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OSTEOPOROSIS

OSTEOPOROZA

Radmila MATIJEVIĆ

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1] **(Figure 1).** This definition, developed by international consensus in 1993, accentuates two important characteristics of osteoporosis: its adverse effects on bone mass and microstructure, and fractures as its clinical outcome. In 1994, diagnostic criteria were defined by the World Health Organization (WHO) using standard deviation (SD) scores of bone mineral density (BMD) related to peak bone mass in healthy young women, with osteoporosis being defined as a BMD T score of −2.5 or less and low bone mass (osteopenia) as a BMD T-score between −1 and −2.5 [2]. Low BMD is recognized as an important diagnostic criterion in the pathogenesis of fragility fractures, and a tool that can be used in epidemiological studies to evaluate the prevalence of osteoporosis. However, the benefits of BMD as a clinical benchmark for osteoporosis are limited, because BMD is only one of several important risk factors for fracture, and the majority of fragility fractures occur in persons with BMD values above the defined threshold [3]. Bone density testing by dual energy X-ray absorptiometry (DXA) is a quantitative, non-invasive, comparatively inexpensive, convenient diagnostic procedure for osteoporosis.

Clinical diagnosis of osteoporosis is difficult, because the WHO definition using BMD alone may not take into account other risk factors which independently may cause fragility fracture, whilst fracture-based criteria may exclude populations at risk who also should be treated. More recently, fracture risk calculators, such as the FRAX® algorithm, developed by Professor John Kanis and his team at the University of Sheffield, have facilitated assessment of an individual's fracture risk using clinical risk factors such as age, previous fractures, positive family history, etc. with only partial consideration of BMD. In 2019, FRAX® was available in 65 countries including 10 Asian, 35 European, 9 from the Middle East & Africa, 2 from North America, 7 from Latin America, and 2 from Oceania. Since 2018, Serbia also has a country-specific risk estimator in FRAX®. While it is important to

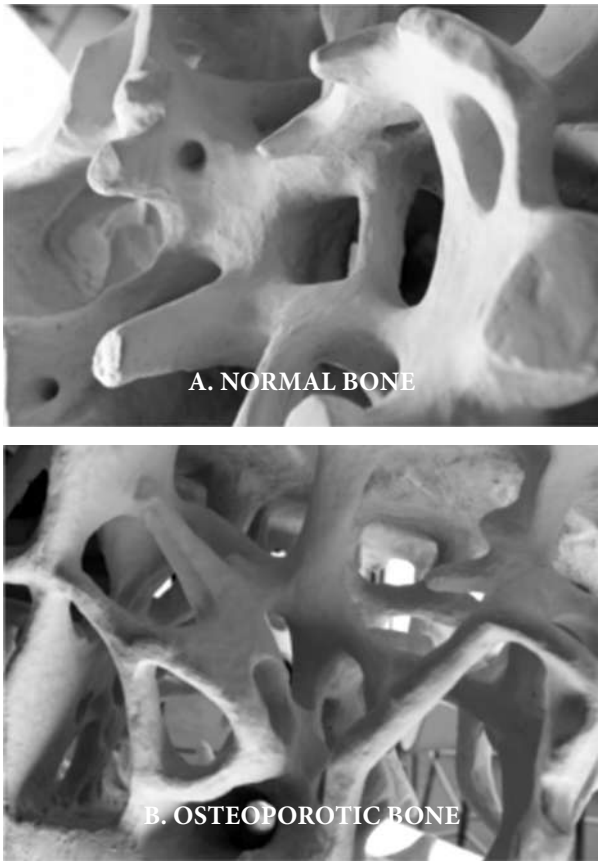

Figure 1. A. Normal vs. **B.** osteoporotic bone
Slika 1. A. *Normalna i* ***B.*** *osteoporotična kost*

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Abbreviations

WHO – World Health Organization
SD – standard deviation
BMD – bone mineral density
FRAX – fracture risk assessment
RCT – randomized controlled trial
US – United States

have a reliable screening tool to identify high-risk patients for interventions, it is equally or more important to have intervention thresholds appropriate for the country or populations. FRAX® is now a part of 120 guidelines and many are using it for treatment decision making even without BMD [4].

Osteoporosis has a systemic nature and because of it associated increase in fracture risk is present at all skeletal sites, although hip, wrist and spine are considered as prototypical osteoporotic fractures and they are strongly associated with BMD reduction. However, the incidence of all other fractures (non-hip, non-vertebral) is much higher and collectively these fractures result in more immense economic burden for the society [5].

Hip fractures, associated with pain and an inability to put weight on the affected leg, usually require surgical treatment and are correlated with substantial decline in functional status and quality of life, more than all other types of fractures, high mortality (21% to 30% of patients who experience a hip fracture die within 1 year), and consequent medical costs. An estimated 2.7 million hip fractures occurred in 2010 worldwide, of which 1 364 717 (51%) were calculated to be potentially preventable (264 162 in men, and 1 100555 in women), if osteoporosis (defined as a femoral neck T score of – 2.5 SD or less) could be avoided [6].

Although various treatment modalities for osteoporosis have been shown to be highly effective, there is evidence to suggest that only a minority of patients receive treatment. At the turn of the century, 9 million fragility fractures occurred annually. This included 1.6 million hip fractures which impose a devastating burden on sufferers and their families, and all too often result in premature death. The 1.4 million individuals who sustained vertebral fractures endure back pain, loss of height and many other adverse effects on the quality of their lives. The cost that osteoporosis imposes on healthcare budgets is staggering. In 2010, the European Union countries spent € 37 billion (US$ 40 billion), while in 2015 the United States (US) spent US$ 20 billion [7]. A recent report issued by the US National Osteoporosis Foundation estimated that 2 million Americans had 2.3 million osteoporotic fractures in 2015, with only 9% undergoing BMD testing within 6 months of the fracture. During the first 2 – 3 years after fracture, a succeeding fracture occurred in 307 000 of these individuals incurring a cost of more than 6.3 billion US dollars [8].

This untreated population with osteoporosis is referred to as 'the osteoporosis treatment gap', and recent studies have sought to introduce interventions to reduce it [7]. Despite the introduction of fracture risk assessment tools, and variety of available drugs, there has been a reduction in prescribing treatment for osteoporosis in

Table 1. Anti-fracture efficacy of approved treatments for postmenopausal osteoporosis
Tabela 1. *Antifrakturna efikasnost osteoporotskih lekova*
Available at http://www.worldosteoporosisday.org/sites/default/WOD-2019/resources/compendium/2019-IOF-Compendium-of-Osteoporosis

	Effect on vertebral fracture risk/*Efekat na vertebralne frakture*	Effect on non-vertebral fracture risk/*Efekat na nevertebralne frakture*	Effect on hip fracture risk/*Efekat na prelome kuka*
Alendronate/*Alendronat*	+	+	+
Risedronate/*Risendronat*	+	+	+
Ibandronate/*Ibandronat*	+	–	–
Hormone replacement therapy *Hormonska supstituciona terapija*	+	+	+
Zoledronic acid/*Zolendrična kiselina*	+	+	+
Raloxifene/Bazedoxifene *Raloksifen/Bazedoksifen*	+	–	–
Teriparatide/*Teriparatid*	+	+	–
Abaloparatide/*Abaloparatid*	+	+	–
Denosumab/*Denosumab*	+	+	+
Romosozumab/*Romosozumab*	+	+1	+1

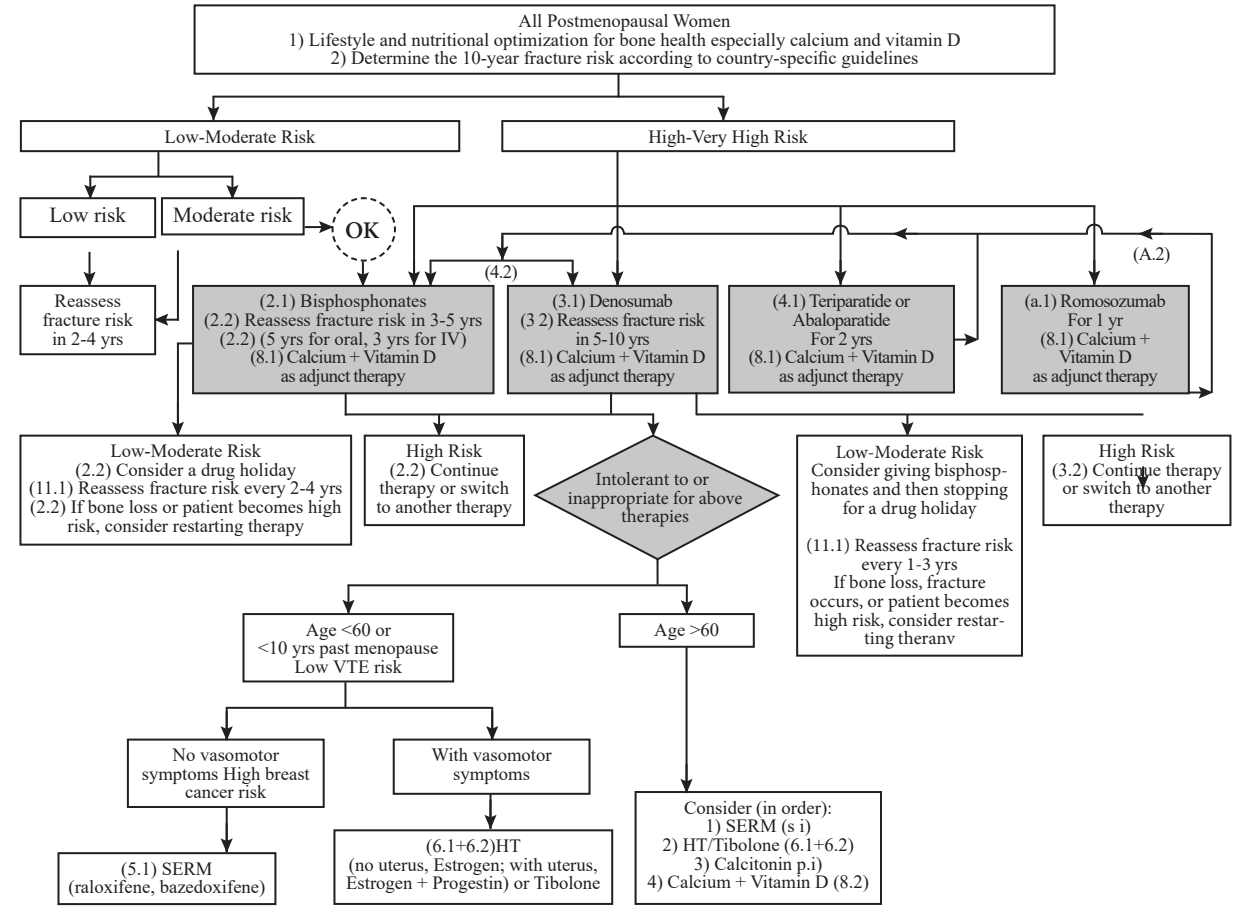
Legend: + significant reduction of fracture in randomized placebo-controlled clinical trials (RCTs) of variable duration (18 months to 6.8 years); - not demonstrated in primary risk; +1 in sequence with alendronate vs alendronate alone
Note: results from subgroup and post-hoc analyses or meta-analyses have not been considered.
As of September 2019, romosozumab has been approved in Australia, Canada, Japan, South Korea and the United States of America. Abaloparatide has been approved in the United States of America.
Legenda: + značajno smanjenje incidence preloma u randomizovanoj placebo kontrolisanim kliničkim studijama (RCT) različite dužine trajanja (od 18 meseci do 6,8 godina); - Nije dokazano u RCT; +1 u sekvenci sa alendronatom u odnosu na primenu samo alendronata
Napomena: rezultati subgrupa i post-hok analiza ili meta-analiza nisu uzimane u razmatranje.
Od septembra 2019. godine Romosozumab je registrovan u Australiji, Kanadi, Južnoj Koreji i Sjedinjenim Američkim Državama. Abaloparatid je registovan u Sjedinjenim Američkim Državama.

some developed countries, United Kingdom and United States of America included [9, 10]. This trend may reflect inadequate spotlighting in the mass media of rare adverse events associated with bisphosphonate use, such as osteonecrosis of the jaw and atypical femoral fractures [7]. There is, however, little evidence to suggest that the risk of these adverse events is significantly higher in individuals taking bisphosphonates for 10 years, compared to age-matched controls [11].

In order to increase identification of individuals at risk of fracture, prescribing rates of osteoporosis drugs, and thus reduce the osteoporosis treatment gap, vigorous screening programs are required. The WHO recommends that individuals be identified as either at high, medium or low risk of fracture. Following this, they recommend that high-risk individuals be considered for treatment, low-risk individuals not be recommended for treatment and medium-risk individuals be further assessed with a measurement of BMD [2]. Studies and trials from different countries and regions (Aberdeen, COSHIBA, ROSE and SCOOP) had major findings pointing out that allocation to screening increased the prescription of osteoporosis medications, reduced fracture incidence and risk of fracture (any site) in the screened groups [12–15].

The role of calcium supplementation, with or without vitamin D, has been the subject of considerable scientific debate in the literature during the last years. In the 2019 Compendium, on the basis of the current evidence, the International Osteoporosis Foundation and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases recommended that calcium and vitamin D supplements are generally appropriate for those with a high risk of calcium and vitamin D insufficiency and those who are receiving treatment for osteoporosis [7]. The objective of treating osteoporosis is to reduce the likelihood of fragility fractures by strengthening the skeleton and decreasing the fall frequency, or both. Healthy life style (good nutrition, regular physical activity, unfavorable lifestyle habits avoidance) are recommended for all patients at risk of osteoporosis. During the last three decades, a broad range of therapeutic options have become available to reduce risks of fragility fractures. These medicines are available in a uniquely flexible array of dosing regimens,

Scheme 1. Endocrine Society Guideline Update
Shema 1. *Dopunjeni vodič Endokrinološkog društva*



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which includes daily, weekly or monthly oral tablets, daily, three-monthly and six-monthly injections, or annual infusions [7]. The anti-fracture efficacy of the most commonly used agents for postmenopausal osteoporosis is summarized in **Table 1.**

The Endocrine Society has updated treatment guidelines for osteoporosis in postmenopausal women to include or alter treatments with romosozumab, selective estrogen receptor modulators, menopausal hormone therapy and tibolone, calcitonin, and calcium and vitamin D. The update was published in February this year in *The Journal of Clinical Endocrinology &Metabolism*. It was issued, in part, due to the recent approval of romosozumab, a monoclonal antibody targeting sclerostin. The treatment was approved by the United States Food and Drug Administration, the European Medicines Agency, and Health Canada [16] **(Scheme 1).**

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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

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IMAGE-DERIVED INDEX – AS A PARAMETHER FOR THE SEMI-QUANTITATIVE ASSESSMENT OF GLOBAL TUBULAR RENAL FUNCTION

INDEKS DOBIJEN SA SCINTIGRAFSKE SLIKE KAO PARAMETAR ZA SEMIKVANTITATIVNU PROCENU UKUPNE TUBULARNE BUBREŽNE FUNKCIJE

Jelena SAMAC[1], Radmila ŽERAVICA[1, 2], Branislava ILINČIĆ[1, 2], Marija VUKMIROVIĆ PAPUGA[1], Dragan BURIĆ[1] and Tanja OSTOJIĆ[1]

Summary

Introduction. Radionuclide methods are used in the evaluation of different aspects of renal function. The aim of this study was to define and implement an index derived from scintigraphic image and to compare it with ortho-iodohippurate clearance values, an indicator of effective renal plasma flow. **Material and Methods**. A retrospective analysis included 67 adult patients, who underwent static renal scintigraphy and ortho-iodohippurate clearance. We computed the background-to-renal index that represents the ratio of average values of counts per pixel in the background regions and in the regions of kidneys. Patients were divided into three groups according to the values of measured effective renal plasma flow: group 1 - patients with mild renal dysfunction (reduction of effective renal plasma flow ≤ 20%, 17 patients), group 2 - moderate dysfunction (reduction of effective renal plasma flow 20–50%, 25), and group 3 - severe dysfunction (reduction of effective renal plasma flow 50–70%, 25 patients). **Results.** Subjects with mild effective renal plasma flow reduction had significantly lower background-to-renal index values compared to those with moderate and severe reduction [(0.105 ± 0.05) vs. (0.134 ± 0.056) vs. (0.275 ± 0.154), p < 0,001]. A significant linear correlation was found between background-to-renal index and effective renal plasma flow (r = 0.60, p < 0.0001). Sensitivity and specificity of the calculated cut-off value of 0.1335, for the differentiation between the patients with renal reduction higher and lower than 20%, were 62% and 100%, respectively (area under curve 0.85). **Conclusion.** The background-to-renal index is a simple method for semi-quantitative estimation of global tubular renal function that can be a useful tool when determining patients for further in vitro assessment of global renal function.

Key words: Radionuclide Imaging; Perfusion Imaging; Glomerular Filtration Rate; Renal Plasma Flow; Succimer

Sažetak

Uvod. Radionuklidne metode imaju značajnu ulogu u ispitivanju različitih aspekata bubrežne funkcije. Cilj je bio da se definiše i primeni indeks dobijen sa scintigrafske slike, kao i da se njegove vrednosti uporede sa dobijenim vrednostima klirensa hipurana, pokazatelja ukupnog efektivnog bubrežnog protoka plazme. **Materijal i metode.** Retrospektivno je analizirano 67 pacijenata kojima je urađena statička scintigrafija bubrega i klirens hipurana. Računanje indeksa koji predstavlja odnos broja detekcija u pozadini i u bubrezima, podrazumevao je odnos srednjih vrednosti broja detekcija po pikselu u regijama okolnog tkiva sa srednjim vrednostima broja detekcija po pikselu u regijama bubrega. Pacijenti su podeljeni u tri grupe u odnosu na dobijenu vrednost efektivnog bubrežnog protoka plazme: grupa 1 – blaga bubrežna disfunkcija (redukcija efektivnog bubrežnog protoka plazme ≤ 20%, N = 17), grupa 2 – umerena disfunkcija (redukcija efektivnog bubrežnog protoka plazme 20–50%, N = 25) i grupa 3 – teška disfunkcija bubrega (redukcija efektivnog bubrežnog protoka plazme 50–70%, N = 25). **Rezultati.** Kod pacijenata sa blagom redukcijom efektivnog bubrežnog protoka plazme uočene su značajno niže vrednosti *background-to-renal index*, u poređenju sa pacijentima sa srednjom i teškom redukcijom [(0,105 ± 0,05) vs. (0,134 ± 0,056) vs. (0,275 ± 0,154), P < 0,001]. Značajna linearna korelacija uočena je između *background-to-renal index* i efektivnog bubrežnog protoka plazme (r = 0,60, p < 0,0001). Vrednost *background-to-renal index* od 1,3 sa 62% senzitivnošću i 100% specifičnosti diferencira pacijente sa blagom ili umerenom bubrežnom disfunkcijom. **Zaključak.** *Background-to-renal index* predstavlja jednostavnu metodu za semi-kvantitativnu procenu ukupne tubulske bubrežne funkcije i može biti koristan u pravcu odlučivanja za dalju evaluaciju globalne bubrežne funkcije *in vitro* metodama.

