na drugom mjestu su tumori mokraćno – spolnog sustava (9 slučajeva, 21.9%). Ostali tumori su: karcinom dojke (4 slučaja, 9.7%), limfomi (2 slučaja, 4.9%), melanomi (2 slučaja, 4.9%) te po jedan slučaj karcinoma štitnjače i glioma mozga.

Zaključak: Unatoč određenim ograničenjima provedenog istraživanja, poput broja ispitanika te duljine praćenja, vrlo je razvidno da je fenomen pojavnosti drugih tumora uz NET očito vrlo značajan i da je potrebno takve bolesnike pratiti pomnije, a možda i dulje nego kod nekih drugih entiteta, ne samo zbog mogućeg recidiva već i ranog otkrivanja novih tumora koji mogu imati i veći zloćudni potencijal.

OCCURRENCE OF OTHER TUMORS IN PATIENTS WITH NEUROENDOCRINE TUMORS

RACETIN A.[1], Adžić G.[2], Belev B.[2]

[1] University of Zagreb
• *School of Medicine*
[2] University Hospital Centre Zagreb
• *Department of Oncology*

Introduction:The increased frequency of second primary tumors in patients with NET is a phenomenon of great interest. Several theories have been proposed, but no link in their origin has been defined, at least not on their genetic background. The aim of this study was to determine the frequency of other tumors in patients with NET and to make a comparison with published data in the literature.

Materials and methods: We retrospectively analyzed the data in the hospital information system for 201 patients with NET diagnosis. The average time of patient follow-up was 6.73 years (with a range of 1 month to 21 years). Also, data on the incidence of other tumors were recorded, which were then divided into synchronous and metachronous groups. Patients with a diagnosis of MEN-1 or VHL syndrome were excluded, since due to their genetic background and specific mutations, an increased frequency of other tumors is expected.

Results: The diagnosis of NET was confirmed histologically in 201 patients (111 men and 90 women). The average patient age was 57.3 years (19 – 84). The most common site was the pancreas, in 76 cases (37.8%), followed by the small intestine in 40 cases (19.9%). In 17.9% of patients, second primary tumors were found in addition to NET. A total of 41 additional tumors were found in 37 patients with NET. In 4 patients, 2 additional neoplasms were found. From a total of 41 neoplasms, 12 of them (29.3%) were diagnosed simultaneously or < 6 months apart in relation to NET (synchronously). The other 29 neoplasms (70.7%) were diagnosed > 6 months before or after NET (metachronous). Neoplasms of the digestive system were the most common (21 cases, 51.2%), with the highest frequency of colon and rectal tumors (12 cases). In second place are tumors of the genitourinary system (9 cases, 21.9%). Four cases of breast cancer (9.7%), two cases of lymphomas (4.9%) and melanomas (4.9%) and one case of thyroid cancer and brain glioma were also detected.

Conclusion: Despite the limitations of this study, such as the number of observed patients and follow-up time period, it is very clear that the occurrence of other tumors, in patients with NET, is very significant and that it is necessary to follow these patients more closely, and perhaps longer, not only because of the possible recurrence, but also early detection of other primary tumors that may have a higher malignant potential.

PORFIRIJA I USPJEŠNA PRIMJENA SUSTAVNOG ANTITUMORSKOG LIJEČENJA

NOVAK S.[1], Belev B.[2]

[1] Opća bolnica Varaždin
• *Odjel za hematologiju, onkologiju i kliničku imunologiju i alergologiju*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
krajnik.sara@gmail.com

Uvod: Porfirije su nasljedne ili stečene metaboličke bolesti karakterizirane poremećajem enzima koji sudjeluju u sintezi molekule hema, što rezultira nakupljanjem molekula prekursora porfirina ili porfirina. Prema mjestu poremećaja razlikujemo hepatičke i eritropoetske. Hepatičke porfirije zahvaćaju živčani sustav što se manifestira pojavom abdominalne boli, povraćanjem, proljevom, neuropatijom, aritmijama, i psihičkim poremećajima (anksioznost, halucinacije). Pojavu simptoma mogu potaknuti određeni lijekovi-citostatici, gladovanje, hormoni i stres. Stoga je vrlo važno kod pitanja komorbiditeta imati saznanje o prisutnoj porfiriji.

Prikaz slučaja: 43 godišnja bolesnica od 12. godine boluje od porfirije. Imala jednu ataku nakon poroda. Operirala papilarni karcinom štitnjače. Rutinskim UZV-om otkrivena fokalna promjena u jetri uz povišenu vrijednost CEA. Kolonoskopski je ektomirano više polipa od kojih jedan iz sigmoidnog kolona PH odgovara adenokarcinomu s invazijom submukoze uz LVI. MSCT-om prikazane suspektne promjene u jetri koje su potvrđene MR-om od čega je najveća 45x42x42 mm.

Na Multidisciplinarnom timu za probavne tumore odlučeno započeti neoadjuvantnu kemoterapiju po FOLFIRINOX + bevacizumab protokolu, a prethodno je konzultiran tim Odjela za metaboličke bolesti zbog

prevencije/prekida akutnog napada porfirije. Sugerirano je osigurati hemin iako se većina akutnih napada porfirije uspješno prekida 10%-tnom glukozom uz adekvatnu antiemezu i redovitim obrocima. Bolesnica je pri prvoj aplikaciji kemoterapije razvila simptome: crvenilo, mučninu i proljev koji su uz 10%-tnu glukozu i pojačanu antiemezu u potpunosti regredirali.

Tokom daljnjih ciklusa pacijentica je povremeno javljala simptome u vidu anksioznosti i straha. Ukupno je primila 6 ciklusa kemoterapije, a reevaluacijom je evidentirana regresija sekundarizama u jetri. Učiniti će se metastazektomija navedene ostatne intrahepatalne bolesti.

Zaključak: Određene vrste porfirije imaju povećanu učestalost malignih bolesti. Liječenje bolesnika s porfirijom zahtijeva posebne mjere opreza kako bi se smanjio rizik od akutnog napada i kako bi se osiguralo optimalno liječenje zloćudne bolesti. Obzirom da akutni napad porfirije može završiti fatalno, vrlo je važno prilikom odabira kemoterapije birati onu koja ima najmanji porfirogeni rizik.

PORPHYRIA AND THE SUCCESSFUL APPLICATION OF SYSTEMIC ANTI-TUMOR TREATMENT

NOVAK S.[1], Belev B.[2]

[1] General Hospital Varaždin
• *Department of Medical Oncology and Hemathology, Clinical Imunology and Alergology*
[2] University Hospital Centre Zagreb
• *Department of Oncology*

Introduction: Porphyrias are hereditary or acquired metabolic diseases characterized by a disruption of the enzymes involved in the synthesis of the heme molecule, which results in the accumulation of porphyrin or porphyrin precursor molecules. Hepatic porphyrias affect the nervous system, which is manifested by the appearance of abdominal pain, vomiting, diarrhea, neuropathy, arrhythmias, and psychological disorders (anxiety, hallucinations). The appearance of symptoms can be triggered by certain drugs – cytostatics, starvation, hormones and stress. Therefore, it is very important to know about the present porphyria when dealing with comorbidities.

Case report: A 43-year-old patient has been suffering from porphyria since the age of 12. She had one attack after giving birth. She underwent surgery for papillary thyroid cancer. A routine USG revealed a focal change in the liver with an elevated CEA value. Colonoscopically, several polyps were excised, one of which from the sigmoid colon PH corresponds to adenocarcinoma with invasion of the submucosa with LVI. MSCT showed suspicious changes in the liver, which were confirmed by MR, the largest of which is 45x42x42 mm.At the Multidisciplinary Team for Digestive Tumors, it was decided to start neoadjuvant chemotherapy according to the FOLFIRINOX + bevacizumab protocol, and the team of the Department of Metabolic Diseases was previously consulted for the prevention/interruption of an acute attack of porphyria. It was suggested to provide hemin, although most acute attacks of porphyria are successfully terminated with 10% glucose with adequate antiemesis and regular meals. During the first application of chemotherapy, the patient developed symptoms: redness, nausea and diarrhea, which completely regressed with 10% glucose and increased antiemesis.During further cycles, the patient occasionally reported symptoms of anxiety and fear. She received a total of 6 cycles of chemotherapy, and a reevaluation showed the regression of secondaries in the liver. Metastasectomy will be performed for the remaining intrahepatic disease.

Conclusion: Certain types of porphyria have an increased frequency of malignant diseases. Treatment of patients with porphyria requires special precautions to minimize the risk of an acute attack and to ensure optimal management of the malignancy. Given that an acute attack of porphyria can end fatally, it is important when choosing chemotherapy to choose the one with the lowest porphyrogenic risk.

PROCJENA UDJELA POJEDINIH TUMORSKIH SIJELA U RADNOM OPTEREĆENJU DNEVNE BOLNICE KLINIKE ZA ONKOLOGIJU KLINIČKOG BOLNIČKOG CENTRA ZAGREB

KUKAL GJERGAJ I.[1], Dedić Plavetić N.[2,3], Silovski T.[2], Herceg D.[4,2], Pleština S.[2,3]

[1] Klinički bolnički centar Zagreb, Zagreb, Croatia
• *Klinika za ženske bolesti i porode, Zavod za ginekološku onkologiju,*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[3] Sveučilište u Zagrebu
• *Medicinski fakultet*
[4] Sveučilište u Zagrebu
• *Stomatološki fakultet*
iva.kukal.gj@gmail.com

Uvod: Dnevna bolnica Klinike za onkologiju jedna je od ustrojbenih jedinica Klinike za onkologiju namijenjena u prvom redu aplikaciji sustavne onkološke terapije, a potom i simptomatskoj terapiji onkoloških bolesnika. Cilj istraživanja bio je procjena udjela pojedinih tumorskih sijela u svakodnevnom radu Dnevne bolnice Klinike za onkologiju kako bi se u budućnosti bolje planirali vremenski i kadrovski resursi ovisno o udjelu pojedinih terapijskih protokola.

Materijali i metode: Uz prethodnu suglasnost Etičkog povjerenstva Kliničkog bolničkog centra Zagreb (Klasa:8.1-22/151-4; broj: 02/013 AG) učinjena je retrospektivna presječna analiza koja je uključila bolesnike primljene u Dnevnu bolnicu onkologije u razdoblju od 1.6.2022. do 30.6.2022.

Rezultati: U promatranom jednomjesečnom intervalu obavljeno je 1228 pregleda u Dnevnoj bolnici, od kojih je 1142 (93%) bilo u svrhu aplikacije sustavne terapije, dok je razlog ostalih 86 (7%) pregleda bila heparinizacija PORT sustava ili evakuacija pleuralnog izljeva, odnosno ascitesa. Najzastupljenije sijelo bio je rak dojke s 504 (41%) pregleda, zatim slijede probavni tumori s 335 (27,3%), potom urogenitalni tumori sa 148 (12%) pregleda te melanomi 109 (8,9%) i mezenhimalni tumori 55 (4,7%) pregleda dok su ostala sijela činila 77 (6,3%) pregleda. Obzirom da je liječenje bolesnika s rakom pluća u nadležnosti pulmologa u Klinici za plućne bolesti, isto nije uključeno u navedenu analizu.