Ključne reči: radionuklidni imidžing; perfuzioni imidžing; brzina glomerularne filtracije; bubrežni protok krvi; DMSA

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Abbreviations

DMSA – 2.3-dimercaptosuccinic acid
OIH – ortho-iodohippurate
ERPF – effective renal plasma flow
BRI – background-to-renal index
AUC – area under curve
GRU – global renal uptake
SPECT – single photon emission tomography
ROC – receiver operating characteristic curve
ROI – region of interest

Introduction

Radionuclide methods are used in the evaluation of different aspects of renal function after intravenous injection of radioisotopes by blood volume/time (ml/min) measurements (glomerular filtration rate, effective renal plasma flow) or visualization in the form of images or graphic display (renal scintigraphy, sequential study, renography).

In the evaluation of renal function, ^{99m}Tc-2.3-dimercaptosuccinic acid (DMSA) scintigraphy is used for quantitative analysis of individual renal function by calculating the uptake ratio and represents a gold standard in detection of cortical abnormalities related to urinary tract infection. ^{131}I-ortho-iodohippurate (OIH) clearance is used for measuring the effective renal plasma flow (ERPF) and tubular function. Measurement of absolute clearances of these radiopharmaceuticals provides quantitative information concerning global renal function. Scintigraphy provides an image of the functional renal parenchyma, and the renal uptake of ^{99m}Tc-DMSA has been shown to correlate well with the ERPF [1, 2].

Attempts to quantify global renal uptake (GRU) using ^{99m}Tc-DMSA scintigraphy were made soon after it became available in clinical practice. However, the number of uncertainties, caused by lack of standardization, production by different manufacturers, labelling, analogue imaging equipment etc. slowed down further progress [3]. Quantification of DMSA renal uptake, by using single photon emission tomography (SPECT), was considered to be a reliable technique for GRU measurement [4–6]. Recently, some image-derived quantitative and semi-quantitative parameters have been proposed for assessing different renal anatomical and functional characteristics from ^{99m}Tc-DMSA planar scintigraphy or SPECT, both in children and adults [7–11]. Unlike quantitative, semi-quantitative analysis does not require data obtained by standard, precise activity measurements, detector efficiency, activity correction for radioactive decay etc., and thus does not provide information about the amount of activity in certain regions of interest (ROI). However, it can be used to determine relative radioactivity ratio in two or more ROI within the same system of radiopharmaceutical distribution, such as a static scintigraphy image.

To the best of our knowledge, there are no recommendations on the semi-quantitative GRU assessment using ^{99m}Tc-DMSA scintigraphy images. We aimed to define and implement a simple image-derived index and to test its value in decision making when determining patients for OIH-clearance, which represents the limitation in clinical, economic and radiation protection terms.

Material and Methods

A retrospective analysis included a total of 67 adult patients who were referred to the Nuclear Medicine Department for evaluation of renal function between 2017 and 2019 and who underwent both DMSA scintigraphy and ^{131}I-OIH clearance. Two examinations were performed between 2 and 7 days apart. The study was approved by the Ethics Committee of the Clinical Centre of Vojvodina.

All patients were divided into three groups according to the values of measured ERPF by ^{131}I-OIH clearance method: the first group included patients with a mild renal dysfunction (reduction of ERPF ≤ 20%, N=17), the second group included those with a moderate renal dysfunction (reduction of ERPF by 20 – 50%, N=25), whereas the third group included those with severe renal dysfunction (reduction of ERPF by 50 – 70%, N=25). Exclusion criteria were a solitary kidney, congenital renal position malformations and anomalies, congenital and acquired tubular disorders, ERPF reduction over 70% and body mass index (BMI) > 35 kg/m^2.

DMSA static scintigraphy

The ^{99m}Tc-DMSA was prepared by adding freshly eluted ^{99m}Tc to a commercially available cold kit (Institute of Nuclear Sciences "Vinča", Serbia). Radiochemical purity of every labelled vial was determined to be > 95%, using paper chromatography. Dual head gamma camera (Symbia E, Siemens, Germany) with low energy high resolution collimators was used to obtain anterior-posterior (AP) and posterior-anterior (PA) images, with a patient in the supine position. Two hours after injecting 74 MBq of ^{99m}Tc-DMSA, planar static images were taken using 256 x 256 matrix and 500,000 counts.

ERPF measurement by ^{131}I-OIH clearance method

The ^{131}I-OIH clearance method was performed using a single injection of 1.5 MBq of ^{131}I-OIH, and by taking two blood samples, 20 and 30 minutes post injection, according to Blaufox single compartment, slope intercept method [12]. Radioactivity in the plasma was measured using a gamma counter (Captus 3000, Capintec), by selecting measurement channels appropriate for the energies of ^{131}I gamma peaks (3 photopeaks, 364 keV, 637 keV and 284 keV, window widths 18%, 14% and 21%, respectively). The ^{131}I-OIH used for performing isotopic clearance had a radiochemical purity of > 99.9%, determined by the manufacturer (INN "Vinča"). The ERPF values were expressed in ml/min/1.73 m^2 and variations in ERPF values compared to reference values (expected values for sex and age) in ml/min and percentages.

Semi-quantitative image analysis

After visual inspection of images, 4 ROI, one around each kidney and two background ROIs in the external inferior region of each kidney, were drawn on PA images. The number of counts and number of pix-

els were noted for each ROI. Background-to-renal index (BRI) was calculated using the following formula:

$$\frac{Left\ Kidney\ [\text{cts}] + Right\ Kidney\ [\text{cts}]}{NLeft\ Kidney\ [\text{pixels}] + NRight\ Kidney\ [\text{pixels}]} = C\ [\text{cts/pixel}]$$

$$\frac{Left\ Bckg\ [\text{cts}] + Right\ Bckg\ [\text{cts}]}{NLeft\ Bckg\ [\text{pixels}] + NRight\ Bckg\ [\text{pixels}]} = B\ [\text{cts/pixel}]$$

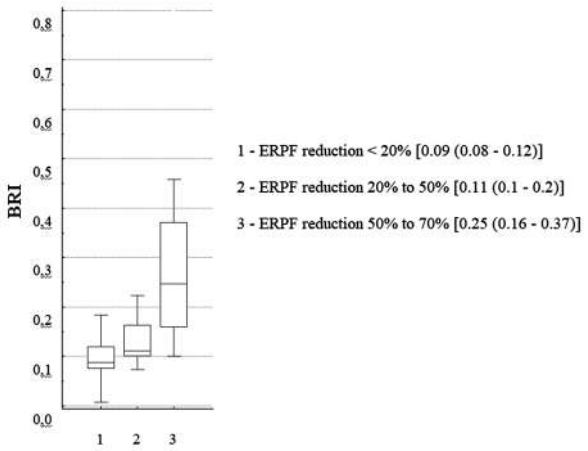
$$BRI = \frac{B}{C - B}$$

The formula shows that numbers used for calculating BRI are average numbers of counts per pixel in the regions of kidneys and regions of background, in order to compensate for the differences in ROIs sizes. Also, the formula shows that background correction was performed. Reproducibility of the ROI-based measurements was observed in all patients, whose measurements were taken within one hour by both nuclear medicine specialist and medical physicist. The coefficient of variation (intraobserver and interobserver) for measurements was 2.8% and 3.2%, respectively.

The normality of continuous variables was assessed with Shapiro-Wilk test. Data are presented using descriptive statistical methods, continuous variables as mean ± standard deviation, median (Q1 – Q3), while categorical data were summarized as percentages. The dichotomous variable differences between defined groups (Mild vs. Moderate vs. Severe ERPF reduction) were tested by using χ^2 test and continuous variables by using t-test, Man–Whitney test, and Kruskal–Wallis H nonparametric with post-test for multiple comparisons of mean values. A receiver operating characteristic curve (ROC) was used to compare the diagnostic value of BRI compared with OIH-clearance, trying to distinguish between mild reduction (less than 20%) on one hand, and severe and moderate reduction (more than 20%) on the other [13]. This cut-off was used to calculate the sensitivity and specificity of BRI in estimation of renal dysfunction. A two-tailed $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the MedCalc Statistical Software version 19.2.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

The **Table 1** shows characteristics of the study group.

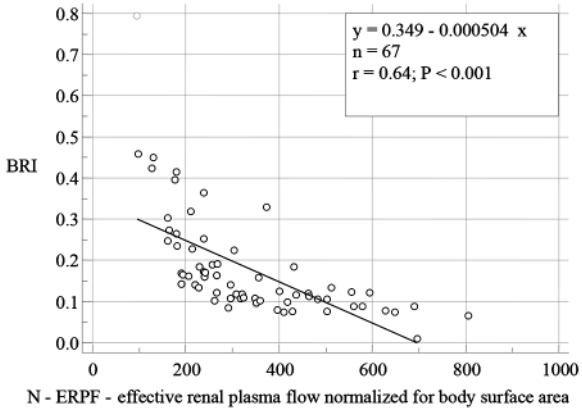


Graph 1. BRI values in groups defined by the percentage of ERPF reduction
Grafikon 1. *Vrednosti BRI u grupama definisanim u odnosu na procenat redukcije EBPP*
Legend: BRI – background-to-renal index; ERPF - reduction of effective renal plasma flow
Legenda: BRI – background-to-renal index, EBPP – efektivni bubrežni protok plazme

Table 1. Characteristics of the study group
Tabela 1. *Karakteristike ispitivane grupe*

	Mild ERPF reduction *Blaga redukcija EBPP* (≤ 20%) N = 17	Moderate ERPF reduction *Umerena redukcija EBPP* (20 – 50%) N = 25	Severe ERPF reduction *Teška redukcija EBPP* (50 – 70%) N = 25	p
Age (years)/*Starost (godine)*	45.47 ± 15.6[b,c]	59.48 ± 13.79[a]	62.48 ± 14.65[a]	0.001
Male sex/*Muški pol (n/N)*	8/17	13/25	16/25	0.511
BMI/*ITM (kg/m²)*	25.9 ± 4.58	26 ± 4.65	26.82 ± 4.1	0.921
BRI/*BRI*	0.09 (0.08 – 0.12)	0.11 (0.1 – 0.2)	0.25 (0.16 – 0.37)[a,b]	< 0.001
R – ERPF/*R – EBPP (%)*	0.02 ± 0.12[b,c]	- 0.35 ± 0.08[a,c]	-0.62 ± 0.08[a,b]	< 0.001
N – ERPF/*N – EBPP (ml/min/1.73 m²)*	553.73 ± 113.6[b,c]	341.3 ± 73.3[a,c]	193.5 ± 48.3[a,b]	< 0.001
E – eRPF/*O – EBPP (ml/min/1.73 m²)*	563.04 ± 60.8[c]	531.2 ± 72.7	508.5 ± 62.3[a]	0.041

Legend: Continuous variables are expressed as mean ± SD; median (Q1 - Q3); age – median (min - max); BMI - body mass index; BRI – background-to-renal index; R -ERPF – reduction of effective renal plasma flow; N–ERPF – effective renal plasma flow normalized to body surface area; E–ERPF - effective renal plasma flow expected according to age and sex; [a]Krushall–Walis test, (post hoc test), $p < 0.05$ vs. mild ERPF reduction; [b]Krushall–Walis test, (post hoc test), $p < 0.05$ vs. moderate ERPF reduction; [c]Krushall–Walis test (post hoc test), $p < 0.05$ vs. severe ERPF reduction
Legenda: Kontinuirane varijable su prikazane kao srednja vrednost ± SD; medijana (Q1-Q3), godine života – medijana (min-max). ITM – indeks telesne mase; BRI – background-to-renal index; R -EBPP – redukcija efektivnog bubrežnog protoka plazme; N –EBPP – efektivni bubrežni protok plazme normalizovan na telesnu površinu; O–EBPP– efektivni bubrežni protok plazme očekivan za godine života i pol. [a]Krushall–Walistest, (post hoct est), p< 0,05 vs. Blaga EBPP redukcija; [b]Kruskal–Volisov test, (post hoc test), p < 0,05 vs. Umerena EBPP redukcija; [c]Kruskal–Volisov test, (post hoc test), p < 0,05 vs. Teška EBPP redukcija

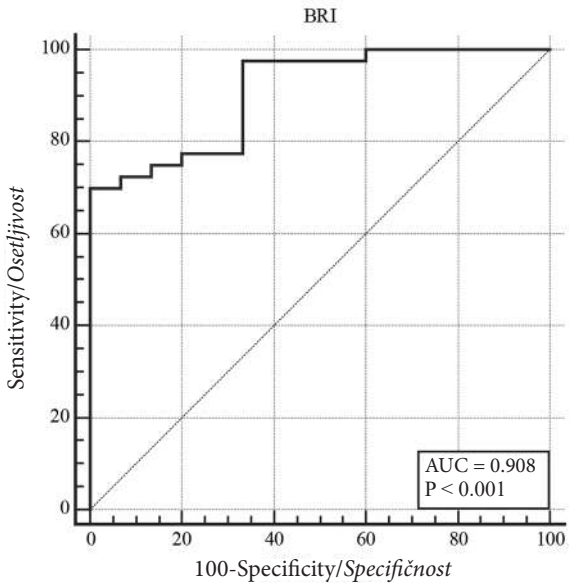


Graph 2. Corelation between BRI and effective renal plasma flow

Grafikon 2. *Korelacija između vrednosti BRI i efektivnog bubrežnog protoka plazme*

Legend: BRI – background-to-renal index; N–ERPF – effective renal plasma flow normalized for body surface area

Legenda: BRI – background-to-renal index, N-EBPP – normalizovani efektivni bubrežni protok plazme na telesnu površinu



Graph 3. ROC curve for the model investigating BRI in patients with mild ERPF reduction (< 20%)

Grafikon 3. *ROC kriva za model u kome se ispituje vrednost BRI kod pacijenata koji imaju blagu redukciju EBPP (< 20%)*

Legend: BRI - background-to-renal index, AUC - area under curve

Legenda: BRI – background-to-renal index, AUC – površina ispod krive

The differences between age groups were significant ($p < 0.05$, for all). There was no significant difference among groups in terms of sex and BMI. Considering BRI values, we observed a statistically significant trend of BRI increase with R-ERPF decrease **(Graph 1).**

The subjects with mild ERPF reduction had significantly lower BRI values compared to those with severe reduction [0.09 (0.08 – 0.12) vs. 0.25 (0.16 – 0.37), $p < 0{,}001$]. Also, subjects with severe ERPF reduction had significantly higher BRI values compared to those with moderate ERPF reduction [0.11 (0.1 – 0.2) vs.0.25 (0.16 – 0.37), $p < 0{,}001$]. A significant linear correlation was found between BRI and E–ERPF ($r = 0.60$, $p < 0.0001$) **(Graph 2).**

Graph 3 shows the ROC curve of BRI as a diagnostic tool predicting the degree of renal dysfunction. In this analysis, 20% ERPF reduction was used to discriminate the patients with mild reduction on one hand, and those with moderate and severe reduction on the other. A cut-off value of BRI = 0.1335 was fund to be able to distinguish between the two groups, with the sensitivity of 62% and specificity of 100% (AUC = 0.85, SE = 0.05, 95% CI 0.74 – 0.92).

Discussion

The main task of radionuclide techniques applied in nephrourology is quantification of renal function, which is information not easily obtained by other diagnostic modalities. In this paper, we have introduced BRI for the estimation of global renal dysfunction, obtained through semi-quantitative analysis of static ^{99m}Tc-DMSA scintigraphy. We tested the potential application of this index, derived from renal scans, in clinical practice.

The results of our study show that this parameter may be a useful indicator in the precise assessment of global renal function by OIH clearance method in previously selected cases. In our study we have selected patients with symmetrical ^{99m}Tc-DMSA distribution in cortical mass, whereas the kidneys with serious defects in radiopharmaceutical uptake caused by other renal diseases (congenital malformations, hydronephrosis, multiple cysts, scarring etc.) were excluded among other reasons due to the inability to precisely draw ROIs around the kidney.

For the assessment of ERPF, we used an OIH-clearance, as the reference method and a well known indicator of tubular function. Our semi-quantitatively derived parameter could represent the global tubular function as well, considering that mechanism of ^{99m}Tc-DMSA uptake in the renal cortex reflects the receptor-mediated endocytic activity in the proximal tubule [14]. Previously, Nimmo et al. [1] reported that other semi-quantitative renal parameters such as relative renal function, can be measured equally well in most cases using ^{99m}Tc-DMSA and ^{131}I-OIH, as a result of the same binding mechanism of the two radiopharmaceuticals.

We have shown that BRI correlates with the extent of ERPF reduction. The BRI was calculated by processing the scintigraphy images, as the ratio of average number of counts per pixel in the regions of background, and the average number of counts per pixel in the kidney regions, where the latter was previously corrected for background. Several factors may influence the quantification of renal uptake from scintigraphy images, such as background correction [15, 16], renal depth correction [15, 17, 18], or size and

place of ROIs [19, 20]. We applied background correction prior to calculation of the BRI. The index we introduced is a unitless value, semi-quantitative i.e. relative ratio of the activity in the background and the activity in the kidney, as opposed to quantitative i.e. absolute measure of renal uptake, so we considered that depth correction is not necessary. Hence, the ROIs were drawn in the PA image only, which is in accordance with other methods for semi-quantitative image analysis [21]. Size and place of the chosen ROI is the subject of several interobserver studies. While some older papers [19, 20] agree on the existence on interobserver variabilities and the need for standardization of protocols, others [22, 23] found that the use of standardized criteria for the interpretation leads to low variability between observers.