Zaključak: Putem Dnevne bolnice Klinike za onkologiju na dnevnoj bazi liječi se velik broj onkoloških bolesnika. Obzirom na mali uzorak, plan je istu analizu napraviti kroz dulji vremenski period, ali i za ostala radilišta u kojima se aplicira sustavna terapija. Ova analiza ne uključuje pripravke primijenjene oralnim putem i potkožnim injekcijama, što se provodi kroz kabinete ONC1 i ONC2. Budući da se kao najčešće zastupljeno sijelo u Dnevnoj bolnici izdvaja rak dojke, a iza kojeg slijede probavni tumori, planiranje vremenskih i kadrovskih resursa u skladu s navedenim rezultatima povećalo bi kvalitetu zdravstvene skrbi onkoloških bolesnika.

ASSESSMENT OF THE SHARE OF INDIVIDUAL TUMOR SITES IN THE WORKLOAD OF THE DAY HOSPITAL OF THE DEPARTMENT OF ONCOLOGY OF THE UNIVERSITY HOSPITAL CENTRE ZAGREB

KUKAL GJERGAJ I.[1], Dedić Plavetić N.[2,3], Silovski T.[2], Herceg D.[4,2], Pleština S.[2,3]

[1] University Hospital Centre Zagreb
• *Department of Gynecoloy and Obstetric, Department of Gynecologic Oncology*
[2] University Hospital Centre Zagreb
• *Department of Oncology*
[3] University of Zagreb
• *School of Medicine*
[4] University of Zagreb
• *School of Dental Medicine*

Introduction: Day oncology hospital is one of the organizational units of the Department of Oncology delivering systemic oncology therapy as well as symptomatic therapy to oncology patients. The aim of this study was to analyze the frequency of various tumor sites in order to better organise Day hospital's working hours and personnel, according to the prevalence of respective therapy plans.

Materials and methods: With the prior consent of the Ethics Committee of University Hospital Centre Zagreb (Class: 8.1-22/151-4; number: 02/013 AG), a retrospective cross-sectional analysis was performed, which included patients admitted to the Day oncology hospital in the period from June 1st, 2022 to June 30th, 2022.

Results: In the observed one-month period, 1228 examinations were performed of which 1142 (93%) were for the purpose of applying systemic therapy, while the remaining 86 (7%) examinations were due to the heparinization of the PORT system, evacuation of pleural effusion or ascites.The most common site, from the most to the least prevalent, were breast cancer with 504 (41%) examinations, digestive tumors with 335 (27.3%) examinations, urogenital tumors with 148 (12%) examinations, melanoma 109 (8.9%), and mesenchymal tumors 55 (4.7%) of examinations, while all other sites accounted for 77 (6.3%) examinations.Considering that the treatment of patients with lung cancer is within the competence scope of pulmologists at the Clinic for Lung Diseases, it was not included in the above analysis.

Conclusion: While a large number of oncology patients are treated on a daily basis in the Day Hospital of the Department of Oncology. Considering the small sample size of this study, the plan is to do the same analysis over a longer period of time, as well as for other workplaces where systemic therapy is delivered. This analysis does not include medications administered orally and by subcutaneous injections, which are carried out through ONC1 and ONC2 cabinets. Since breast cancer is the most common disease in the Day Hospital, followed by digestive tumors, planning time and personnel resources in accordance with the above results would increase the quality of health care for oncology patients.

RAZMIŠLJAMO LI DOVOLJNO O RIJETKIM NASLJEDNIM SINDROMIMA U ONKOLOGIJI?

MLADINOVIĆ M.[1], Belev B.[2]

[1] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*
[2] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
martina.mladinovic@hotmail.com

Uvod: Multipla endokrina neoplazija (MEN-I sindrom) ili Wermer's sindrom, rijetka je nasljedna bolest. Vjerojatno je posljedica inaktivirajuće mutacije tumor – supresorskog gena koji kodira transkripcijski faktor menin. MEN-I sindrom obilježen je obično trijasom – tumorima paratireoidnih žlijezda, otočića gušterače i hipofize. U oko 40% slučajeva zahvaćene su sve tri endokrine žlijezde.

Prikaz slučaja: 30-godišnja bolesnica, sportašica, do sada liječila gastritis, poznate ciste u mozgu, bubrežni kamenci i ciste na bubrezima, bolest je otkrila genetskim testiranjem. Majki bolesnice u 2/2021 postavljena dijagnoza MEN-I sindroma. Majčin otac preminuo od posljedica tumora na gušterači, vjerojatno MEN-I, što nije dokumentirano. Provedeno je genetsko testiranje naše bolesnice i njezine sestre. Kod naše bolesnice utvrđena je mutacija c.1546dupC u 10. eksonu u heterozigotnom statusu koja se povezuje s MEN-I. Opsežno je endokrinološki obrađena. Utvrđen je primarni hiperparatireoidizam, inzulinska rezistencija, hiperprolaktinemija, povišen IGF-I uz uredan test supresije lučenja hormona rasta, povišene vrijednosti CgA i gastrina. Na scintigrafiji SESTA-MIBI-jem nađeno je pojačano nakupljanje u području donje desne paratireoidne žlijezde te donje lijeve paratireoidne žlijezde u području koje je opisan adenom. MR abdomena ukazuje na cistu u glavi gušterače veličine 8 mm, a EUZ-om vidljiva tvorba uz glavu gušterače veličine 22 mm uz opisanu cistu. Punkcijom cistične lezije u glavi gušterače citološki dokazan neuroendokrini tumor. PET/CT sa Ga-68 pokazao je patološku ekspresiju somatostatinskih receptora u cističnoj tvorbi glave gušterače i mekotkivnom nodusu anteriornije od glave gušterače, što je uz prethodno učinjenu ultrazvučnu i slikovnu dijagnostiku potvrdilo sumnju na tumorsku tvorbu. Na nalazu MR-mozga nađen cistični tumor veličine 3 mm nije relevantan za osnovnu bolest. Na temelju učinjene dijagnostike postavljena je indikacija za operativni zahvat paratireoideje i gušterače. Prva operacija učinjena je u 12/2021 – obostrana donja paratireoidektomija i resekcija cervikalnog dijela timusa (PHD adenomi), potom u 1/2022 operacija tvorbe gušterače po Whipple-u. PHD nalaz tvorbe gušterače govori za neuroendokrini tumor glave gušterače gr I, Ki 67 1% (pT2N1Mx).