The sensitivity and specificity of the calculated cut-off value of 0.1335, for the differentiation between the patients with renal reduction higher and lower than 20%, are 62% and 100%, respectively (AUC 0.85). Other papers show similar values of sensitivity and specificity of semi-quantitative image-derived parameters. Hitzel et al. [24] found a cut-off value of C70% index, derived from the 99mTc-DMSA scintigraphy during acute pyelonephritis in children, in order to predict scarring. This author reports the cut-off value of 0.45 with the sensitivity of 83% and specificity of 78% and concludes that this value may be useful for detecting kidneys at risk of scarring. Demir et al. [11] used the same C70% index in children with pyelonephritis, and calculated the cut-off value to distinguish between normal and defected kidneys, previously categorized by visual analysis. The authors reported a cut-off value of 0.34 with sensitivity of 55% and specificity of 100% (AUC 0.79), and concluded that this method might show significant interobserver variation and suggested that other quantitative parameters were needed to make more objective evaluations. Sampedro et al. [10] proposed a computational framework for the observer-independent quantification of structural renal damage in DMSA scans. They reported that their lesion detection, segmentation and measurement form distribution histogram system was able to distinguish DMSA positive from negative images, with the sensitivity of 81% and the specificity of 94% (AUC 0.92), as well as to detect the permanent renal damage with sensitivity of 100% and specificity of 75% (AUC 0.86). With these results, authors stated that the proposed framework had a potential to complement visual diagnosis and non-imaging indicators.

There are a number of papers on the quantification of absolute renal uptake of ^{99m}Tc-DMSA [25], some from planar images [26], and others from SPECT [4–6], both in children [27, 28] and in adults [8, 26, 29]. They all had in common to precisely measure injected activity (as a difference in measured activity in syringe before and after injection), apply corrections for kidney depth, use phantoms, and all apply decay correction in order to quantify absolute renal uptake. As for semi-quantitative methods, determining left-to-right ratio, i.e. relative renal function, is a well established and routinely used method in clinical practice. However, to the best of our knowledge, there are no papers on semi-quantitative indices for the assessment of global renal function and comparison of such indices with ERPF. Moreover, there were no published papers regarding ERPF in the past couple of years; one of the possible reasons may be that OIH is not a registered radiopharmaceutical in most countries. On the other hand, our nuclear medicine department uses OIH routinely for many years to determine ERPF; hence one of our goals is to share our experience and results regarding this radiopharmaceutical.

Limitations of the study: possible need of renal depth correction, time of imaging - results are comparable for scintigraphic images obtained 2 – 3 hours post injection, other factors that may interfere with accumulation of radiopharmaceutical in the target tissue, a small number of patients.

Further research should focus on the follow up of patients, with the aim to investigate the reproducibility of BRI index in the same patients on repeated examinations and to assess BRI values as a predictor of changes that may occur in the kidneys.

Conclusion

We believe that the index we introduced is a simple method for a semi-quantitative estimation of global tubular renal function, while its cut-off value may be a useful tool when determining whether the patient should undergo further in-vitro assessment of global renal function. However, further verification may be necessary before its application in routine clinical practice.

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SOCIAL PARTICIPATION OF ONCOLOGY PATIENTS OVER 60 YEARS OF AGE

SOCIJALNA PARTICIPACIJA ONKOLOŠKIH PACIJENATA STARIJIH OD ŠEZDESET GODINA

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Summary

Introduction. Social participation is a critically important aspect of life in older adults. Also, it is one of the major subjects of research in the field of aging. Old age and its implications can have both positive and negative effects on social participation in the elderly population. Older oncology patients also face additional challenges in achieving active aging and full social participation. The goal of this study was to establish the prevalence and variety of social participation of oncology patients over the age of 60, as well as to determine any possible correlation between specific demographic characteristics and social participation. **Material and Methods.** The study included 100 persons aged 60 to 92 treated for malignant diseases. The Maastricht social participation profile and a demographic questionnaire designed for the purpose of this study were used as research instruments. Data analysis included the t-test for independent samples, correlation analysis, linear regression analysis, and one way analysis of variance. **Results.** Persons over the age of sixty have a low level of social participation, particularly in the domains of contacts with friends and family. A statistically significant difference was found in social participation in regard to different demographic characteristics: type of residence ($t = 6.765$, $p < .01$) and disability ($t = 5.663$, $p < .01$), and age ($R = 0.478$, $p < .01$). There were no statistically significant differences in regard to gender, education and presence/absence of chronic disease. **Conclusion.** Oncology patients over the age of 60 have a very low social participation. Considering its importance for health and quality of life in the elderly, it is crucial to develop a support system for these persons and to recognize the significance of including social support in the care of this population.

Key words: Social Participation; Patients; Medical Oncology; Aging; Aged; Demography

Sažetak

Uvod. Socijalna participacija predstavlja veoma važan aspekt života starih osoba. Takođe, predstavlja jednu od centralnih tema u istraživanjima starenja. Starost kao i druge implikacije kod ove populacije mogu ostavljati i pozitivne i negativne efekte na socijalnu participaciju. Stare osobe koje su i onkološki pacijenti imaju dodatne izazove u procesu dostizanja aktivnog starenja i pune socijalne participacije. Cilj ovog istraživanja bio je da se odredi učestalost i raznolikost socijalne participacije osoba starijih od šezdeset godina koje su onkološki pacijenti, kao i da se utvrdi povezanost između određenih sociodemografskih karakteristika i socijalne participacije ovih osoba. **Materijal i metode.** Istraživanje je obuhvatilo 100 osoba starosti od 60 do 92 godine koji su lečeni od malignih tumora. Korišćeni su instrumenti *Mastriht* profil socijalne participacije i sociodemografski upitnik koji je konstruisan u svrhu ovog istraživanja. Da bi se dobili odgovori na postavljene ciljeve sproveden je t-test za nezavisne uzorke, korelaciona analiza, linearna regresiona analiza i jednosmerna analiza varijanse. **Rezultati.** Osobe starije od šezdeset godina imaju nizak nivo socijalne participacije, a posebno niski rezultati su u domenima kontakta sa prijateljima i kontakta sa porodicom. Postoji statistički značajna razlika u izraženosti socijalne participacije u odnosu na različite sociodemografske karakteristike: mesto stanovanja ($t = 6,765$, $p < ,01$), invaliditet ($t = 5.663$, $p < ,01$), starost ($R = 0,478$, $p < ,01$). Ne postoji statistički značajna razika u odnosu na pol, obrazovanje i prisustvo/odsustvo hronične bolesti. **Zaključak.** Onkološki pacijenti stariji od 60 godina imaju veoma nisku socijalnu participaciju. Imajući u vidu njen značaj za zdravlje i kvalitet života starih osoba, neophodno je razviti sistem podrške ovim osobama i prepoznati uključivanje i podršku zajednice kao važnu komponentu usluga i podrške ovoj populaciji.

Ključne reči: socijalna participacija; pacijenti; onkologija; starenje; osobe starije životne dobi; demografija

Introduction

Old age is a period of life when biological, psychological and social potentials are in constant decline. The elderly are a vulnerable population group whose needs are highly specific, varied and complex. While the aged population is growing, the life expectancy is getting higher [1].

Aging, old age, quality of life, and life of the elderly in general, are topics that draw attention of professionals of different profiles, as well as of the general population worldwide, particularly in the last few years [2]. The increasing percentage of older adults in the general population requires from the social community to recognize their needs and provide adequate support [2, 3].

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Abbreviations
MSPP – Maastricht Social Participation Profile

The World Health Organization defines old age as the age of 60 years and over and divides it into three groups: elderly persons (60 to 75 years of age), old persons (76 to 90) and very old persons (over 90 years of age) [4].

Demographically, Serbia is an "old country" by all conventional criteria of population aging [5]. According to the estimates made in 2017, by the State Institute for Statistics of the Republic of Serbia, the percentage of people aged 65 and over in the total population was 19.6% [6]. The reasons for increased proportion of the elderly in general population in the recent years are numerous. The proportion of the young in the general population has been reduced by half, while the proportion of the elderly has increased more than threefold. Among other factors, the increase is due to higher life expectancy, influenced by recent advances in medicine, particularly prevention and treatment, leading to a drop in mortality rate [7].

Active aging is a more recent term that gained a significant amount of scientific and professional publicity in a short amount of time [5]. It is defined as a process of taking full advantage of health possibilities, participation and safety in order to enhance quality of life in the process of aging [8].

Active aging allows individuals to continuously take part in social, cultural and economic activities according to their needs and possibilities, while being provided with adequate support and care. The main idea in this concept is that persons can be active participants in the life of their families, as well as the society, despite the existing cognitive, physical or other difficulties that often accompany old age [9]. Namely, the word "active" has its social, cultural, economic, civil and spiritual aspects and means a lot more than just physical activity. It takes into account the social participation of persons with disabilities or chronic diseases who, despite their impairment, can contribute to their families, the local community and beyond [10].

Michael et al. describe active aging as a desire and ability of older adults to integrate physical activity, such as walking to public transportation or exercising, into their daily routine. They also emphasize that active aging includes taking part in economic and socially productive activities such as playing in the park with their grandchildren or working in their homes or gardens [11]. In 2011, the European Parliament gave a recommendation to support the policy of active aging in programs and systems of health and social security, and to aim the activities towards these important areas: comprehensive development of elderly persons, quality of life enhancement, and adequate environment structuring [12].

Social participation, as an important aspect of active aging, is a multifaceted concept which still lacks a clear and undisputed definition, although it is commonly used in health and social literature [13–15]. It is regarded as one of the major goals of rehabilitation as well as a basic indicator of health, well-being, and positive social behavior [14, 16–18].

The International Classification of Functioning, Disability and Health (ICF) defines social participation as involvement in life situations, i.e. a person's experience in real-life circumstances and situational contexts. Two components of this concept are specified as capacity and performance. Capacity represents people's abilities, what they can do, regardless of the context, while performance is a capability to adequately apply one's abilities in real-life situations [19].

In the elderly, social participation involves a series of activities such as individually aimed activities (for example hobbies, neighborhood ties etc.) or those that are organized in the community (cultural events, volunteer work, church events, senior citizens homes) [13, 20].

Along with the benefits that social participation has on overall functioning and life of the elderly, studies have focused on identifying all relevant factors that influence social participation in old age. Some studies have focused on personality features [21–25], while others dealt with environmental factors [23, 25, 26] that affect the level of social participation. The analysis of available literature yielded the following factors that were included in most studies: physical ability, social support, depression, disability, chronic and malignant diseases, environment, older age, lower socio-economic status, ethnic minority status, lack of trust, lack of finances, difficulties adjusting to the process of aging, personality features, visual impairment, emotional stress [21, 23–27]. Each of these factors may lead to decreased social participation of the elderly which leads to social isolation, feelings of low self-esteem and loneliness, which in turn leads to certain health problems.

The process of aging is manifested by constant and gradual decreased functioning of organs and organ systems. Consequently, elderly persons are more prone to chronic diseases, followed by gradual loss of ability to function independently [28]. Some of the common conditions in old age include hearing loss, cataract, back and neck pain, degenerative diseases, chronic obstructive lung disease, cardiovascular diseases, diabetes, depression, dementia, and malignant diseases [20].

The impact of oncological diseases or disabilities on social participation of affected individuals has become an important topic of research in the past few decades [29]. Multiple studies point to a correlation between oncological diseases and the onset of disability in the elderly [30, 31]. Also, many studies have found an impact of oncological illnesses and disability on social participation and the degree of variability thereof in older persons [18, 32, 33]. In fact, the onset of health problems represents the main reason for decreasing social participation in old age [34]. Multiple chronic health conditions, which may lead to functional limitations, affect the mobility of the elderly, as well as the relative ease of participating in social activities [33].

The aim of this study was to determine the prevalence and variability of social participation of on-

cology patients over the age of sixty, as well as to identify its demographic determinants. We hypothesized that oncology patients over the age of sixty have a low level of social participation, and that gender, age, comorbidity etc. are significant determinants of their social participation.

Material and Methods

The study was conducted on a sample of 100 participants over 60 years of age who suffered from malignant diseases. The study only included participants who had not been receiving treatment for at least a year. The average age of participants was 73.52 (SD = 7.64). Out of the total 100 participants, 39 were men and 61 women. With regard to education, 32 had a primary education, 41 were high-school graduates, and 27 were college or university graduates. Nearly a half of the sample, 44 participants, were widows/ers, 38 were married, 11 divorced, 5 single and 2 in a romantic relationship. Around 86% of participants had at least one chronic disease. A cardiovascular disease was reported by 39% of participants, a respiratory illness by 19%, a rheumatic disease by 38%, a musculoskeletal disorder by 23%, diabetes by 18%, dementia by 2%, and urinary tract illness by 9%.

Some type of disability was found in as many as 46% of participants. Physical disability was reported by 22 participants, visual impairment by 64, hearing impairment by 14, speech and language difficulties by 5, and intellectual difficulties by 1 participant.

The study was partly conducted at the Senior Citizens Home "Novi Sad" and the Association of Old Age Pensioners of the City of Novi Sad, and partly among community dwelling participants in the wider Novi Sad area. Seventy five participants lived in individual housing, while 25 resided in senior citizens homes. All persons who took part in the study were given a written explanation of the purpose of the study. Participation was completely anonymous and voluntary. Participants were asked questions by interviewers who then recorded the answers in writing. The study was approved by the Ethical Committee of the Faculty of Medicine Novi Sad.

The used questionnaire consisted of two sections. The demographic questionnaire was constructed for the purpose of this study and it gathered information about the participants' age, gender, place of residence (town/village), type of residence (senior citizens home or individual housing), income, education and marital status. This section also included questions on the presence of chronic illnesses and disability. The second part was the Maastricht Social Participation Profile (MSPP). This scale was constructed by Mars GMJ, Kempen GIJM, Post MWM, Proot IM, Mesters I, and van Eijk JTM in 2009 in the Netherlands [35]. It was intended to measure real-life social participation in older adults with chronic illness, and it was based on the definition of social participation given by the participants of the original study. Older adults defined social participation as a positive experience that includes one or more of the following: social contact, contribution to society or social benefits. The questionnaire was intended for persons over 60 years of age. It included 25 items, divided into three sections: social activity, contact with friends, and contact with family.

The Maastricht Social Participation Profile measured the prevalence and variability of social participation (how often people engage in social participation and in how many different types of social participation they were involved in) in the past 4 weeks. All responses were given on the same scale: 0 = never, 1 – 3 = less than once a week, 4 – 8 = once or twice a week, 9 + = more than twice a week. A higher score indicated higher social participation. Social participation was operationalized through the MSPP that consists of 3 subscales: social activity (9 items), contact with friends (8 items), and contact with family (8 items). The instrument was found to have solid metric characteristics. The reliability of the instrument measured by Cronbach alpha coefficient was .909, which is highly reliable, while values of Cronbach alpha coefficients for individual subscales ranged from .744 to .875.

The data obtained in this study were analyzed using the Statistical Package for the Social Sciences package 21.0. In order to check the postulated hypotheses and reach the intended goals we performed methods of descriptive statistics, t-test for independent samples, correlation analysis, linear regression analysis and one way analysis of variance.

Results

The total scores on subscales were calculated by adding scores of the corresponding items. The **Table 1** shows the participants' average scores on subscales and their correlations with each other.

The results indicate a statistically significant positive correlation between all domains of social

Table 1. Descriptive characteristics and correlations between different domains of social participation
Tabela 1. *Deskriptivne karakteristike i povezanost različitih domena socijalne participacije*

Domains/*Domeni*				
Social activity/*Socijalne aktivnosti* M 4.21(SD 3.84)	1	.474**	.413**	.691**
Contact with friends/*Kontakt sa prijateljima* M 11.32(SD 5.76)	.474**	1	.683**	.892**
Contact with family/*Kontakt sa porodicom* M 11.91(SD 6.05)	.413**	.683**	1	.881**
Total score/*Ukupan skor* M 27.44(SD 13.13)	.691**	.892**	.881**	1

**p < .01

Table 2. Differences in social participation between men and women
Tabela 2. *Razlike između muškaraca i žena u socijalnoj participaciji*

Subscale/*Supskale*	Gender/*Pol*	N	M	SD	t	p
Social activity/*Socijalna aktivnost*	Men/*Muškarci*	39	4.74	4.38	1.744	>.05
	Women/*Žene*	61	3.87	3.42		
Contact with friends/*Kontakt sa prijateljima*	Men/*Muškarci*	39	13.47	5.80	-.510	>.05
	Women/*Žene*	61	13.88	6.34		
Contact with family/*Kontakt sa porodicom*	Men/*Muškarci*	39	9.20	5.46	-.685	>.05
	Women/*Žene*	61	9.71	5.78		
Total score/*Ukupan skor*	Men/*Muškarci*	39	27.42	12.85	-.026	>.05
	Women/*Žene*	61	27.46	13.35		

Table 3. The effect of age on social participation
Tabela 3. *Efekat starosti na socijalnu participaciju*

	R	R^2	F	B	SEB	B
Social activity/*Socijalna aktivnost*	.320	.103	28.21**	-.160	.030	-.320**
Contact with friends/*Kontakt sa prijateljima*	.362	.131	37.32**	-.289	.047	-.362**
Contact with family/*Kontakt sa porodicom*	.504	.254	84.264**	-.371	.040	-.504**
Total score/*Ukupan skor*	.478	.228	72.975**	-.821	.096	-.478

**p < .01

Table 4. Social participation of oncology patients with regard to the type of residence
Tabela 4. *Socijalna participacija onkoloških pacijenata koji jesu i koji nisu u ustanovama za smeštaj starih lica*

Subscale/*Supskala*	Residence/*Smeštaj*	N	M	SD	t	p
Social activity *Socijalna aktivnost*	Senior citizens home/*Dom*	25	2.16	2.10	-4.956	<.01
	Individual housing/*Kuća/stan*	75	4.86	4.03		
Contact with friends *Kontakt sa prijateljima*	Senior citizens home/*Dom*	25	11.41	5.36	-3.414	<.01
	Individual housing/*Kuća/stan*	75	14.45	6.19		
Contact with family *Kontakt sa porodicom*	Senior citizens home/*Dom*	25	4.66	3.70	-8.690	<.01
	Individual housing/*Kuća/stan*	75	11.05	5.29		
Total score *Ukupan skor*	Senior citizens home/*Dom*	25	18.25	8.78	-6.765	<.01
	Individual housing/*Kuća/stan*	75	30.37	12.95		

participation as well as a significant correlation of each domain with the total score; it means that oncology patients who had high scores in one domain, had equally high scores in all the other domains of social participation **(Table 1)**.