Zaključak: MEN-I je autosomalno dominantni nasljedni poremećaj, što znači da je dovoljan jedan gen za fenotipsko očitovanje bolesti. Svako dijete ima 50% šanse da naslijedi mutirani gen, upravo kao što je to slučaj i

kod naše bolesnice. Danas je postavljanje dijagnoze ovakvih bolesti olakšano primjenom dostupnih dijagnostičkih testova za određivanje genetski nasljednih bolesti, te je važno kod pojedinih entiteta imati svijest o mogućoj pojavi sindroma čime se ostali tumori mogu na vrijeme otkriti i time uspješno izliječiti.

DO WE THINK ENOUGH ABOUT RARE HEREDITARY SYNDROMES IN ONCOLOGY?

MLADINOVIĆ M.[1], Belev B.[2]

[1] General Hospital „dr. Josip Benčević" Slavonski Brod
• *Department of Oncology and Hematology*
[2] University Hospital Centre Zagreb
• *Department of Oncology*

Introduction: Multiple endocrine neoplasia (MEN-I syndrome) or Wermer's syndrome, is a rare hereditary disease. It is probably the result of an inactivating mutation of the tumor-suppressor gene that encodes the transcription factor menin. MEN-I syndrome is usually characterized by a triad – tumors of the parathyroid glands, pancreatic islets and pituitary gland. In about 40% of cases, all three endocrine glands are affected.

Case report: 30-year-old patient, an athlete, until now treated for gastritis, known cysts in the brain, kidney stones, and cysts on the kidneys, discovered the disease through genetic testing. The patient's mother was diagnosed with MEN-I syndrome in February 2021. The mother's father died as a result of a pancreatic tumor, probably MEN-I, which is not documented. Genetic testing of our patient and her sister was performed. In our patient, the mutation c.1546dupC in the 10th exon was found in heterozygous status, which is associated with MEN-I. Extensively endocrinologically treated. Primary hyperparathyroidism, insulin resistance, hyperprolactinemia, elevated IGF-I with a regular growth hormone secretion suppression test, elevated CgA, and gastrin values were found. On scintigraphy with SESTAMIBI, increased accumulation was found in the area of the lower right parathyroid gland and the lower left parathyroid gland in the area described as an adenoma. Abdominal MRI indicates a cyst in the head of the pancreas of size 8 mm, and EUZ shows a mass next to the head of the pancreas of size 22 mm with the described cyst. A neuroendocrine tumor was cytologically proven by puncture of a cystic lesion in the head of the pancreas. PET/CT with Ga-68 showed pathological expression of somatostatin receptors in the cystic formation of the head of the pancreas and a soft tissue nodule anterior to the head of the pancreas, which, along with the previously performed ultrasound and imaging diagnostics, confirmed the suspicion of tumor formation. A cystic tumor with a size of 3 mm was found on the MRI brain, but it's not relevant to the primary disease. Based on the performed diagnostics, an indication was set for surgery of the parathyroid and pancreas. The first operation was performed in 12/2021 – bilateral lower parathyroidectomy and resection of the cervical part of the thymus (PHD adenomas), then in 1/2022 the surgery for the formation of the pancreas according to Whipple. The PHD finding of the formation of the pancreas indicates a neuroendocrine tumor of the head of the pancreas gr I, Ki 67 1% (pT2N1Mx).

Conclusion: MEN-I is an autosomal dominant hereditary disorder, which means that one gene is sufficient for the phenotypic manifestation of the disease. Each child has a 50% chance of inheriting the mutated gene, just as it is the case with our patient. Today, the diagnosis of such diseases is facilitated by the use of available diagnostic tests for the determination of genetically inherited diseases, and it is important for certain entities to be aware of the possible occurrence of syndromes, so that other tumors can be detected in time and thus successfully cured.

ŠTO SKRIVA SRCE BOLESNICE S TROSTRUKO NEGATIVNIM KARCINOMOM DOJKE?

MLADINOVIĆ M.[1], Kovač Peić A.[1], Raguž A.[2]

[1] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za onkologiju i hematologiju*
[2] Opća bolnica „dr. Josip Benčević" Slavonski Brod
• *Odjel za kardiologiju*
martina.mladinovic@hotmail.com

Uvod: Trostruko negativni rak dojke je onaj rak dojke kod kojeg su stanice raka negativne na humani receptor epidermalnog faktora rasta 2, estrogenske i progesteronske receptore. Ima veću vjerojatnost ponovnog povrata bolesti i pojavi metastaza. Standard liječenja je bila kemoterapija, no sada su dostupne i druge terapijske opcije: imunoterapija, PARP inhibitori.

Prikaz slučaja: Bolesnici u dobi 57 godina s mentalnom retardacijom, zbog egzulceriranog tumora desne dojke u 5/2018 učinjena biopsija kojom dokazan invazivni trostruko negativni karcinom dojke s visokim proliferacijskim indeksom, Ki 67 95%. Na razumljiv način upoznata s prirodom bolesti. Inicijalnim CT-om bez sekundarizama, suspektan perikardijalni izljev koji se UZV-om srca isključi, uredne EF LV 62%. Provedena neoadjuvantna kemoterapija po AC-T protokolu. Klinički dvostruka redukcija tumora uz potpunu redukciju sekrecije. Odlukom MDT, učinjena sanitarna mastektomija desne dojke s evakuacijom aksile. PHD operacije potvrdio nalaz biopsije, pT4bN1a. Liječena adjuvantnom radioterapijom, a terapija kapecitabinom prekinuta zbog nuspojava. Kontrolnom obradom u 11/2019 sekundarne promjene u plućima, kostima, limfnim čvorovima medijastinuma. U prvoj liniji liječenja metastatske bolesti ordinirana carboplatina. Na kontroli pojava zaduhe, EKG zapis sinus tahikardija s blokom desne grane, posumnja se na plućnu emboliju. MSCT plućnom angiografijom ista se isključi, opisan veći perikardijalni izljev debljine 2.8 cm. Transtorakalni UZV: desni ventrikul gotovo u potpunosti ispunjen tumorskom masom koja dodiruje i pulmonalnu valvulu, cirkardijalni perikardijalni izljev bez prijeteće tamponade. U 1/2020 prisutni neurološki simptomi, CT – om mozga intracerebralna hemoragija uz vazogeni edem, sekundarizmi. Neurokirurg se u hitnoći odlučio na operativni zahvat, nije prezentirana na MDT timu. Dalje palijativno liječena, opće stanje deteriorira te nastupa smrtni ishod.

Zaključak: Metastatski tumori srca su rijetki, asimptomatski, pronađu se u 1,5–20% obdukcija pacijenata s rakom. Mogu nastati od bilo kojeg malignog tumora, a najčešće se šire limfnim putem. Rak dojke koji je metastazirao u srce nije uobičajen, a ovisno o biologiji može davati atipične metastaze. Pri kliničkim simptomima i nalazima potrebno je učiniti UZV srca.

WHAT HIDES THE HEART OF A PATIENT WITH TRIPLE NEGATIVE BREAST CANCER?

MLADINOVIĆ M.[1], Kovač Peić A.[1], Raguž A.[2]

[1] General Hospital „dr. Josip Benčević" Slavonski Brod
• *Department of Oncology and Hematology*
[2] General Hospital „dr. Josip Benčević" Slavonski Brod
• *Department of Cardiology*

Introduction: Triple negative breast cancer implies that cancer cells are negative for human epidermal growth factor receptor 2, estrogen and progesterone receptors. There is a higher probability of disease recurrence and the occurrence of metastases. The standard treatment was chemotherapy, but now other therapeutic options are available: immunotherapy, PARP inhibitors.

Case report: To 57 years old patient with mental retardation, due to an ulcerated tumor of the right breast, in 05/2018 biopsy confirmed an invasive triple-negative breast cancer with a high proliferation index, Ki 67 95%. She gets acquainted with the nature of the disease in appropriate way. Initial CT without secondaries, suspected pericardial effusion was not confirmed by ultrasound, normal EF LV 62%. Neoadjuvant chemotherapy was performed according to the AC-T protocol. Clinical double tumor reduction with complete reduction of secretion. By decision of the MDT, a sanitary mastectomy of the right breast was performed with evacuation of the axilla. PHD surgery confirmed biopsy findings, pT4bN1a. She was treated with adjuvant radiotherapy, and capecitabine therapy was discontinued due to side effects. Control checkup in 11/2019 revealed secondary changes in the lungs, bones, lymph nodes of the mediastinum. In the first line of treatment for metastatic disease, carboplatin is

prescribed. After she report shortness of breath, ECG record of sinus tachycardia with right bundle branch block, pulmonary embolism is suspected. MSCT pulmonary angiography ruled it out, described a larger pericardial effusion with a thickness of 2.8 cm. Transthoracic USG: right ventricle almost completely filled with tumor mass touching the pulmonary valve, circadian pericardial effusion without threatening tamponade. In 1/2020, neurological symptoms present, brain CT scan describes intracerebral hemorrhage with vasogenic edema, secondaries. The neurosurgeon indicated urgent operation she was not presented to the MDT team. After further palliative treatment, the general condition deteriorates, and she passed away.

Conclusion: Metastatic heart tumors are rare, asymptomatic, found in 1.5–20% of autopsies of cancer patients. They can arise from any malignant tumor, and most often they spread through the lymphatic system. Breast cancer that has metastasized to the heart is not common, and depending on the biology, it can produce atypical metastases. With clinical symptoms and findings, it is necessary to perform an ultrasound of the heart.

UČINKOVITOST PERKUTANE TRANSLUMINALNE ANGIOPLASTIKE (PTA) KAO PALIJATIVNE MOTODE LIJEČENJA BOLESNIKA S KARCINOMOM PLUĆA

JURIĆ M.[1], Jurić G.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za plućne bolesti Jordanovac*
monikajrc@gmail.com

Uvod: Perkutana transluminalna angioplastika je minimalno invazivni postupak koji se koristi za otvaranje blokirane ili sužene krvne žile nakon koje se omogućava uspostavljanje nesmetane cirkulacije krvi. Hibridnom intervencijskom žicom i kateterom prijeđe se kroz subokluziju, a potom se postavi stent. Cilj ovoga istraživanja je ispitati učinkovitost postavljanja PTA stenta kod bolesnika oboljelih od karcinoma pluća.