With regard to the relationship between social participation and the patients' gender, there were no statistically significant differences between men and women in any of the domains of social participation or in the total score **(Table 2)**.

The linear regression analysis showed that the age of oncology patients was a statistically significant predictor in all three domains of social participation. The negative effect of age was obtained in all three domains, meaning that older participants had lower scores in all domains of social participation, compared to the younger examinees **(Table 3)**.

With regard to the type of residence, statistically significant differences were obtained in the total score as well as in individual scores on each subscale between oncology patients living in a house/flat and those living in senior citizens homes **(Table 4)**. Persons living in individual housing scored higher compared to those residing in senior citizens homes.

To investigate the effects of disability on social participation, we created a dichotomous variable (with disability/without disability). The results presented in **Table 5** showed that there were statistically significant differences in all three domains of social participation as well as in the total score between patients with and without disability, the scores being higher in participants without disability.

Discussion

In the course of aging, many aspects of people's lives change, including the quality and quantity of their social networks, as well as the frequency of their social participation activities. Additionally, social participation may be affected by many factors including: personal factors (gender, health, income, education),

Table 5. Social participation of oncology patients with regard to disability
Tabela 5. *Socijalna participacija onkoloških pacijenata u odnosu na invaliditet*

Subscale/*Supskala*	Disability/*Invaliditet*	N	M	SD	t	p
Social activity *Socijalna aktivnost*	Absent/*Nema*	54	4.75	3.88	2.422	<.05
	Present/*Ima*	46	3.58	3.70		
Contact with friends *Kontakt sa prijateljima*	Absent/*Nema*	54	15.68	6.04	5.801	<.01
	Present/*Ima*	46	11.43	5.42		
Contact with family *Kontakt sa porodicom*	Absent/*Nema*	54	11.12	5.89	5.096	<.01
	Present/*Ima*	46	7.63	4.74		
Total score *Ukupan skor*	Absent/*Nema*	54	31.56	13.15	5.663	<.01
	Present/*Ima*	46	22.65	11.41		

contextual (social support, physical barriers, opportunities for participation), and life events common for older age, such as retirement or loss of spouse [36]. Our study primarily investigated the total level of social participation in elderly oncology patients.

The obtained results indicate that oncology patients over the age of 60 have a rather low social participation. Similar studies on social participation in the elderly conducted in the Netherlands show that 56% of the sample of older adults are involved in social participation activities [37]**,** while this percentage in rural China is only 26% [38]. Pinto and Neri performed an analysis of 31 longitudinal studies on social participation in the elderly, mostly studies published between 2009 and 2015, and found that 21 studies reported on diminished social participation in old age [36]. A study titled "Social involvement of the elderly in Serbia" was conducted between 2016 and 2019. It demonstrated that despite a widespread belief that family relationships and social networks are more developed in Serbia compared to western countries, due to traditional patterns in which these informal networks play a major role, the reality is quite the opposite. Although it is believed that people are more estranged in developed countries, and that families spend less time together etc., this study did not find more social involvement of the elderly in Serbia [9]. This kind of data, combined with information on the effect of age, chronic diseases and other factors on social participation, provide valuable information for structuring rehabilitation programs and programs of care for the elderly. The results we obtained in the current study indicate that social participation of oncology patients is more varied and frequent in persons living in individual housing compared to those residing in senior citizens homes, and this was determined for all domains of the instrument used. This finding should be taken with caution, since the reasons for our findings can lie in different factors. Senior citizens homes can provide many possibilities for socializing such as cultural and recreational events and entertainment, while living in one's own home gives a greater sense of belonging, a stronger cohesion and family ties. Difficulties in everyday functioning and the inability to live safely and peacefully in one's own home, are the predominant reasons for a person to seek accommodation in a senior citizens home [9]. This factor can influence the results of social participation in older adults in general, as well as those who are oncology patients.

We attempted to establish whether there is a difference in frequency and variety of social participation in oncology patients over the age of 60 with regard to demographic variables like age, gender, living arrangements, and disability. The participants' age was found to be a significant predictor of social participation. It was also established that there is a significant difference in the level of social participation with regard to the type of residence, while gender was not found to be a significant predictor of social participation.

Our results point to a negative impact of age on social participation. This means that older participants scored lower compared to younger ones. In a Brazilian study by Pinta and Neri, the results are in accordance with ours [26]. Also, in a study by Desrosiers et al. in Quebec [25] and Kurvers et al. in Limburg, the Netherlands [37], social participation was found to decrease with increasing age. A study conducted in Chile in 2014, showed that social participation increases until the age of 80, after which it decreases [39]. These results can be consequent to compounded effects of dealing with a malignant disease, and events common in old age, such as retirement, health issues, declining functionality, and loss of a spouse [36].

As far as the participants' gender was concerned, our study found no differences in social participation between men and women. A study in Japan, which included 12.991 elderly persons, found equal social participation in men and women [40]. In a study by Lefransoa et al. women were found to be less involved in all activities of social participation compared to men [41], while a study in Serbia established low levels of social participation in men and women alike, with the only difference being in the involvement in political organizations which was more frequent in men [9].

We attempted to determine if disability is a significant predictor of social participation. The obtained results indicate that the level of social participation is higher in oncology patients without disability compared to those with disabilities. Studies that dealt with the relationship between disability and social participation mainly defined disability as a function of needing help with activities, being able to perform self-help tasks, strength, mobility, and upper and lower limb

functionality [42, 43]. Studies focusing on a particular type of disability are rare [44], especially those involving oncology patients. Avlud et al. found that more comprehensive social relationships ease the disability [42]. In a study by Mendes de Leon, more socially active persons reported on lower levels of disability [43].

Conclusion

Implications of the current study include the need for further research aimed at identifying why and how encouragement and support affect social participation in older adults who are also oncology patients. After examining the existing literature, we found social participation of the elderly to be widely covered in studies in other countries, while very little information on this subject is available in Serbia, which can create a challenge and a task to be accomplished in future studies. Having in mind the reciprocal causation of social participation (the impact of the onset of malignant disease on lowering the levels of social participation, but also the impact of a low level of social participation on the onset of disability and chronic diseases), persons over the age of 60 should be offered programs and resources in order to encourage social participation.

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THE OUTCOMES OF TRIPLET PREGNANCIES

ISHODI TROPLODNIH TRUDNOĆA

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Summary

Introduction. Extensive use of assisted reproduction has resulted in an increased incidence of triplet pregnancies, which are associated with higher risk of complications in mothers and newborns. **Material and Methods.** A retrospective study reviewed a total of 85 triplet pregnancies delivered at the Department of Obstetrics and Gynecology, Clinical Center of Vojvodina, Novi Sad, from January 1, 2010 to December 31, 2017. **Results.** The average maternal age was 32 years and the average body mass index was 30.56 kg/m^2. The average gestational age at birth was 32 weeks. One patient (1.18%) had vaginal delivery, while 84 (98.82%) pregnancies were completed by cesarean section. The average blood loss was 1294 ml and there was one postpartum hysterectomy. The most common maternal pregnancy-induced complications were sideropenic anemia (70.58%), hypertensive syndrome (40%) and obstetric cholestasis (35.29%). Preterm premature rupture of membranes was observed in 17 (20%) patients. Prophylactic cerclage was performed in 57 patients (67.05%) and 12 patients (14.11%) received tocolytic therapy. The average birth weight of the first newborn was 1838 g, 1755 g of the second, and 1695 g of the third. Body weight ≤ 1500 g was observed in 61 newborns (24.01%). The mean Apgar score in the first minute was 7, while in the fifth minute it was 8. Respiratory distress syndrome was found in 64 newborns (25.19%). **Conclusion.** Monitoring and treatment of triplet pregnancies remains a complex task for obstetricians due to the increased incidence of prematurity and perinatal morbidity.

Key words: Pregnancy, Triplet; Triplets; Maternal Health Services; Maternal Mortality; Puerperal Disorders; Pregnancy Complications; Pregnancy Outcome; Reproductive Techniques, Assisted

Sažetak

Uvod. Povećana upotreba metoda asistirane reprodukcije rezultirala je povećanom incidencijom troplodnih trudnoća, koje su praćene komplikacijama kako majki tako i novorođenčadi. **Materijal i metode.** Retrospektivna studija obuhvatila je 85 trudnica porođenih na Klinici za ginekologiju i akušerstvo, Kliničkog centra Vojvodine u Novom Sadu, u periodu od 1. 1. 2010. do 31. 12. 2017. godine. **Rezultati.** Prosečna starost majki iznosila je 32 godine, prosečan indeks telesne mase bio je 30,56 kg/m^2. Prosečna gestacijska starost trudnoća u vreme porođaja bila je 32 nedelje. Jedna trudnica (1,18%) porođena je vaginalnim putem, dok su 84 (98,82%) trudnice porođene carskim rezom. Prosečan gubitak krvi bio je 1.294 ml; načinjena je jedna postpartalna histerektomija. Najčešće maternalne komplikacije u toku trudnoće bile su: malokrvnost (70,58%), hipertenzivni sindrom (40%) i opstetrička holestaza (35,29%). Preterminska preuranjena ruptura ovojaka uočena je kod 17 (20%) pacijentkinja. Šav serklaža postavljen je kod 57 pacijentkinja (67,05%), a 12 pacijentkinja (14,11%) primilo je tokolitičku terapiju. Prosečna telesna masa prve bebe iznosila je 1.838 g, druge bebe 1.755 g i treće bebe 1.695 g. Porođajna telesna masa ≤ 1.500 g uočena je kod 61 (24,01%) novorođenčeta. Prosečna ocena po Apgaru u prvom minutu iznosila je 7, dok je u petom minutu bila 8. Respiratorni distres sindrom je potvrđen kod 64 novorođenčeta (25,19%). **Zaključak.** Praćenje i tretman troplodnih trudnoća i dalje je kompleksan zadatak za akušere zbog povećane učestalosti prevremenih porođaja i perinatalnog morbiditeta.

Ključne reči: troplodna trudnoća; trojke; zdravstvena zaštita majki; mortalitet majki; puerperalne komplikacije; komplikacije trudnoće; ishod trudnoće; asistirana reprodukcija

Introduction

The worldwide incidence of multiple pregnancies has increased over the last ten years. One of the reasons is more frequent use of assisted reproduction technology (ART) that led to an increase in triplet pregnancies by 4 to 5 times. Also, the trend of advanced age of mothers in spontaneous conception is another risk factor for multiple pregnancies [1]. Despite daily advances in obstetric and neonatal care, triplet pregnancies remain a challenge to treat. Compared with singleton pregnancies, triplet

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Abbreviations
BMI – body mass index
PPROM – preterm premature rupture of membranes
IUGR – intrauterine growth restriction
RDS – respiratory distress syndrome
LBW – low birth weight
VLBW – very low birth weight
ELBW – extremely low birth weight
ART – assisted reproduction technology

pregnancy is accompanied with severe newborn complications, which are the consequence of prematurity [2, 3]. In addition to the increased risk of neonatal mortality, premature birth and low birth weight, there is also a higher incidence of long-term complications in children from triplet pregnancies [4]. Multiple pregnancies are associated with poor maternal outcomes accompanied by gestational diabetes, hypertensive syndrome, placental abruption and more frequent obstetric surgery (cesarean section) [5]. Numerous studies clearly show that the consequences of triplet pregnancies affect both maternal and infant health, as well as the health system and society as a whole [6].

The purpose of our study was to determine the contemporary maternal and neonatal outcomes of triplet pregnancies.

Material and Methods

This retrospective study reviewed triplet pregnancies delivered at the Department of Obstetrics and Gynecology, Clinical Centre of Vojvodina, Novi Sad, from January 1, 2010 to December 31, 2017. The study included triplet pregnancies where chorionicity, gestational age of pregnancy as well as the estimated date of delivery were determined by first-trimester ultrasound. The exclusion criteria from the study were pregnancies with known fetal reduction and those with incomplete medical data. We evaluated maternal parameters: age, body mass index (BMI), mode of conception, antepartum complications (sideropenic anemia, hypertensive syndrome, gestational diabetes, obstetric cholestasis) and mode of delivery. From fetal and neonatal parameters we examined: chorionicity, intrauterine growth restriction (IUGR), intrauterine fetal death, gestational age at delivery, birth weight, Apgar score, respiratory distress syndrome (RDS), pneumothorax, and congenital anomalies. We also evaluated the use of antenatal corticosteroids and tocolytic therapy during pregnancy, presence of cerclage, preterm premature rupture of membranes (PPROM) and postpartum complications (hemorrhage, blood transfusion and postpartum hysterectomy). Tocolytic agents (magnesium sulfate and nifedipine) were administered if clinically indicated. Corticosteroids were administered between 24 and 34 weeks of gestation for fetal lung maturation in all triplet pregnancies. Sideropenic anemia was diagnosed if hemoglobin values were < 10.5 g/dL in the second trimester of pregnancy or < 11.0 g/dL in the third trimester. A planned cesarean section was the dominant mode of delivery. The collected data were presented as median values and relative numbers (the measure of variability). Statistical data processing was performed using softwares Excel and Statistical package for the social sciences.

Results

During the study period, 85 triplet pregnancies were managed and delivered after 24 weeks of gestation, leading to birth of 254 live babies. The mean maternal age was 32 years (range 21–39 years), and the average BMI, based on standard guidelines, corresponded to the overweight group (mean 30.56 kg/m^2). The average gestational age at delivery was 32 weeks. There were 9 (10.58%) spontaneous triplet pregnancies in the sample, 6 (7.05%) were pregnancies after intrauterine insemination, while the number of pregnancies conceived by in vitro fertilization (IVF) procedures was 70 (82.35%). In terms of chorionicity, the largest part of our sample were trichorionic pregnancies 52 (61.17%). Prophylactic cerclage was performed in more than half of the patients (67.05%). Majority of the patients (78.82%) received

Table 1. Maternal pregnancy induced complications and interventions in triplet pregnancies
Tabela 1. *Maternalne komplikacije i intervencije u troplodnim trudnoćama*

Complications and interventions *Komplikacije i intervencije*	Period of time (2010–2017)/*Vremenski period (2010–2017)* N = 85/*Br. = 85*	 Percentage/*Procenat*
Sideropenic anemia/*Sideropenijska anemija*	60	70.58%
Hypertensive syndrome/*Hipertenzivni sindrom*	34	40%
Cholestasis/*Opstetrička holestaza*	30	35.29%
PPROM/*Prevremena preuranjena ruptura ovojaka*	17	20%
GDM/*Gestacijski dijabetes melitus*	7	8.23%
Postpartum hysterectomy/*Postpartalna histerektomija*	1	1.17%
Blood transfusion/*Transfuzija krvi*	15	17.64%
Cerclage/*Serklaž*	57	67.05%
Antenatal steroids/*Kortikosteroidna terapija*	67	78.82%
Tocolytic therapy/*Tokolitička terapija*	12	14.11%

Table 2. Fetal and neonatal complications in triplet pregnancies
Tabela 2. *Fetalne i neonatalne komplikacije troplodnih trudnoća*

Complications *Komplikacije*	Period of time (2010−2017)/*Vremenski period (2010−2017)*	
	N = 254/*Br. = 254*	Percentage/*Procenat*
RDS/*Respiratorni distres sindrom*	64	25.19%
IUGR/*Intrauterini zastoj u rastu ploda*	8	3.15%
Pneumothorax/*Pneumotoraks*	3	1.18%
Congenital anomalies/*Kongenitalne anomalije ploda*	2	0.78%
LBW/*Novorođenčad niske telesne mase*	254	100%
VLBW/*Novorođenčad veoma niske telesne mase*	45	17.71%
ELBW/*Novorođenčad ekstremno niske telesne mase*	16	6.29%

a therapy for fetal lung maturation. Twelve patients (14.11%) received magnesium sulfate as tocolytic therapy and preventive therapy for cerebral palsy. During the antenatal period, sideropenic anemia, hypertensive syndrome and obstetric cholestasis were the most common maternal complications **(Table 1).** Preterm premature rupture of membranes was found in 17 patients (20%). Only one patient underwent vaginal delivery, while 84 (98.82%) pregnancies were completed by cesarean section. Although delivery was planned at 34 weeks, 35 patients (41.17%) delivered before 34 weeks by emergency cesarean section. The main postpartum complication of triplet pregnancy was hemorrhage. The average blood loss during delivery was 1294 ml. One of the patients had a postpartum hysterectomy. Fifteen patients (17.64%) received blood transfusion. There were no maternal deaths in our study. The average birth weight of the first newborn was 1838 g, 1755 g of the second, and 1695 g of the third. All the newborns had a low birth weight (LBW), while 45 (17.71%) had a very low birth weight (VLBW) and 16 (6.29%) had an extremely low birth weight (ELBW) **(Table 2).** The mean Apgar score AS) in the first minute was 7, while in the fifth minute it was 8. A RDS was observed in 64 neonates (25.19%) and IUGR was present in 8 neonates (3.15%). Congenital anomalies were confirmed in 2 neonates (0.78%): atrial septal defect (ASD) and spina bifida. Pneumothorax was fund in 3 newborns (1.18%). There was one intrauterine death diagnosed at 26 weeks of gestation of a triplet pregnancy.