Materijali i metode: Istraživanje je provedeno na 14 bolesnika kojima je postavljen PTA stent tijekom prvih 8 mjeseci 2022. godine na KBC-u Zagreb, Kliničkog zavoda za intervencijsku radiologiju. Svi pacijenti se primarno liječe na Zavodu za tumore pluća i sredoprsja Klinike za plućne bolesti Jordanovac. Uvidom u medicinsku i sestrinsku dokumentaciju prikupljeni su podaci o načinu prijema u bolnicu, oksigenoterapiji, dispneji, otečenosti glave i vrata, subjektivnom osjećaju pritiska u prsima prije i poslije postavljenog stenta, te tijeku onkološkog liječenja.

Rezultati: Obradom podataka doznajemo da je kod 100% bolesnika u tijeku aktivno onkološko liječenje, 41% bolesnika je primljeno putem hitne službe kao progresija osnovne bolesti, 100% bolesnika se žalilo na osjećaj pritiska u prsima prije postavljanja stenta, dok je kod 15% bolesnika taj osjećaj bio prisutan i nakon postavljanja PTA stenta. Prije postavljanja stenta kod 83% bolesnika je zabilježena dispneja, dok se kod svega 10% zadržala i poslije zahvata. Oksigenoterapiju je zahtijevalo 25% bolesnika prije postavljanja stenta, dok je 12% zahtijevalo primjenu kisika i poslije zahvata. Otečenost glave i vrata je bila prisutna u 100% ispitanika, poslije zahvata nitko od bolesnika nije imao taj simptom.

Zaključak: Intervencijska radiologija je grana radiologije koja se bavi minimalno invazivnim postupcima u terapiji tumora, koji se izvode pod kontrolom kompjuterizirane tomografije. Obradom prikupljenih podataka bolesnika s karcinomom pluća liječenih u Zavodu za tumore pluća i sredoprsja, Klinike za plućne bolesti Jordanovac vidljivo je da je postavljanje perkutane transluminalne angioplastike učinkovita metoda palijativnog liječenja te doprinosi cjelokupnom poboljšanju stanja bolesnika.

EFFECTIVENESS OF PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY (PTA) AS A PALLIATIVE METHOD OF TREATMENT OF PATIENTS WITH LUNG CARCINOMA

JURIĆ M.[1], Jurić G.[1]

[1] University Hospital Centre Zagreb
• *Department of Pulmology Jordanovac*

Introduction: Percutaneous transluminal angioplasty is a minimally invasive procedure used to open a blocked or narrowed blood vessel, after which it is possible to establish unhindered blood circulation. A hybrid interventional wire and catheter are passed through the subocclusion, and then a stent is placed. The aim of this research is to examine the effectiveness of PTA stent placement in patients with lung cancer.

Materials and methods: The research was conducted on 14 patients who were placed with a PTA stent during the first 8 months of 2022 at KBC Zagreb, Clinical Institute for Interventional Radiology. All patients are primarily treated at the Institute for Lung and Middle Chest Tumors of the Jordanovac Pulmonary Diseases Clinic. By inspecting the medical and nursing documentation, data were collected on the method of admission to the hospital, oxygen therapy, dyspnea, swelling of the head and neck, the subjective feeling of pressure in the chest before and after the stent was placed, and the course of oncological treatment.

Results: Data processing shows that 100% of patients are undergoing active oncological treatment, 41% of patients were admitted through the emergency department as a progression of the underlying disease, 100% of patients complained of a feeling of pressure in the chest before stent placement, while 15% of patients had this feeling was also present after PTA stent placement. Dyspnea was noted in 83% of patients before stent placement, while only 10% had dyspnea after the procedure. Oxygen therapy was required by 25% of patients before the placement of the stent, while 12% required the use of oxygen after the procedure. Swelling of the head and neck was present in 100% of the subjects, none of the patients had this symptom after the procedure.

Conclusion: Interventional radiology is a branch of radiology that deals with minimally invasive procedures in tumor therapy, which are performed under the control of computerized tomography. Processing the collected data of patients with lung cancer treated at the Institute for Lung and Mid-thoracic Tumors, Clinic for Pulmonary Diseases Jordanovac shows that percutaneous transluminal angioplasty is an effective method of palliative treatment and contributes to the overall improvement of the patient's condition.

PRIMJENA CDK 4/6 INHIBITORA U BOLESNICA S METASTATSKIM HR+/HER2– RAKOM DOJKE U KBC ZAGREB

ČULAR K.[1], Gudelj D.[1], Toula L.[1], Vičić I.[1], Dedić Plavetić N.[2,1], Popović M.[1], Križić M.[1], Pleština S.[2,1], Silovski T.[1]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Sveučilište u Zagrebu
• *Medicinski fakultet*
katarinacular96@yahoo.com

Uvod: Metastatski rak dojke je neizlječiva bolest sa skromnim petogodišnjim preživljavanjem. Iako je terapija i dalje palijativne naravi, iskorak u liječenju predstavlja kombinacija CDK4/6 inhibitora i endokrine terapije (ET). U liječenju metastatskog HR+/HER2– raka dojke se na pozitivnoj listi HZZO-a nalaze od 1. kolovoza 2018. Prilikom uvođenja u kliničku praksu većina bolesnica već je bila u tijeku liječenja metastatske bolesti te su prethodno bile tretirane drugim terapijskim opcijama. Cilj ovog rada bio je utvrditi zastupljenost pojedine linije terapije u kojoj su se CDK 4/6 inhibitori prinijenjeni u razdoblju od 2018. do 2022. godine u KBC Zagreb.