Discussion

In this study, we presented the outcomes of triplet pregnancies in 85 pregnant women and 254 newborns during an eight year period. The mean maternal age in this study was 32 years (range 21−39 years) and it is in agreement with other studies [7–9]. The reduced fertility at older age significantly increases the need for infertility treatment [10]. Studies dealing with the issue of triplet pregnancies have shown that women older than 35 have a higher frequency of triplet pregnancies (up to ten times) [11]. In our study, mean gestational age at delivery was 32 weeks. A large study of births in the United States, showed that the mean gestational age at delivery in triplet pregnancies was 32.5 weeks compared to the singleton pregnancies (39 weeks) [12]. Literature data show that compared to singletons, mean gestational age at delivery was 7.0 weeks shorter for triplet pregnancies [13]. The results of the epidemiological analysis showed that only 16% of triplet pregnancies remain undelivered until the 36 week of gestation [14]. More research is needed to indicate which gestational age is associated with the lowest percentage of poor birth outcomes of triplet pregnancies. Efforts should not be made to postpone a triplet pregnancy until the due date, but on the contrary, careful monitoring should assess at what point such pregnancies should be completed in order to achieve the most favorable outcomes for mothers and newborns. The largest number of pregnancies in our study (82.35%) resulted from ART. The rate of multiple pregnancies has risen in all parts of the world, primarily as a result of increased use of ART [15]. The high rate of multiple births after ART was explained by the number of embryos transferred during treatment in order to improve the success of the procedure [16]. Depending on the medications and techniques used in the treatment of infertility, the ART procedure itself carries 30−50% risk for multifetal pregnancy [17, 18]. In 61.17% of the triplet pregnancies, the chorionicity was trichorionic triamniotic and this is similar to other reports [19]. In contrast, Mazhar et al. reported 61% prevalence of dichorionic placenta [7]. Studies have shown that chorionicity determines the perinatal outcome in multiple pregnancies [20]. Our study did not investigate perinatal outcome in relation to chorionicity. Prophylactic cerclage was performed in 57 patients (67.05%) and 12 patients (14.11%) received tocolytic therapy (magnesium sulfate, nifedipine). There are still different opinions regarding the prophylactic cerclage in multiple pregnancies. On the one hand, there are still opinions that prophylactic cerclage has its benefits [21, 22], while on the other, some researches showed that prophylactic cerclage is not justified in triplet pregnancies [23, 24]. However, there is evidence that prophylactic cerclage reduces the frequency of newborns with extremely low birth weight in triplet pregnancies and significantly increases the incidence of newborns born after 31 weeks of gestation [25]. In our study, all newborns (254) were born before term and PPROM occurred in 17 patients (20%). About 75 to

100% of triplets are born prematurely, which makes premature birth the most common complication of multiple pregnancies [26]. That is the only complication that affects significantly more often triplet in regard to twin pregnancies [27]. Although delivery was planned at 34 weeks, 35 patients (41.17%) delivered before 34 weeks by cesarean section, due to maternal or fetal indications. Cesarean section is preferred around the world, as the most common way to complete triplet pregnancy. It makes it easier for the obstetrician to deliver the second and third newborn and it is a more comfortable way to complete a triplet pregnancy [28]. It has long been known that multiple pregnancies are associated with poorer maternal outcomes and an increased need for obstetric interventions [5]. Pregnant women with triplets require twice as much intensive care and six times more frequent hospitalization compared to singleton pregnancies [29, 30]. This is an important fact not only in terms of the burden on the health system, but also in the quality of life of the pregnant women. Sideropenic anemia and hypertensive syndrome were the commonest maternal complications in most of the studies, although sideropenic anemia was diagnosed more frequently in our study (70.58%) compared with other studies (18–24%). Gestational diabetes mellitus (GDM) was confirmed in 7 patients (8.23%) in our study, which is in agreement with the results of other literature reports where the incidence was 5–16% [19]. The average birth weight of the first newborn in our study was 1838 g, 1755 g of the second, and 1695 g of the third. All the newborns were of LBW, while 45 (17.71%) had a VLBW, and 16 (6.29%) had an ELBW. The obtained data were in accordance with the results reported in the literature, where in triplet pregnancies the highest proportion of newborns had birth weights between 1500–2499 g [31]. Compared to singleton pregnancies, where the average birth weight and gestational age at birth are 3332 g and 38 weeks, in triplet pregnancies these values are 1687 g and 32.2 weeks [32]. Most recent data show that 34.5% of triplets weigh less than 1500 g (in our study 24%) [33]. The intrauterine death rate is significantly higher in triplet pregnancies (17%) than in singleton pregnancies (4.3%) [34]. In our study, intrauterine death (one of the three fetuses) was diagnosed at 26 gestational weeks in a patient who was delivered by cesarean section 3 weeks later. In a similar study, this occurrence was more common accounting for 7.4% [7]. Eight of 254 fetuses (3.15%) have been diagnosed with IUGR which is far less than in the literature data [19]. Similar to the results of our study, prematurity and RDS are the most common causes of neonatal morbidity in most studies [2, 3]. The RDS was found in 64 neonates (25.19%) while pneumothorax and congenital anomalies were present in 3 (1.18%) and 2 newborns (0.78%), respectively. The main postpartum maternal complication of triplet pregnancy is hemorrhage due to uterine atony [35]. There is a significantly higher frequency of postpartum hemorrhage after the birth of triplet pregnancies (10–35%), compared to singleton pregnancies (2–11%) [36]. In our study, 21.14% patients suffered from postpartum hemorrhage. Multiple gestations have a significantly higher occurrence of peripartum hysterectomy than singletons [37]. In our study, only one patient underwent postpartum hysterectomy. As the results show, a triplet pregnancy significantly increases the risk of poor outcomes for both the mothers and newborns.

There is clear evidence that children from triplet pregnancies have health complications not only in the neonatal period, but also in later life. Because of all the above, triplet pregnancies are associated with a fivefold increased risk of parental stress [38], increased incidence of maternal depression and a lower quality of life [39]. For these reasons, the implementation of individual approach to infertility treatment and single embryo transfer should be an imperative.

Conclusion

We should be aware of maternal and especially neonatal risks in triplet pregnancies and consider them before counseling the continuation of multiple pregnancies. Triplet pregnancies require continuous antenatal monitoring due to higher frequency of complications. Appropriate antenatal and perinatal care with neonatal support result in optimal outcomes of triplet pregnancies.

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CONTRIBUTIONS OF THE NEWLY REVISED 2018 INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS STAGING OF CERVICAL CANCER

DOPRINOSI NOVE REVIDIRANE KLASIFIKACIJE KARCINOMA GRLIĆA MATERICE MEĐUNARODNE FEDERACIJE GINEKOLOGA I OPSTETRIČARA IZ 2018. GODINE

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Summary

Introduction. According to the latest data from International Agency for Research on Cancer from 2018, global burden of cancercervical cancer is the fourth most common cancer in women worldwide. The aim of this article was to present the contributions of the new, revised 2018 International Federation of Gynecology and Obstetrics staging of carcinoma of the cervix uteri, allowing much more precise staging with the use of any imaging modalities and/or pathological findings to allocate the stage and provide more effective treatment. **International Federation of Gynecology and Obstetrics staging system.** The main changes in the new staging system were made in IB stage of the disease, which now includes 3 subgroups i.e. substages for every 2 cm increments in tumor size: stage IB1 (< 2 cm), stage IB2 disease (2 to < 4 cm), and stage IB3 (≥ 4 cm). This system also incorporates the lymph node status into stage III cervical cancer, allowing imaging and/or pathological findings of lymph nodes to the pelvic and/or para-aortic nodes to assign stage IIIC disease. **Conclusion.** The main goal of the new staging system revision was to improve the accuracy of staging in order to provide more refined understanding of prognostic groups and facilitate better treatment for women with invasive cervical cancer.

Key words: Classification; Neoplasm Staging; Uterine Cervical Neoplasms; Diagnostic Imaging; Lymph Nodes; Prognosis

Sažetak

Uvod. Prema najnovijim podacima Interncaionalne agencije za istraživanje o raku iz 2018, karcinom grlića materice četvrti je najčešći tumor kod žena na svetu. Cilj ovog stručnog članka je da prikaže novi revidirani stejdžing sistem za karcinom grlića materice Međunarodne federacije ginekologa i obstetričara iz 2018. godine, koji omogućava mnogo preciznije određivanje stadijuma karcinoma upotrebom slikovne dijagnostike i patohistoloških nalaza, sa ciljem preciznog određivanja stadijuma i uspešnijeg lečenja. **Klasifikacioni sistem Međunarodne federacije ginekologa i obstetričara.** Glavne promene u novom stejdžing sistemu odnose se na stadijum bolesti IB, koji sada podrazumeva tri podstadijuma: IB1 (tumor manji od 2 cm), IB2 (tumor veličine od 2 do 4 cm) i IB3 (tumor veći od 4 cm). Ovaj sistem takođe uzima u obzir i status karličnih i paraaortnih limfnih čvorova kod bolesti III stadijuma, omogućavajući da se na osnovu nalaza slikovne i patohistološke dijagnostike odredi stadijum IIIC. **Zaključak**. Osnovni cilj nove revizije stejdžing sistema je poboljšanje preciznosti stejdžinga što pospešuje formiranje prognostičkih grupa i samim tim pospešuje se i lečenje žena sa invazivnim karcinomom grlića materice.

Ključne reči: klasifikacija; stadijumi neoplazmi; neoplazme grlića materice; dijagnostički imidžing; limfni čvorovi; prognoza

Introduction

Cervical cancer is ranked as the fourth most commonly diagnosed tumor and the fourth leading cause of cancer mortality in women [1]. According to currently available data, provided by the Global Cancer Observatory published in 2018, the total number of women with a diagnosed cervical cancer worldwide was approximately 570,000 and the number of deaths was approximately 311,000 [1]. After breast, colorectal and lung cancer, cervical cancer has the highest incidence [2]. According to the latest data of the Institute of Public Health from 2015 in Serbia, the number of new cases was 1,095 annually, and the number of women who died from cervical cancer was 424 per year. These epidemiological data remind us of the need for permanent improvement of clinical practice in terms of improving diagnostics, precise determination of the disease stage and selection of the optimal treatment procedure.

The assessment of the stage of disease is of utmost importance in oncology, because it is crucial for the adequate choice of treatment options and prognosis of the disease [3]. A good staging system should be valid and practical, based on and updated according to the latest scientific knowledge and achievements [4]. A unique staging classification for gynecological cancers, published by the International Federation of Gynecology and Obstetrics (FIGO), has been present since 1954, and it has been adopted by the American Joint Committee on Cancer (AJCC) since 1976 [3–5]. So far, all staging

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Abbreviations

AJCC	– American Joit Commitee on Cancer
FIGO	– International Federation of Gynecology and Obstetrics
MRI	– magnetic resonance imaging
PET	– positron emission tomography
TNM	– tumor, nodes, and metastases
LVSI	– lymphovascular space invasion
CT	– computed tomography

systems for gynecological malignancies, except for cervical cancer and gestational trophoblastic neoplasia, have been modified and shifted from clinical to a surgical–pathological basis [4].

Very important changes in cervical cancer staging were made in a revision of the FIGO classification published in 2018. According to FIGO classification, the stage is determined for the purpose of disease prognosis and the choice of treatment procedure, from radical surgical method to chemo-radiation or palliative chemotherapy [3, 6]. The previous FIGO classification was based primarily on clinical assessment of the disease stage, based on gynecological examination and on the other diagnostic methods (hysteroscopy, cystoscopy, proctoscopy, colposcopy and biopsy) [6–8]. The main changes in the revised classification are inclusion of radiological imaging methods and pathological assessments in the determination of the stage of cervical cancer, at all stages of the disease, in addition to clinical assessment whenever radiological methods are available [8, 9].

Main changes and recommendations in the revised 2018 FIGO classification

A good staging system gives the most accurate information on the disease prevalence and prognosis [9]. In the new revised 2018 FIGO classification, the application of any available imaging modalities and/or pathological findings that complement and allow accurate estimation of tumor size is crucial, which is especially important in the first FIGO stage [9]. Imaging has the main role in the evaluation of the cancer size and its extensiveness [7]. Another major change is in the first stage of the disease where there are now three subgroups for stage IB [10].

The evaluation of pelvic and retroperitoneal para-aortic lymph nodes is now also included and it is introduced into the stage IIIC, accordingly.

Any available imaging method can be used to determine disease stages, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and less commonly hybrid imaging (PET/CT, PET/MRI) [9].

Endovaginal ultrasound examination can measure the size of the tumor and estimate infiltration of cervical stroma or parametria. Transabdominal ultrasound examination can diagnose hydronephrosis in the advanced stage of disease [3]. Among these radiological methods, the most superior is MRI due to its high resolution and tissue characterization, as well as the exact measurement of tumor size, assessment of local distension and evaluation of pathologically enlarged lymph nodes [11]. Carcinoma in situ is usually too small and often cannot be detected by MRI.

Pathologic diagnosis includes lymph node biopsy, fine needle biopsy and postoperative histopathological evaluation. If these methods are not available, as in undeveloped countries and in unequipped health centers, the previous method, such as clinical determination of the stage of cervical cancer, is applied.

Cervical cancer limited strictly to the cervix corresponds to stage I, and it is divided into subgroups IA and IB. Microscopic tumor invasion of the cervix less than 5 mm corresponds to stage IA, and depending on the depth of stromal invasion < 3 mm or > 3 mm, there are sub-stages IA1 and IA2. In the revised classification, lateral tumor extension is no longer considered [8, 9]. Stage IB corresponds to a clinically visible tumor (invasion depth greater than 5 mm). A significant change is the division of the stage IB into three subgroups IB1, IB2 and IB3, while previously there were two subgroups. This division is based on the measurement of maximum tumor dimensions in all three planes on imaging methods and pathology analysis [7]. A cut-off value for invasive carcinoma of less than 2 cm in the greatest dimension with stromal invasion of less than 5 mm in depth indicates stage IB1. The tumor $\geq$ 2 cm and < 4 cm corresponds to stage IB2, and the tumor size ≥ 4 cm to stage IB3.

In order to preserve the fertility of younger patients with stage IA1 disease, conization of the cervix can be used as a therapeutic method of choice. In early stages, IA2 and IB1, if the disease is confined to the upper third of vaginal canal and the greatest dimension of the lesion is less than or equal to 2 cm, radical trachelectomy is used [7, 9]. This new cut-off value for IB1 stage was introduced in 2018 classification. To preserve the fertility, a new approach to treating cervical cancer in the early stages such as stage IA2, conization, and laparoscopic pelvic lymphadenectomy should be considered. In such cases, the role of imaging techniques is essential. MRI of cervical cancer should detect a minimum distance of 1 cm between the isthmus of the uterus and stromal invasion. The possibility of applying these surgical procedures to preserve the reproductive function of young women with the early-stage disease has not been considered in older versions of FIGO classification.

The new division into stages IB1 and IB2 is of great importance because the tumor in these two stages usually has different characteristics. Low-grade adenocarcinoma is more often confirmed by histological examination in IB1 stage, which has a better prognosis than the high-grade squamous cell carcinoma [8, 10]. The risk of fatal outcome is twice higher in stage IB2 compared to IB1 [10]. According to new recommendations, if pathologically suspected enlarged lymph nodules are observed in the pelvis or retroperitoneum (para-aortic) regardless of tumor size, the disease stage is immediately classified as IIIC [9]. Histopathological findings of lymphovascular space invasion (LVSI) in cervical stroma invasion do not change the stage of the disease [8]. **Table 1** shows the main changes in 2018 revision com-

Table 1. Main changes in FIGO 2018 classification compared to FIGO 2009.
Tabela 1. *Glavne promene FIGO 2018 klasifikacije u poređenju sa FIGO 2009.*

FIGO 2009/*FIGO* 2009*	2018/*2018*	Comment/*Komentar*
IA: Invasive carcinoma with maximum depth of invasion ≤ 5 mm and largest extension ≤ 7 mm *IA: Invazivni karcinom sa maksimalnom dubinom invazije ≤ 5 mm i najvećom ekstenzijom ≤ 7 mm*	IA: Invasive carcinoma with maximum depth of invasion < 5 mm *IA: Invazivni karcinom sa maksimalnom dubinom invazije < 5 mm*	Lateral extent of the carcinoma is no longer considered in distinguishing between FIGO Stage IA and IB carcinomas. If margins of loop excision are involved the patient is allocated to Stage IB1./*Bočna ekstenzija tumora više nema uticaja na razlikovanje FIGO stadijuma IA i IB. Ako su margine ekscizije zahvaćene tumorom, pacijent se svrstava u stadijum IB1.*
IB: Clinically visible lesions limited to the cervix or pre-clinical cancers greater than stage IA *IB: Klinički evidentna bolest ograničena na cerviks ili pretklinička bolest veća nego u IA*	IB: Invasive carcinoma with measured deepest invasion ≥ 5 mm, lesion limited to the cervix uteri *IB: Invazivni karcinom sa maksimalnom dubinom invazije ≥ 5 mm, ograničen na cerviks uterusa*	LVSI must be commented upon, although it does not affect FIGO stage. *LVSI se mora navesti ako postoji, iako ne utiče na FIGO stadijum.*
IB1: Clinically visible lesion ≤ 4.0 cm in greatest dimension *IB1: Klinički evidentna bolest najvećeg dijametra ≤ 4,0 cm*	IB1: Invasive carcinoma ≥ 5 mm depth of stromal invasion, and < 2 cm in greatest dimension *IB1: Invazivni karcinom sa dubinom stromalne invazije ≥ 5 mm, i najvećeg dijametra < 2 cm*	New cut-off value for IB1 stage is introduced due to trachelectomy as a fertility-sparing treatment option/*Uvedena je nova granična vrednost za stadijum IB1 zbog trahelektomije kao terapijske opcije u cilju očuvanja fertiliteta*
	IB2: Invasive carcinoma ≥ 2 cm and < 4 cm in greatest dimension *IB2: Invazivni karcinom najvećeg dijametra ≥ 2 cm i < 4 cm*	
IB2: Invasive carcinoma > 4 cm in greatest dimension/*IB2: Invazivni karcinom najvećeg dijametra > 4 cm*	IB3: Invasive carcinoma ≥ 4 cm in greatest dimension/*IB3: Invasive carcinoma ≥ 4 cm in greatest dimension*	
There are no major changes in Stage II/*Nema većih promena u II stadijumu*		
There are no changes in Stages IIIA and IIIB/*Nema promena u IIIA i IIIB stadijumima*		
	IIIC: Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)/*IIIC: Zahvaćenost karličnih ili paraaortnih limfnih čvorova, nezavisno od veličine tumora i proširenosti (sa r i p oznakama)*	New stage category. Notation of r (imaging) and p (pathology) is added to indicate the findings that are used to allocate the case to Stage IIIC *Nova kategorija stadijuma. Oznake r (radiološki) i p (patološki) označavaju na osnovu koje dijagnostičke metode je određen stadijum IIIC*
	IIIC1: Pelvic lymph node metastasis only/*IIIC1: Metastaze samo u karličnim limfnim čvorovima*	
	IIIC2: Para-aortic lymph node metastasis/*IIIC2: Metastaze u paraaortnim limfnim čvorovima*	
There are no changes in Stage IV/*Nema promena u IV stadijumu*		

**FIGO – Međunarodna federacija ginekologa i opstetričara*

pared to the one published in 2009 [12]. The **Table 2** shows a comparison between tumor, nodes, and metastases (TNM) and FIGO classification [13].