Metode: Retrospektivnim opservacijskim ispitivanjem analizirani su podatci iz bolničkog informatičkog sustava (BIS) uz prethodno odobrenje Etičkog povjerenstva KBC Zagreb za 317 bolesnica koje su započele liječenje kombinacijom CDK 4/6 inhibitora i ET-a u razdoblju od 1.8.2018. do 30.6.2022. U svih bolesnica utvrđena je linija liječenja CDK 4/6 inhibitorima.

Rezultati: U 2018. godini, 40,91% (18/44) bolesnica je započelo terapiju kombinacijom CDK 4/6 inhibitorima i ET u prvoj liniji terapije za metastatsku bolest, a 56,82% (26/44) u drugoj ili višoj liniji. Naredne 2019. godine, 55,56% (55/99) ih je započelo primati CDK 4/6 inhibitore u prvoj liniji, a 44,44% (44/99) u višim linijama. Udio pacijentica koje su započele terapiju CDK 4/6 inhibitorima u prvoj liniji u 2020. godini je bio 65,38% (51/78), a u višim linijama 34,62% (27/78), dok je u 2021. godini 76,71% (56/73) bolesnica je započelo terapiju u prvoj liniji, a 23,29% (17/73) u drugim linijama. U analiziranom dijelu 2022. godini do kraja lipnja 95,65% (22/23) bolesnica je započelo terapiju CDK 4/6 inhibitorima u prvoj liniji, a samo 4,35% (1/23) u drugoj liniji.

Zaključak: U trenutku uvođenja CDK 4/6 inhibitora u standardnu kliničku praksu, veliki udio bolesnica bio je prethodno tretiran drugim terapijskim opcijama te su se CDK 4/6 inhibitori koristili u višim linijama liječenja. Analizom gotovo pet godina, ustanovljen je kontinuiran porast korištenja CDK 4/6 inhibitora u prvoj liniji liječenja metastatskog HR+/HER2– raka dojke.

APPLICATION OF CDK 4/6 INHIBITORS IN PATIENTS WITH METASTATIC HR+/HER2– BREAST CANCER IN UHC ZAGREB

ČULAR K.[1], Gudelj D.[1], Toula L.[1], Vičić I.[1], Dedić Plavetić N.[2,1], Popović M.[1], Križić M.[1], Pleština S.[2,1], Silovski T.[1]

[1] University Hospital Centre Zagreb
• *Department of oncology*
[2] University of Zagreb
• *School of medicine*

Introduction: Metastatic breast cancer is an incurable disease with poor five-year survival. Even though treatment is still palliative, an important step forward was the combination of CDK 4/6 inhibitors with endocrine therapy (ET). They have been approved for treatment of HR+/HER2– metastatic breast cancer by HZZO since first of august 2018. When they started being used in clinical practice, most of the patients were already being treated for metastatic disease and had already been given other therapeutic options in the first line of treatment. The aim of this study was to analyse the lines of treatment in which the CDK4/6 inhibitors were used as between 2018 and 2022 in UHC Zagreb.

Methods: In a retrospective observational study data from the hospital information system for 317 patients who started treatment with a combination of CDK 4/6 inhibitors and ET between 01.01.2018. and 30.06.2022 was analysed with the prior approval from the UHC Zagreb Ethics Committee. The line of treatment in which the CDK 4/6 inhibitors were used was analysed in all the patients.

Results: In 2018, 40.91% (18/44) of patients began treatment with CDK 4/6 inhibitors and ET as first-line therapy, while 56.82% (26/44) started as second or higher line. In 2019, 55.56% (55/99) started treatment in first line, and 44.44% (44/99) in other lines. Of the patients who started treatment in 2020., 65.38% (51/78) were first-line, and 34.62% (27/78) were higher line of treatment. In 2021 76.71% (56/73) of patients started in first line and 23.29% (17/73) in other lines. In 2022 by the end of June, 95.65% (22/23) of patients started treatment in first line of therapy, and only 4.35% (1/23) in second line.

Conclusion: When CDK 4/6 inhibitors started being used for treatment of metastatic breast cancer, many of the patients had already been treated with other therapies, therefore CDK 4/6 inhibitors were used as a higher line of treatment. By analysing the data from almost five years, a continuous rise in the use of CDK 4/6 inhibitors in first-line treatment for metastatic HR+/HER2– breast cancer was observed.

HITOTRIOZIDAZA KAO POTENCIJALNI BIOMARKER U RANOM OTKRIVANJU HEPATOCELULARNOG KARCINOMA

KULIĆ A.[1], Belev B.[1,4], Gojević A.[2], Orešković I.[1], Premužić M.[3], Čuković Čavka S.[3,4], Sirotković-Skerlev M.[4], Sedlić F.[4], Vranić M.[2], Ostojić R.[3], Pleština S.[1,4], Zaninović Lj.[5], Herceg D.[1,6], Knežević Štromar I.[3]

[1] Klinički bolnički centar Zagreb
• *Klinika za onkologiju*
[2] Klinički bolnički centar Zagreb
• *Klinika za kirurgiju*
[3] Klinički bolnički centar Zagreb
• *Klinika za unutarnje bolesti*
[4] Sveučilište u Zagrebu
• *Medicinski fakultet*
[5] Klinički bolnički centar Zagreb
• *Klinički zavod za laboratorijsku dijagnostiku*
[6] Sveučilište u Zagrebu
• *Stomatološki fakultet*
borislavbelev@gmail.com

Uvod: Hitotriozidaza, glikozil hidrolaza, hidrolizira β-(1, 4)-vezu između N-acetil glukozamina i hitina. Povećana je aktivnost u infektivnim bolestima gdje razgrađuje hitin u staničnim strukturama patogena. Nasuprot tome hitotriozidaza oslobođena iz Kupfferovih stanica jetre inducira fibrozu i cirozu jetre.Čini se da enzim ima dvostruku ulogu, regulatornu ili patogenu, ovisno o bolesti i stanicama koje sintetiziraju enzim. Istraživanja su pokazala mogućnost razlikovanja upalnih boesti i karcinoma pluća, kao i povišene koncentracije hitotriozidaze u različitim karcinomima (pluća, dojka, prostata..).