Stage II cervical carcinoma (FIGO II)

If cancer spreads beyond the borders of cervix, but does not affect the lower third of the vagina and the pelvic walls, it is classified as stage II, which is divided into stages IIA and IIB. The tumor that does not infiltrate parametria is stage IIA, that is further divided into IIA1 and IIA2, depending on its size < 4 cm or ≥ 4 cm. Stage IIB is parametria-infiltrating cancer. However, if pathological lymph nodes are detected, the disease stage is IIIC. MRI plays an important role in the assessment of parametrial infiltration.

Stage III cervical carcinoma (FIGO III)

Cervical cancer in stage III infiltrates the lower third of the vagina (IIIA) or reaches to and infiltrates the pelvic walls and/or causes hydronephrosis

Table 2. Comparison of the TNM and FIGO staging systems
Tabela 2. *Komparacija TNM i FIGO sistema klasifikacije*

TNM Categories *TNM kategorije*	FIGO Stages *FIGO stadijum*	Surgical-pathologic findings *Hirurški/patološki nalaz*
TX/*TX*		Primary tumor cannot be assessed/*Nije moguća procena primarnog tumora*
T0/*T0*		No evidence of primary tumor/*Nema dokaza o primarnom tumoru*
Tis/*Tis*		Carcinoma in situ/*Karcinom in situ*
T1/*T1*	I/*I*	Cervical carcinoma confined to the cervix/*Cervikalni karcinom ograničen na cerviks*
T1a *T1a*	IA *IA*	Invasive carcinoma with stromal invasion, maximum depth of < 5.0 mm *Invazivni karcinom sa maksimalnom dubinom invazije < 5 mm*
T1a1 *T1a1*	IA1 *IA1*	Measured stromal invasion < 3.0 mm in depth *Izmerena stromalna invazija dubine < 3 mm*
T1a2 *T1a2*	IA2 *IA2*	Measured stromal invasion ≥ 3.0 mm and < 5.0 mm *Izmerena stromalna invazija dubine ≥ 3 mm i < 5 mm*
T1b *T1b*	IB *IB*	Invasive carcinoma with measured deepest invasion ≥ 5 mm, lesion limited to the cervix/*Invazivni karcinom sa maksimalnom dubinom invazije ≥ 5 mm, lezija ograničena na cerviks*
T1b1 *T1b1*	IB1 *IB1*	Invasive carcinoma with ≥ 5 mm depth of stromal invasion and < 2 cm in greatest dimension/*Invazivni karcinom sa dubinom stromalne invazije ≥ 5 mm i najvećeg dijametra < 2 cm*
T1b2 *T1b2*	IB2 *IB2*	Invasive carcinoma, 2 cm to < 4 cm in greatest dimension *Invazivni karcinom najvećeg dijametra 2 cm do < 4 cm*
T1b3 *T1b3*	IB3 *IB3*	Invasive carcinoma, ≥ 4 cm in greatest dimension *Invazivni karcinom najvećeg dijametra ≥ 4 cm*
T2 *T2*	II *II*	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina/*Cervikalni karcinom se širi izvan uterusa ali ne zahvata karlični zid ili donju trećinu vagine*
T2a *T2a*	IIA *IIA*	Involvement limited to the upper two-thirds of the vagina, without parametrial invasion *Karcinom ograničen na gornje dve trećine vagine, bez zahvatanja parametrijuma*
T2a1 *T2a1*	IIA1 *IIA1*	Invasive carcinoma < 4 cm in greatest dimension *Invazivni karcinom najvećeg dijametra < 4 cm*
T2a2 *T2a2*	IIA2 *IIA2*	Invasive carcinoma ≥ 4 cm in greatest dimension *Invazivni karcinom najvećeg dijametra ≥ 4 cm*
T2b *T2b*	IIB *IIB*	Tumor with parametrial invasion but not up to the pelvic wall *Tumor zahvata parametrijum ali ne dopire do karličnog zida*
T3 *T3*	III *III*	Carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes/*Karcinom zahvata donju trećinu vagine i/ili širi se do karličnog zida i/ili izaziva hidronefrozu ili remeti rad bubrega i/ili zahvata karlične i/ili paraaortne limfne čvorove*
T3a *T3a*	IIIA *IIIA*	Tumor involves lower third of vagina, with no extension to pelvic wall *Karcinom zahvata donju trećinu vagine bez širenja do karličnog zida*
T3b *T3b*	IIIB *IIIB*	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney *Tumor se širi do karličnog zida i/ili izaziva hidronefrozu ili remeti rad bubrega*
T3c *T3c*	IIIC *IIIC*	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent/*Zahvatanje karličnih ili paraaortnih limfnih čvorova nezavisno od veličine tumora*
T3c1/*T3c1*	IIIC1/*IIIC1*	Pelvic lymph node metastasis only/*Metastaze samo u karlične limfne čvorove*
T3c2/*T3c2*	IIIC2/*IIIC2*	Para-aortic lymph node metastasis/*Metastaze u paraaortne limfne čvorove*
T4 *T4*	IV *IV*	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum/*Karcinom se prostire izvan male karlice ili zahvata mukozu mokraćne bešike ili rektuma (potvrđeno biopsijom)*
	IVA/*IVA*	Spread to adjacent pelvic organs/*Širi se u okolne karlične organe*
	IVB/*IVB*	Spread to distant organs/*Širi se u udaljene organe*

Legenda: TNM – tumor, čvor, metastaze, FIGO – Međunarodna federacija ginekologa i opstetričara

(IIIB). According to previous versions of the FIGO classification, cervical cancer was understaging 20–40% of IB - IIIB cases, and overestimating 64% to stage IIIB [7, 8].

A new subgroup of stage III is stage IIIC which is divided depending on whether the affected lymph nodes are in the pelvis (IIIC1) or in the retroperitoneum, paraaortic (IIIC2) [10]. Previous versions of the FIGO classification did not include assessment of lymph nodes, which is one of the most important prognostic factors and affects the choice of treatment [10, 14]. In these patients, the prognosis is usually poor and the five-year survival rate is much lower [9]. Imaging methods have the main role in the detection of suspected pathological lymph nodes with a sensitivity of 60–88% and a specificity of 97% [9]. The additional features *r* (imaging) and *p* (pathology) indicate the methods that were used in the determination of stage IIIC. If any of the imaging methods detects pelvic lymph nodes that are suspected to be metastatic lymph nodes, then the disease stage is evaluated as IIIC1r, and if it is confirmed pathologically, the stage is marked as IIIC1p. It is now necessary to note by which method the stage of the disease was assessed. It is also a rule, if there is a doubt about the stage or sub-stage of cervical cancer, the lower stage should be assigned [8, 9]. In stage III, five-year survival rate varies and it is interesting that for IIIA it is 46%, for IIIB 42.6% and for IIIC1 it is the highest, 62.1% [8]. Stage IIIC1 is a heterogeneous group of cervical cancers and there is a wide range of survival rates depending primarily on local tumor factors [10].

Stage IV cervical carcinoma (FIGO IV)

Stage IV remained unchanged in the 2018 FIGO classification. When cancer infiltrates the bladder or rectal mucosa it is stage IVA, and if there are distant metastases then it is stage IVB. Infiltration of the rectum or bladder mucosa should be confirmed by histology. For example, MRI should point to suspected infiltration of these organs when no line of fat is visible between the organs. If a "fat line" exists, infiltration can be excluded. If the fat line cannot be seen, it is necessary to confirm the infiltration by other examinations, by cystoscopy or proctosigmoidoscopy with a histopathological confirmation.

X-ray examination of the thorax or CT of the thorax and abdomen are most commonly used to evaluate the dissemination of locally advanced cancer, and PET/CT is used in the case of specific clinical indication.

Magnetic resonance imaging and PET/CT imaging modalities are the best to evaluate the lymph nodes. At present, PET/CT has an important diagnostic role due to its high sensitivity especially for paraaortic lymph nodes and occult distant metastases [7]. When evaluating lymph nodes, their morphological characteristics and the measurement of shorter axial diameter are important [7]. Lymph nodes most likely involved by a metastatic process have a shorter axial diameter ≥ 10 mm, and most likely pathologic lymph nodes are those with a diameter ≥ 15 mm [15].

Therefore, the assessment of the stage is extremely important in order to select the optimal treatment procedure. Radical hysterectomy with lymphadenectomy is reserved for early-stage disease, IB - IIA, while radiochemotherapy is an option for larger cancers in stage IIB and other stages [7, 16, 17]. For the management of locally advanced cervical cancer with negative lymph nodes on radiological staging, definitive platinum-based chemoradiotherapy and brachytherapy are the preferred procedures [13]. Stage IB1 can be treated surgically or by radiation therapy [3]. According to the new recommendations, patients with enlarged metastatic lymph node (IIIC) diagnosed by imaging are not candidates for surgery, but they can be treated by chemotherapy [3, 7]. Palliative chemotherapy is indicated in cases of distant metastases [3]. In advanced stages of the disease, such as IVA in a case of free parametria, the treatment of choice is pelvic exenteration, including radical hysterectomy and bilateral adnexectomy with pelvic and paraaortic lymphadenectomy. Depending on which organ of the pelvis is involved, urinary bladder and/or rectum should also be surgically removed.

Conclusion

The 2018 International Federation of Gynecology and Obstetrics staging includes surgical risk factors and lymph nodes status, primarily due to the inclusion of radiological diagnostic modalities, but also pathological diagnostics in the staging of cervical cancer, which have exceptional value. By dividing stage IB into three sub-stages and introducing stage IIIC, the modified International Federation of Gynecology and Obstetrics classification of cervical cancer plays a significant role in the prognosis of the disease and the assessment of the five-year survival of women with a particular stage of the disease. The exact assessment of the stage of the disease and the application of the optimal therapeutic approach are most important. Therefore, these innovations in the International Federation of Gynecology and Obstetrics classification will also have an impact on developing countries that, apart from the clinical determination of the stage of cervical cancer, tend to include imaging techniques into the diagnosis and staging of cervical cancer, especially in cases of fertility-sparing approach.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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BILATERAL AXILLARY ACCESSORY BREASTS – A CASE REPORT AND LITERATURE REVIEW

BILATERALNE AKSILARNE AKCESORNE DOJKE – PRIKAZ SLUČAJA I PREGLED LITERATURE

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Summary

Introduction. Accessory breast is a congenital anomaly where ectopic breast tissue is found at any place other than the normal location. It is an extra tissue or a fully developed breast with a nipple. The incidence of this malformation is 0.4–6%. It is believed that this congenital malformation is associated with incomplete regression of the primitive milk streak during embryonic development. The diagnosis and treatment of accessory breasts is very important, because an ectopic breast tissue can undergo various pathological changes, as well as the normal breast tissue. **Case Report**. The authors present a 45-year-old female patient who was referred to a surgeon by a general practitioner with a diagnosis of lipomas in both axillary regions. After clinical examination and additional imaging diagnostic procedures (ultrasound and mammography) accessory breasts were suspected. The patient underwent surgery and the accessory tissue was resected. The histopathological examination confirmed the clinical diagnosis of ectopic breasts without any pathological processes. **Conclusion.** Accessory breast is a rare congenital malformation and its early diagnosis and surgical removal should prevent development of different pathological processes, including breast cancer.

Key words: Breast; Nipples; Mammary Glands, Human; Axilla; Diagnosis, Differential; Congenital Abnormalities; Risk Factors; Mammaplasty

Sažetak

Uvod. Akcesorne dojke predstavljaju kongenitalnu malformaciju kod koje se tkivo dojke pojavljuje van uobičajene, normalne, pozicije dojke u vidu rudimenta tkiva ili potpuno formirane prekobrojne dojke sa bradavicom. Incidencija ove malformacije je 0,4−6%. Smatra se da je u osnovi malformacije izostanak regresije primitivne mlečne linije tokom embrionalnog razvoja. Dijagnoza i tretman prekobrojnih dojki su veoma važni s obzirom da je tkivo dojke podložno svim patološkim promenama, kao i tkivo normalne dojke. **Prikaz slučaja.** Autori su prikazali pacijentkinju staru 45 godina, koju je hirurgu uputio lekar opšte prakse sa dijagnozom lipoma u obe pazušne jame. Nakon kliničkog pregleda i dodatne dijagnostike (ultrazvuk i mamografija), postavljena je sumnja na akcesorne dojke. U daljem toku lečenja pacijentkinja je operisana, urađena je ekstirpacija obe promene, a patohistološki pregled je potvrdio klničku dijagnozu ektopičnih dojki bez dodatnih patoloških promena. **Zaključak.** Akcesorne dojke su retka kongenitalna malformacija čija pravovremena dijagnostika i hirurška evakuacija treba da spreče postojanje supstrata koji može da bude ishodište različitih patoloških procesa, uključujući i karcinom dojke.

Ključne reči: dojka; bradavice; humane mlečne žlezde; aksile; diferencijalna dijagnoza; kongenitalne anomalije; faktori rizika; mamoplastika

Introduction

Polymastia (mammae erraticae, accessory/ectopic or supernumerary breast) is a congenital abnormality of having accessory breast tissue in addition to normal breasts. The reported prevalence of this malformation in females ranges from 0.4 to 6% and in males from 1 to 3%; the highest prevalence is among Asians, especially the Japanese [1, 2]. It is most commonly located in the axilla (the beginning of the milk line) but it can occur in different locations such as inguinal region [3], vulva [4], back [5], foot [6], sternal part of thoracic wall [7] and others. Accessory breast (AB) is more common in women. Most patients do not have a hereditary component, although it is estimated that about 6–10% have a familial predisposition and the pattern of inheritance is autosomal dominant [8, 10].

Female breasts are mammary glands which are the largest skin glands in a woman's body. Mammogenesis begins at the fifth gestational week when ectodermal folds, called the milk lines, appear on the ventral side of the fetus, extending from the axilla to

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Abbreviations
AB – accessory breast
NAC – nipple-areola complex
HE – hematoxylin-eosin

the groin [10, 11]. In normal development, in the second or third month of embryonic development, this line becomes a thoracic ridge at the front part of the thorax at the height of the fourth intercostal space (orthotopic breast) while the other parts undergo regression. An involution failure of this tissue in any part of the ridge leads to the development of ectopic breast tissue (polymastia, accessory breast) with or without nipple areola complex (NAC). This tissue has characteristics of the primordial mammary gland in both puberty and pregnancy and is as hormone-affected as the orthotopic breast [12, 13]. Patients are usually unaware of this anomaly unless the AB is significantly big or involved in some pathological process.

Case Report

The authors present a case of a 45-year-old woman who was referred by a general practitioner due to subcutaneous tumors in the armpits. She noticed them a few years before when she lost some weight and they were primarily an esthetic problem **(Figure 1)**. Occasionally, she felt pain and discomfort in the axillary region when wearing tight clothes. She was in good general condition with no chronic diseases and no other health problems.

Initially, after the clinical examination, the general practitioner suspected that the tumors were lipomas, so the patient was referred to the Clinic of Plastic and Reconstructive Surgery at the Clinical Center of Vojvodina for further evaluation and surgical treatment. She noticed that both tumors have increased in the last year and she believed that her problems were associated with postpartum ptosis of both breasts and significant weight loss. Clinical examination revealed two, soft, well circumscribed subcutaneous tumors between the anterior and middle axillary lines in both armpits. The tumor size was 70 x 70 x 60 mm in the left armpit and 60 x 50 x 50 mm in the right. Both changes were localized in the subcutaneous layer, free from thoracic wall and fixed to the skin. Palpation was uncomfortable for the patient. The skin above the changes was unchanged and was without a nipple or areola. Due to the location and clinical features of the changes, enlarged lymph nodes, lipomas, fibromas, dermatofibromas, or supernumerary breasts were considered as a possible diagnosis. Additional imaging diagnostic procedures were required. Ultrasonography and mammography showed normal tissue of both orthotopic breasts. However, the ultrasound findings of tumors in the armpits showed fat lobules and fibrous tissue as in orthotopic breasts, but completely separated from "normal" breasts. The mammography finding indicated two subcutaneously vaguely defined

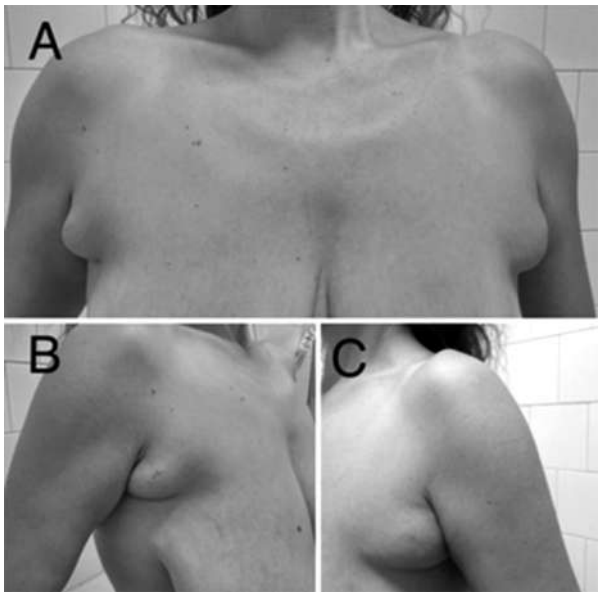

Figure 1. Patient with accessory axillary breasts: A - frontal view; B – right-sided accessory breast; C – left-sided accessory breast
Slika 1. *Pacijentkinja sa akcesornim aksilarnim dojkama: A – frontalni prikaz, B – desna akcesorna dojka, C – leva akcesorna dojka*

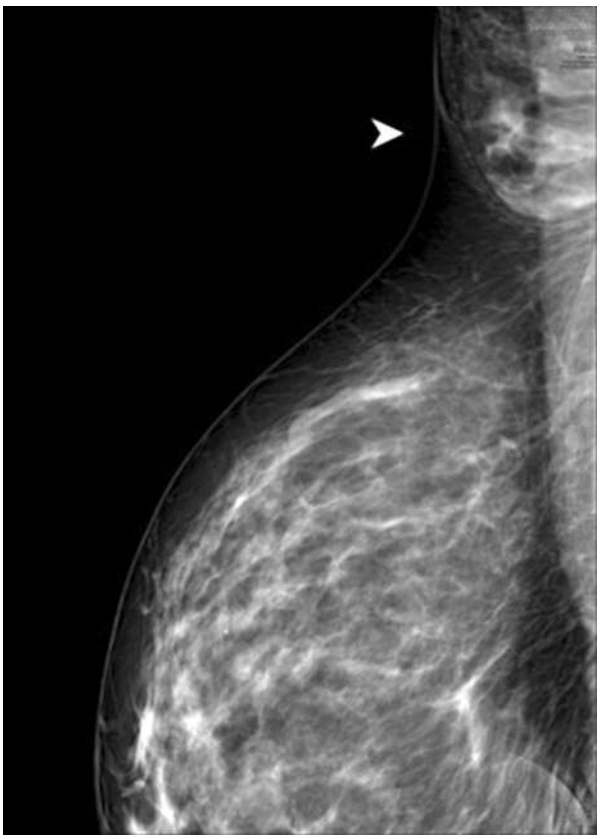

Figure 2. Breast mammography (lateral view): white arrow – accessory breast tissue
Slika 2. *Mamografija dojke (lateralni snimak): strelica – akcesorno tkivo dojke*

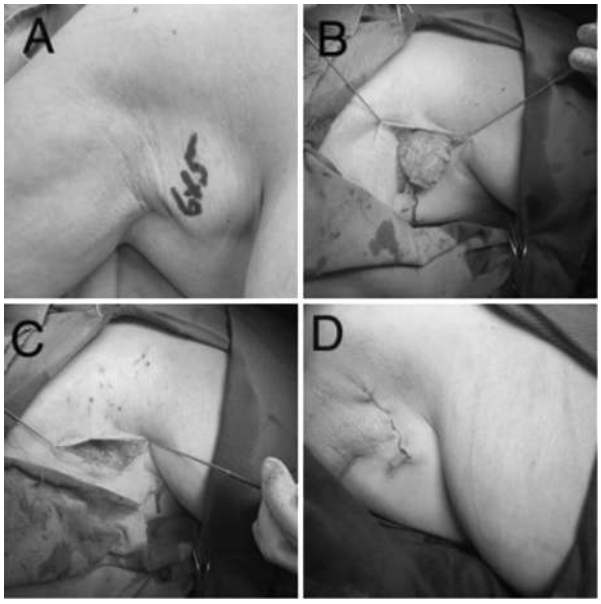

Figure 3. Intraoperative presentation: A - accessory breast before surgery; B - surgical exposition of accessory breast tissue; C - axilla without the accessory tissue; D - closed wound after extirpation of accessory breast tissue
Slika 3. *Intraoperativni prikaz akcesorne dojke: A – akcesorna dojke preoperativno, B – hirurška ekspozicija akcesornog tkiva dojke, C – aksila bez tumora, D – zatvorena rana nakon odstranjenja akcesorne dojke*

changes in both armpits, with signal intensity as in normal breasts **(Figure 2)**.

A preliminary diagnosis of axillary AB was made and a surgical removal was indicated. The surgery was performed under general endotracheal anesthesia. Excision of excess skin and soft tissue was made and tumors were sent for further histopathological evaluation **(Figures 3 and 4)**. The operative and postoperative course was uneventful.

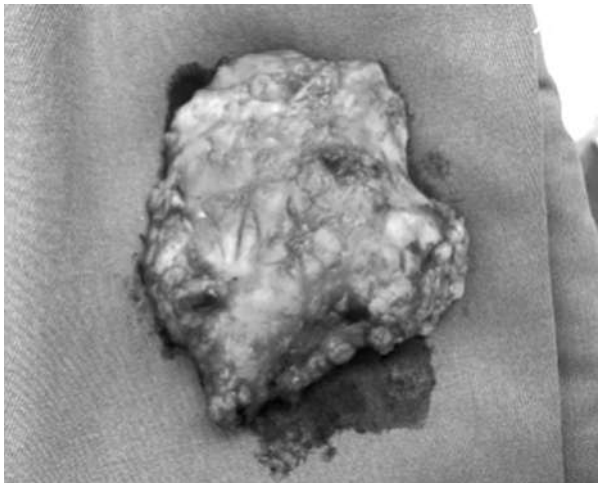

Figure 4. Macroscopic image of the extra breast tissue
Slika 4. *Makroskopski prikaz evakuisane akcesorne dojke*

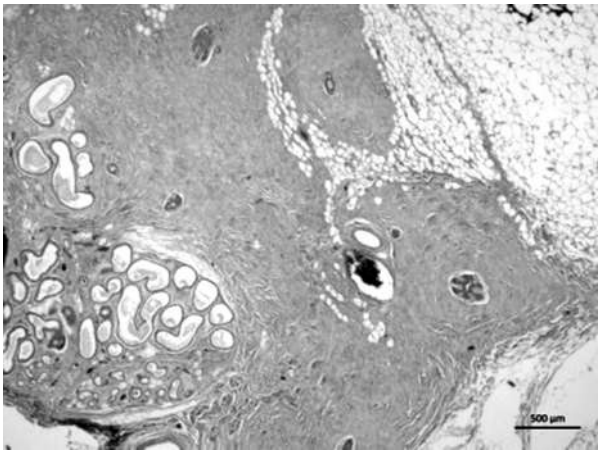

Figure 5. Breast tissue infiltrating the deep dermis (HE x 25)
Slika 5. *Tkivo dojke koje infiltriše duboki dermis (HE x 25)*

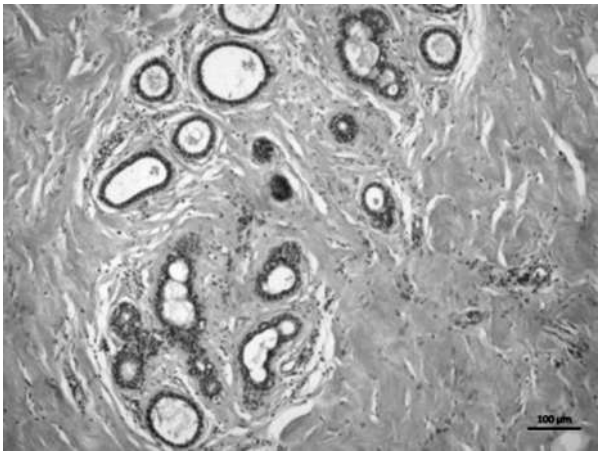

Figure 6. Breast tissue - normal morphology with typical ducts and small lobules (HE x 100)
Slika 6. *Tkivo dojke - uobičajena morfologija sa tipičnim kanalićima i malim lobulima (HE x 100)*

After standardized histopathological procedures, the hematoxylin-eosin (HE) stained sections were histologically examined. The pathologist described the breast tissue within normal limits, localized mainly in subcutaneous adipose layer and partly infiltrating the deep dermis **(Figures 5 and 6)**. There were no skin changes or nipple structures.

Discussion

Congenital anomalies are, by definition, structural or functional defects in tissues or organs that occur during morphogenesis, visible immediately after birth or at a later age. The incidence of congenital anomalies ranges from 0.4–6%, with a lower percentage in Caucasians and higher in other races [11, 12]. As part of this phenomenon, it is clear that the incidence of minor congenital anomalies, which represent only an esthetic problem, is unknown in our geographical area. The literature review of papers dealing with the analysis of acces-

sory breasts from 2010 included a total of 89 papers [14]. Since the problem of AB is regarded as minor, scientific papers usually publish case reports [3–7]. Fewer papers describe a series of cases of supernumerary breasts [1, 13, 15, 16].

There are a few points that need to be addressed considering the problem of AB: differential diagnosis, often nonspecific clinical presentation, association of ectopic breasts with other anomalies, and involvement of ectopic breast tissue in some pathological conditions.

The AB can be of the same shape and size as normal breasts and then the diagnosis is clear. If AB has a NAC, the diagnosis should not be a problem for a general practitioner, but the occurrence of NAC in AB is low, and hence early diagnosis and further treatment can be a problem. If the AB is smaller in size and has no nipple, it is usually not a major issue to the patients and they rarely see a doctor. In such cases, AB is usually asymptomatic and most often represents justs an esthetic problem. Small AB can be treated with minor surgery, sometimes even in local anesthesia combining excision and liposuction. However, the recommendation is to remove all AB if they are classified from one to four (Kajava's classification) [1, 17, 18]. The problem of differential diagnosis of this anomaly is especially difficult when the tissue is localized in the axilla, because it is usually suspected to be an enlarged lymph node, or if it is unilateral, a benign soft tissue tumor [19].

The AB can be associated with various other malformations, so it may be considered as a marker for other anomalies. If it occurs in males, it may be associated with various organ malformations where individual organs grow faster than the other parts of the body pre and postnatally [12]. It is most commonly associated with anomalies in the development of the urinary tract, which is explained by the parallel development of the breast and genitourinary system. Unless associated with genitourinary malformations, they are associated with cardiac or central nervous system abnormalities [1, 20]. Gandhoke CS et al. described a case where a dorsal accessory breast was associated with occult spinal dysraphism and they emphasized that dorsal localization of AB can be considered as a marker of occult spinal dysraphism [5].

Another important issue is that the AB tissue is susceptible to all diseases that affect "normal" breasts [21, 22]. Same pathological conditions, inflammations, different benign or malignant diseases, that can be found in normal breast tissue can also be seen in the ectopic tissue. Cases of benign cysts, adenomas, fibroadenomas, shwannomas, and ectopic breast cancers have been published so far [9, 19, 23, 24]. Malignancies arising from AB are rare, but should not be disregarded as a possibility. According to the literature data, the incidence of accessory breast cancer is 0.2–0.6% [1, 4, 22, 25].

The diagnosis and treatment of AB cancer is the same as in any breast cancer. Early diagnosis requires surgery or at least biopsy, if clinical presentation is not specific, especially if there is no ectopic nipple. A delayed diagnosis can significantly worsen the prognosis if aberrant tissue suffers from malignant breast disease such as cancer or sarcoma.

The AB may be a problem, even without any significant pathological process within the tissue, if it is large or functional [13]. Cases of AB with galactorrhea are also described in the literature [26]. A large AB can also be challenging for the surgeon and requires complex reconstructions.

Last but not the least, in addition to the physical problem, AB is also a psychosocial problem, both at puberty, when they most often occur, and in pregnancy and lactation when they usually increase in size and sometimes become symptomatic.

Surgical treatment is the method of choice in the treatment of AB. Given the association of this congenital malformation with other malformations, thorough examination of body systems is also indicated, particularly of the urogenital system [8, 11]. Considering the fact that AB may be the source of different pathological processes, preoperative ultrasound or, if necessary, mammography or MRI should be done. After imaging diagnostic procedures, biopsy is performed and after histopathological verification, surgical excision with extirpation is done. Sometimes, liposuction can be one of the modalities to treat AB, depending on characteristics of the ectopic breast tissue. Complex reconstructive procedures are usually not necessary, because after extirpation of glandular tissue there is excess skin to properly close the wound [13, 17]. The timing of treatment should be carefully evaluated. It seems reasonable to operate before the onset of pregnancy. Lee SR et al. reported that pregnancy worsens the symptoms, because AB is preparing for lactation like the normal breasts [26]. It becomes bigger, often painful, tender to touch, and sometimes even restricts arm movements if it is located in the axilla. The study also reported that the reoperation rate is lower and postoperative satisfaction is higher if women with AB are operated before pregnancy. Patients who do not want surgical treatment should be monitored clinically from time to time and educated about the risks they are exposed to.

Conclusion

Accessory breast is a congenital malformation that clinicians need to keep in mind when facing patients with excess subcutaneous tissue swelling in the milk line region. The accessory breast-related symptoms such as cyclic changes in ectopic tissue (swelling, pain) during menstruation, enlargement of tissue in pregnancy, secretion of milk after childbirth from accessory nipples, as well as a specific location, should direct clinicians towards the diagnosis of accessory breast. Early diagnosis of accessory breast, proper surgical treatment with histopathological examination of ectopic tissue, are a gold standard that should lead to optimal results and high level of patient satisfaction.

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GENETIC ANALYSIS OF MULTIPLE PRIMARY CANCERS – A CASE REPORT

GENETSKA ANALIZA MULTIPLIH PRIMARNIH KARCINOMA – PRIKAZ SLUČAJA

Marko JEVRIĆ[1], Emilija FILIPOVIĆ[1] and Ana KRIVOKUĆA[2]

Summary

Introduction. The occurrence of more than one primary cancer in the same patient is not very common. Multiple cancer prevalence is about 7.9% and the percentage is lower as the number of multiple primary cancers is higher. The incidence of four or more primary cancers in one patient is very rare and its prevalence is around 0.07%. **Case Report.** We report a rare case of a female with four histopathologically confirmed primary malignant neoplasms. The first tumor was endometrial carcinoma diagnosed at the age of 52. Three additional metachronous tumors were diagnosed as follows: left breast cancer, melanoma, and contralateral breast cancer. Extensive genetic testing was performed and 19 genes were sequenced using the next generation sequencing (BRCA1, BRCA2, ATM, BRIP1, CDH1, CHEK2, MSH2, MLH1, MSH6, PMS2, EPCAM, NBN, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11 and TP53). Even with the existing indicators of genetic etiology, this case showed no pathogenic mutations in any of these genes. This indicates the existence of other underlying mechanisms such as hormonal factors, previous treatment of the primary and subsequent tumors, environmental factors, gene-gene and gene-environment interactions, as well as immunosuppression that could increase the risk for the second and subsequent malignancies. **Conclusion.** Detailed information on the biology of multiple primary tumors is important for both clinicians and cancer patients during medical management following primary treatment. In addition, genetic information is very important because it has future implications for both patients and their family members.

Key words: Genetic Testing; Neoplasms, Multiple Primary; Endometrial Neoplasms; Breast Neoplasms; Melanoma; High-Throughput Nucleotide Sequencing; Biomarkers, Tumor; Risk Factors

Sažetak

Uvod. Pojava više od jednog primarnog karcinoma kod istog pacijenta nije čest događaj. Učestalost multiplih primarnih karcinoma iznosi oko 7,9%, a ovaj procenat opada sa povećanjem broja multiplih primarnih karcinoma. Pojava četiri ili više karcinoma kod istog pacijenta je veoma retka pojava i prijavljuje se sa učestalošću od 0,07%. **Prikaz slučaja.** Predstavljamo redak slučaj pacijentkinje sa četiri, histološki potvrđena primarna karcinoma. Prvi je dijagnostikovan karcinom endometrijuma u 52. godini života. Tri dodatna metahrona tumora dijagnostikovana su sledećim redom: karcinom u levoj dojci, melanom i kontralateralni karcinom desne dojke. Urađena je kompleksna genetička analiza 19 gena novom generacijom sekvenciranja (BRCA1, BRCA2, ATM, BRIP1, CDH1, CHEK2, MSH2, MLH1, MSH6, PMS2, EPCAM, NBN, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11 i TP53). Iako su postojali indikatori koji su ukazivali na genetičku etiologiju, analiza nije pokazala prisustvo štetnih mutacija u ispitivanom panelu gena. Ovaj rezultat ukazuje na postojanje drugih mehanizama uzrokovanih hormonskim faktorima, faktorima spoljašnje sredine, terapijama primarnog i ostalih tumora, imunosupresijom, genskim interakcijama kao i interakcijama gena sa spoljašnjom sredinom, koji su uticali na povećani rizik za nastanak multiplih karcinoma. **Zaključak.** Detaljne informacije o biologiji multiplih primarnih karcinoma značajne su za adekvatno kliničko zbrinjavanje pacijenata nakon primarnog terapijskog tretmana. Takođe, genetička informacija je veoma važna zbog budućih implikacija koje nosi kako za pacijente tako i za članove njihovih porodica.

Ključne reči: genetičko testiranje; multipli primarni karcinomi; karcinom endometrijuma; karcinom dojke; melanom; sekvenciranje nukleotida velike propusnosti; tumorski biomarkeri; faktori rizika

Introduction

Multiple primary malignant neoplasms (MPMNs) are defined as two or more malignant tumors in the same individual, histopathologically distinct with excluded possibility that one is a metastasis of the other. It has been estimated that multiple cancer prevalence is about 7.9%. Four or more cancers appear in patients with primary malignant tumors with prevalence around 0.07% [1]. The incidence of MPMNs has been increasing with the increase of cancer survivors and aging of the population. The risk of developing primary cancer is 20% higher in persons who have already had a malignant tumor than in the general population [2]. The profile of patients with more than two primary cancers is still unclear because of their rarity. Multiple reasons may contribute to the occurrence of MPMNs such as pathogenic mutation in susceptibility genes, radiotherapy or cytotoxic chemotherapy regimens for the initial tumor, or exposure to carcinogens. Also, MPMNs may arise due to chance alone, or due to the underlying developmental abnormalities [3]. Numerous studies indicate the need for

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Abbreviations

MPMNs – multiple primary malignant neoplasms
CMF – cyclophosphamide, methotrexate, fluorouracil
DNA – deoxyribonucleic acid
SPCs – second primary cancers
SIN – standardized incidence ratio
NGS – next generation sequencing

epidemiological, clinical and pathological reports on MPMNs in order to detect high-risk patients [1, 4].

It has been previously reported that genetic susceptibility can be a major cause of MPMNs and that many familial cancer syndromes are associated with the pathogenic mutations in susceptibility genes [5–7]. Due to this phenomenon, many patients with MPMNs are referred to the clinical geneticists for genome profiling. Even so, there is a lack of genetic data on the individuals with MPMNs. It is of high relevance to investigate whether the genomic profile of the individuals with MPMNs fit in the suspected familial cancer syndrome, or there is a need to perform more extensive genetic testing that includes wider gene panels and epigenetic changes. In this paper, we present a very rare case of a patient who developed four primary malignant neoplasms including endometrial cancer, breast cancer, melanoma, and contralateral breast cancer. We investigated the possible genetic cause of the MPMNs occurrence.