Cilj: Ispitati prisutnost i moguću razliku u aktivnosti hitotriozidaze u serumu bolesnika s različitim bolestima jetre.

Materijali i metode: U serumu 189 bolesnika (21–84 godine; median 60) s različitim bolestima jetre (33 s HCC, 42 s cirozom jetre, 43 s virusnim hepatitisom B ili C, 40 s autoimunom bolesti jetre (ALD), 24 s NAFLD (non-alcoholic fatty liver disease) i 7 bolesnika s nedefinranom bolesti jetre) te 87 zdrava ispitanika izmjerene su aktivnosti hitotriozidaze metodom fuorometrije. Aktivnost hitotriozidaze izražena je u nmol/ml/satu, a cut off vrijednosti prema ROC krivulji su 99.82 nmol/ml/h (AUC 0.940; 95% CI 0.819to 0.989, p=0.0001).

Rezultati: Aktivnosti hitotriozidaze u serumu bolesnika s bolestima jetre bile su: u ALD 14,7–194,1 nmol/ml/h;Median 60,23): NAFLD 43,7–59,2 nmol/ml/h;Median 52,8: virusni hepatitis A ili B 31,1–47,4nmol/ml/h; Median 35,3: HCC 19,1–139,3 nmol/ml/h; Median 67,5: ciroza jetre 2,7–140,3nmol/ml/h; Median 41,6. Utvrdili smo statistički značajnu razliku u aktivnosti hitotriozidaze između bolesnika s cirozom i HCC (p=0,0123). Statistički značajnu razliku nismo dobili između ostalih bolesti jetre.

Zaključak: Navedeno istraživanje upućuje na moguću vrijednost nalaza aktivnosti hitotriozidaze u serumu bolesnika s hepatocelularnim karcinomom jetre kao mogućeg biomarkera u ranom otkrivanju tumora.

CHITOTRIOSIDASE AS A POTENTIAL BIOMARKER FOR EARLY DETECTION OF HEPATOCELLULAR CARCINOMA

KULIĆ A.[1], Belev B.[1,4], Gojević A.[2], Orešković I.[1], Premužić M.[3], Čuković Čavka S.[3,4], Sirotković-Skerlev M.[4], Sedlić F.[4], Vranić M.[2], Ostojić R.[3], Pleština S.[1,4], Zaninović Lj.[5], Herceg D.[1,6], Knežević Štromar I.[3]

[1] University Hospital Centre Zagreb
• *Department of Oncology*
[2] University Hospital Centre Zagreb
• *Department of Surgery*
[3] University Hospital Centre Zagreb
• *Department of Internal Medicine*
[4] University of Zagreb
• *School of Medicine*
[5] University Hospital Centre Zagreb
• *Department of Laboratory Diagnostics*
[6] University of Zagreb
• *School of Dental Medicine*

Introduction: Chitotriosidase, glycoside hydrolase, is hydrolysing β-(1, 4)-bond between N-acetyl glucosamine and chitin. Higher activity is found in infectious diseases where it is degrading the chitin in cellular structures of the pathogens. Opposed to that, chitotriosidase released from Kupffer cells in the liver, induces fibrosis and cirrhosis development. It seems that enzyme has a dual role, regulatory and pathogenetic, depending on disease and cells involved in its synthesis. According to the literature data so far, there is a possibility to use chitotriosidase concentration in distinguishing inflammation and lung malignancy. It is also seen that there are higher chitotriosidase concentrations in sera of patients with different malignancies (lungs, breast, prostate...)

Goal: We aimed to determine chitotriosidase activity and difference of it in sera of patients with liver diseases of different aetiologies, as well as in patients with developed cirrhosis with or without malignant alteration.

Materials and methods: In sera of 189 patients (age 21–84, median 60) with different liver diseases (33 with hepatocellular carcinoma, HCC, 42 with developed cirrhosis, 43 with hepatitis B or C, 40 with autoimmune liver diseases, ALD, 24 wit non-alcoholic fatty liver disease, NAFLD, 7 with liver disease of unknown origin) and 87 healthy controls, activity of chitotriosidase was determined by fluorometry. Chitotriosidase activity was measured in nmol/ml/h, and cut off values according to the ROC curve are 99.82 nmol/ml/h (AUC 0.940; 95% CI 0.819to 0.989, p=0.0001).

Results: Chitotriosidase activity in sera of patients with liver diseases were: 14,7–194,1 nmol/ml/h, Median 60,23; 43,7–59,2 nmol/ml/h, Median 52,8; 31,1–47,4nmol/ml/h, Median 35,3; 19,1–139,3 nmol/ml/h, Median 67,5 and 2,7–140,3nmol/ml/h, Median 41,6 in ALD, NAFLD, Hepatitis B and C, HCC and cirrhosis, respectively. There was statistically significant difference in chitotriosidase activity between cirrhosis and HCC (p=0,0123), and no statistically significant difference between other entities.

Conclusion: According to our data there is a possible place for chitotriosidase activity as a biomarker for early detection of hepatocellular carcinoma development. Further investigations on a larger scale of patients should be done.