Case Report

A 67-year-old female patient was referred to the surgery department of the Institute of Oncology and Radiology of Serbia in 2009, because of a suspicious pigmented skin lesion on the right foot which was defined as a melanocytic lesion prone to developing melanoma by dermoscopy. The patient underwent surgical excision of the lesion with "safety margins". Histopathology examination showed an invasive skin melanoma (Clark III, Breslow II thickness - 1 mm, absent ulceration, mitotic rate 2/10 high power fields, nevoid type of cells, pigmentation grade II, without blood vessels or lymphatic invasion, and without malignant elements in margins). The patient's medical history showed two previously diagnosed and treated malignant tumors. At the age of 52, the patient was diagnosed with endometrial carcinoma. Hysterectomy with bilateral adnexectomy was performed followed by postoperative radiotherapy. Nine years later, at the age of 61, she was diagnosed with left breast cancer and she underwent a modified radical mastectomy. Histopathology showed grade 2 invasive ductal carcinoma, without evidence of metastasis in 12 examined lymph nodes. Treatment was continued with six cycles of cyclophosphamide, methotrexate, fluorouracil (CMF) chemotherapy regimen and postoperative radiotherapy. In 2012, at the age of 70, the patient was diagnosed with contralateral breast cancer. Histopathological analysis showed invasive grade 2 ductal carcinoma. Around 30% of tumor revealed lobular differentiation with 2 metastatic lymph nodes of 21 examined. The treatment included modified radical mastectomy and tamoxifen. The patient was a nonsmoker, but suffered from hypertension for 20 years, diabetes mellitus since 2003, and gout since 2002. The patient was not insulin dependent and her family medical history showed only one case of lung cancer diagnosed in her father.

Due to four metachronous cancers, the patient was referred to the Genetic Counseling Department at the Institute of Oncology and Radiology of Serbia for risk assessment and genetic testing. The patient was tested for mutations in 19 cancer related genes (*BRCA1*, *BRCA2, ATM, BRIP1, CDH1, CHEK2, MSH2, MLH1, MSH6, PMS2, EPCAM, NBN, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53).* A Nextera deoxyribonucleic acid (DNA) Library Preparation Kit combined with TruSight® Cancer Panel (Illumina, San Diego, USA) was used for coding sequence and exon/intron boundaries enrichment. The next generation sequencing (NGS) was performed using MiSeq Sequencing System (Illumina) according to the manufacturer's protocol. Classification of detected variations was done through Illumina Variant Interpreter Software (Illumina) and Geneticist Assistant (Soft Genetics) **(Table 1)**. All detected variations were annotated as either benign or likely benign according to the databases (ClinVar, BIC, HGMD, BRCAShare, LOVD) and available published literature.

Discussion

Multiple primary malignant neoplasms may occur in a single organ or involve multiple organ systems and they may be synchronous or metachronous. Among patients with multiple primary malignancies, double cancers are commonly observed, triple cancers occur in 0.5% of these patients, and quadruple or quintuple cancers occur in < 0.1% [8]. The mechanisms responsible for the development of MPMNs are not yet fully elucidated. Factors that are frequently implicated in the MPMNs include genetic susceptibility, immune status and previous intensive exposure to carcinogens, such as chemo- and/or radiotherapy. For example, there are specific genetic factors predisposing to the development of certain types of cancers. Mutations in genes with high penetrability, such as BRCA1 or BRCA2, lead to significantly elevated risk for breast and ovarian cancers (up to 85% life-time risk). Furthermore, Li-Fraumeni syndrome is an example of a rare disorder that greatly increases the risk of developing various types of cancer such as breast cancer, osteosarcoma and soft tissue sarcomas, as well as brain tumors, leukemias and adrenocortical carcinoma [9]. More than 50% of families with this syndrome exhibit inherited TP53 gene mutations [10]. The vast majority of tumors, however, are non-hereditary and may be attributed to environmental and/or life style factors. The epigenetic changes, such as DNA methylation events, histones modifications and chromatin remodeling, are now known to cooperate with genetic alterations to drive the cancer phenotype. According to the Curtis et al., the relative risk of second cancer differs mark-

Table 1. Detected gene variants
Tabela 1. *Detektovane genske varijante*

Gene *Gen*	Zygosity* *Zigotnost**	HGVS** cDNA *HGVS** cDNA*	HGVS Protein *HGVS Protein*	Annotation *Klasifikacija*
BRCA1	het	c.4837A>G	p.Ser1613Gly	benign/*benigni*
LRG_292	het	c.4308T>C	p.Ser1436=	benign/*benigni*
	het	c.3548A>G	p.Lys1183Arg	benign/*benigni*
	het	c.3113A>G	p.Glu1038Gly	benign/*benigni*
	het	c.2612C>T	p.Pro871Leu	benign/*benigni*
	het	c.2311T>C	p.Leu771=	benign/*benigni*
	het	c.2082C>T	p.Ser694=	benign/*benigni*
	het	c.1067A>G	p.Gln356Arg	benign/*benigni*
BRCA2	het	c.1114A>C	p.Asn372His	benign/*benigni*
LRG_293	het	c.3807T>C	p.Val1269=	benign/*benigni*
	hom	c.4563A>G	p.Leu1521=	benign/*benigni*
	het	c.5199C>T	p.Ser1733=	benign/*benigni*
	hom	c.6513G>C	p.Val2171=	benign/*benigni*
	het	c.7242A>G	p.Ser2414=	benign/*benigni*
	hom	c.7397C>T	p.Ala2466Val	benign/*benigni*
ATM	het	c.5557G>A	p.Asp1853Asn	benign/*benigni*
LRG_135	hom	c.5948A>G	p.Asn1983Ser	benign/*benigni*
BRIP1	hom	c.3411T>C	p.Tyr1137=	benign/*benigni*
LRG_300	hom	c.2755T>C	p.Ser919Pro	benign/*benigni*
	hom	c.2637A>G	p.Glu879=	benign/*benigni*
CDH1	hom	c.164-14627G>A		benign/*benigni*
LRG_301	het	c.2076T>C	p.Ala692=	benign/*benigni*
	het	c.2292C>T	p.Asp764=	likely benign/*verovatno benigni*
MSH6 LRG_219	het	c.116G>A	p.Gly39Glu	benign/*benigni*
NBN LRG_158	het	c.1197T>C	p.Asp399=	benign/*benigni*
NF1 LRG_214	hom	c.702G>A	p.Leu234=	benign/*benigni*
PMS2	het	c.1621A>G	p.Lys541Glu	benign/*benigni*
LRG_161	het	c.1408C>T	p.Pro470Ser	benign/*benigni*
	het	c.780C>G	p.Ser260=	benign/*benigni*
RAD51D LRG_516	het	c.494G>A	p.Arg165Gln	benign/*benigni*
TP53 LRG_321	hom	c.215C>G	p.Pro72Arg	benign/*benigni*

Legend**:** *Zygosity: hom – homozygote; het – heterozygote; **Human Genome Variation Society (HGVS – a nomenclature that serves as an international standard in gene variants found in DNA, ribonucleic acid and protein sequences)
*Legenda: *Zigotnost: hom - homozigot, het – heterozigot; ** Društvo za varijacije u humanom genomu (HGVS – nomenklatura predstavlja internacionalni standard za obeležavanje deoksiribonukleinske kiseline, ribonukleinske kiseline i proteinskih sekvenci)*

edly by age at diagnosis of the first tumor and it was found to be 6-fold higher in childhood cancer survivors. It was also found that the greatest burden of MPMNs was diagnosed at the age of 30 to 59 [11]. The type and the cause of the secondary malignancies may depend on the first primary malignancy or may be entirely independent. Urinary bladder is the initial primary cancer site with the highest percentage of individuals with multiple primary cancers (16%), followed by oral cavity and pharynx (15%), and uterus (11%) [12]. Liver cancer showed the fewest multiple primary occurrences compared to all other primaries (1%).

Demirci et al. presented a woman with quadruple adenocarcinoma, including bilateral breast cancer, ovarian cancer and retroperitoneal neuroendocrine carcinoma. They argued that the association of breast and ovarian cancer had been likely an effect of genetic and/or hormonal factors. The contralateral breast cancer seemed to be caused by chemotherapy, radiotherapy and insufficient hormone therapy [13]. Kapoor et al. reported a case of a female patient who developed breast cancer eighteen years after contralateral breast cancer, then adenocarcinoma of the endometrium, and finally esophageal squamous cell carcinoma. Their conclusion, corroborated with researched literature, pointed to smoking and family history as the main factors for MPMNs. Attention was also paid to the impact of tamoxifen as a risk factor for endometrial cancer, as well as to radio-

therapy as a risk factor for esophageal squamous cell carcinoma [14]. In Korea, Noh et al. described a case of quadruple cancer of the breast, rectum, and synchronous ovarian and endometrial cancer in one woman, with a suspicion that pathogenesis might have been related with genetic factors or family history, but the patient refused genetic testing [15]. In China, Jiao et al. reported a case of quadruple primary malignancy involving the small intestine, descending colon, renal pelvis and pancreas, 20 years after the first diagnosis. They connected the occurrence of MPMNs with genetic susceptibility given that other family members did not get cancer. The second hypothesis was immune abnormality [16].

Our patient was diagnosed with primary endometrial carcinoma at the age of 52 and a primary breast cancer at the age of 61. At the age of 67, she was diagnosed with melanoma, and at the age of 70 with contralateral breast cancer. In our patient the risk factors were diabetes mellitus, chemotherapy and radiotherapy. According to the literature, patients with cervical and uterine cancers as initial tumors have more chances to develop a second malignancy. A population-based study using data from Germany and Sweden provided an overview on the risk of specific second primary cancers (SPCs) in women diagnosed with endometrial cancer [17]. They showed that breast cancer is the leading SPC after diagnosis of endometrial cancer. This study indicated increased risk for second ovarian cancer and kidney cancer for patients with endometrial cancer. According to the Hemminki et al., many subsequent neoplasms can be expected after women are diagnosed with endometrial carcinoma, both because of their favorable survival rate and because of the high frequency of this malignancy. Similar with the German and Swedish study, Hemminki et al. reported a significantly increased SPCs after endometrial carcinoma at several sites, ovarian carcinoma, standardized incidence ratio (SIN) - 3.16, and urinary bladder carcinoma, SIN - 2.35 being the most frequent [18].

The fact that our patient developed four metachronous carcinomas led us to believe that underlying genetic factors might have contributed to this specific phenotype. However, NGS showed no pathogenic mutations in the panel of 19 analyzed cancer related genes. The limitation of this study was that we were not able to detect large genomic rearrangements (deletions and duplications of whole exons) or structural rearrangements, so we believe that there might be other genetic conditions underlying this specific phenotype. Also, genes not previously associated with cancer risk may be significant in a proportion of MPMNs cases. For example, recently identified inherited cancer genes (e.g. POLD1, POLE) associated with colorectal and endometrial cancers, were not included in the gene panel and were not tested in our patient. Thus, expanding the gene panel might have been helpful in determining possible genetic causes of MPMNs. In case genetic variants of unknown significance occur in these larger gene panels they should be regularly reclassified, unlike benign and likely benign polymorphisms that do not require reclassification.

There might be a couple of possible reasons for MPMNs case testing negative after genetic analysis, even with other indicators suggestive of genetic etiology. For example, ovarian and endometrial carcinomas are linked to reproductive hormones and the number of ovulatory cycles which is a risk factor for both malignancies [18]. Similarly, hormonal factors may explain the occurrence of breast carcinoma after endometrial carcinoma in our patient. She also had diabetes, which is associated with an increased risk for several types of cancers, including pancreatic, liver, breast, colorectal, urinary tract, and female reproductive organs [19]. Because of many confounding factors such as diabetes duration, different levels of metabolic control, drugs, therapies and chronic complications, it is difficult to assess cancer risk in diabetes patients. Nevertheless, this risk factor should be taken into account especially in the complex etiology of MPMNs. Another explanation for the MPMNs development in our patient may be exposure to radiotherapy and chemotherapy agents in the treatment of the primary and subsequent tumors. Radiotherapy is a well known mutagenic factor and alkylating agents are involved in the pathogenesis of secondary cancers [20, 21]. The exposure to radiotherapy and antineoplastic agents may lead to the development of subsequent neoplasms due to the DNA damage. Our patient was treated with postoperative radiotherapy after the primary diagnosis of endometrial carcinoma and with CMF chemotherapy regimen after the second primary breast cancer. In addition to cancer treatment as a risk factor, MPMNs can also arise as a result of environmental factors as well as gene-gene and gene-environment interactions [22]. Environmental exposures relevant to the development of two or more tumor types are important to consider in the assessment of such patients. Sometimes, these factors may easily be clinically identified. For example, an increased risk of oral and pharyngeal cancers is observed after an initial lung adenocarcinoma [23]. On the other hand, these factors may be less obvious or may be shared between family members and mimic genetic factors underlying risk of the disease. Furthermore, a gene can be switched off in a somatically heritable fashion, rather than by mutation of the DNA sequence, which may help explaining at least part of MPMNs cases [24]. In addition, we should not disregard the age of the patient as one of the factors that may have influenced the cancer occurrence since the first one developed in her 50s and the last one in her 70s. Factors involved in multiple primary cancers in different sites may also include various infections and immunosuppression. The increased occurrence of second primary malignancies may also result from intensive medical surveillance after the first diagnosis, or multiple tumors may occur by chance alone. Detailed information on multiple primary tumors as well as on their causes is important for both clinicians and cancer patients during medical management following the primary treatment.

Conclusion

Although occurrence of more than two cancers in a single patient is very rare, it is important for clinicians to consider genetic testing in order to provide adequate treatment and follow up as well as to minimize the negative effects of cancer treatment. Also, it is very important to provide adequate support and genetic counseling because of the important implications genetic testing results may have on patients and their family members.

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Case report
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MARTORELL HYPERTENSIVE ISCHEMIC LEG ULCER – A CASE REPORT

MARTORELOV HIPERTENZIVNI ISHEMIČNI ULKUS POTKOLENICE – PRIKAZ SLUČAJA

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Summary

Introduction. Hypertensive ischemic leg ulcer, also known as Martorell ulcer, is not very rare, but an under-recognized type of leg ulcer. It has specific clinical and histopathological characteristics. It occurs almost exclusively in patients with arterial hypertension. It is more common in women and in patients with type 2 diabetes. It is localized particularly in the laterodorsal distal third of the lower leg. This ulcer is extremely painful. Its clinical features may very much resemble pyoderma gangrenosum. **Case Report.** We are presenting a case of a 40-year-old obese male, who suffered from arterial hypertension during the past 26 years. His ulcer appeared spontaneously on the lateral aspect of the right lower leg and progressed gradually. From the very onset, the ulcer was extremely painful. At first, it was diagnosed as pyoderma gangrenosum and treated with systemic corticosteroids and immunosuppressants. Since the response to therapy was not satisfactory, the histopathology was revised and the diagnosis of hypertensive ischemic leg ulcer was made. After initial wound debridement and local negative pressure therapy, split-thickness skin grafting was performed. The pain disappeared right away almost completely and complete epithelization was achieved two weeks after skin grafting. **Conclusion.** It is important to consider Martorell ulcer in hypertensive patients with extremely painful ulcers of the lower leg. In order to establish the appropriate diagnosis, it is essential to take a deep skin biopsy and correlate the finding with a specific histopathological picture. It is the only way not to confuse hypertensive ischemic leg ulcer with pyoderma gangrenosum, since the management of the two conditions is completely different.

Key words: Leg Ulcer; Hypertension; Atherosclerosis; Risk Factors; Diagnosis, Differential; Chronic Pain; Skin Transplantation; Negative-Pressure Wound Therapy

Sažetak

Uvod. Hipertenzivni ishemični ulkus potkolenice takođe poznat kao Martorelov ulkus, nije redak, ali je uglavnom neprepoznat tip ulkusa potkolenice. Ima specifične kliničke i patohistološke karakteristike. Javlja se skoro isključivo kod pacijenta sa arterijskom hipertenzijom. Češći je kod žena i obolelih od dijabetesa tip 2. Lokalizacija na latero-dorzalnoj trećini potkolenice je specifična. Ovaj tip ulceracija je izuzetno bolan. Klinička slika može u znatnoj meri da podseća na *Pyoderma gangrenosum*. **Prikaz slučaja.** Prikazujemo slučaj gojaznog muškarca, starosti 40 godina, koji se prethodnih 26 godina lečio od arterijske hipertenzije. Ulceracija se pojavila spontano na lateralnoj strani desne potkolenice sa postepenom progresijom. Od samog početka bila je izuzetno bolna. Prvobitna dijagnoza bila je *Pyoderma gangrenosum*, te je lečen sistemskim kortikosteroidima i imunosupresivima. Pošto terapijski odgovor nije bio zadovoljavajući, načinili smo reviziju histopatologije i tada je postavljena dijagnoza hipertenzivni ishemični ulkus potkolenice. Pošto je načinjen debridman i aplikovana lokalna terapija negativnim pritiskom, postavljeni su kožni graftovi. Bol je skoro sasvim nestao odmah posle intervencije, a ulceracija je u potpunosti zarasla dve nedelje posle postavljanja grafta. **Zaključak.** Važno je imati na umu Martorelov ulkus kod svih bolesnika sa hipertenzijom i izuzetno bolnim ulkusom potkolenice. Kako bi se postavila prava dijagnoza, suštinski je važno da se uzme duboka biopsija kako bi se videla specifična histopatološka slika. To je jedini način da se ne pomeša hipertenzivni ishemični ulkus potkolenice sa *Pyoderma gangrenosum*, pošto je lečenje ova dva stanja u potpunosti različito.

Ključne reči: ulkus potkolenice; hipertenzija; ateroskleroza; faktori rizika; diferencijalna dijagnoza; hronični bol; transplantacija kože; terapija rane negativnim pritiskom

Introduction

Hypertensive ischemic leg ulcer (HYTILU), also known as Martorell ulcer, after the author who first described it [1], is not very rare but an under-recognized type of leg ulcers.

Leg ulcers should be considered a major health problem due to their prevalence, significant impact on the quality of life, as well as their direct and indirect costs. The burden of skin diseases, according to the joined project of the American Academy of Dermatology and the Society for Investigative Dermatology published in 2006, showed that different kinds of wounds had the highest relative cost/prevalence ratio of all skin diseases [2]. This information was confirmed by a report on the same topic in 2017 [3].

Although the great majority of leg ulcers are vascular in origin, a wide range of non-vascular medical conditions, as well as contributors can be responsible for their occurrence [4]. A profound knowledge of all these etiologic factors, from the most common to the very rare, is essential for cor-

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Abbreviations
HYTILU– hypertensive ischemic leg ulcer Introduction

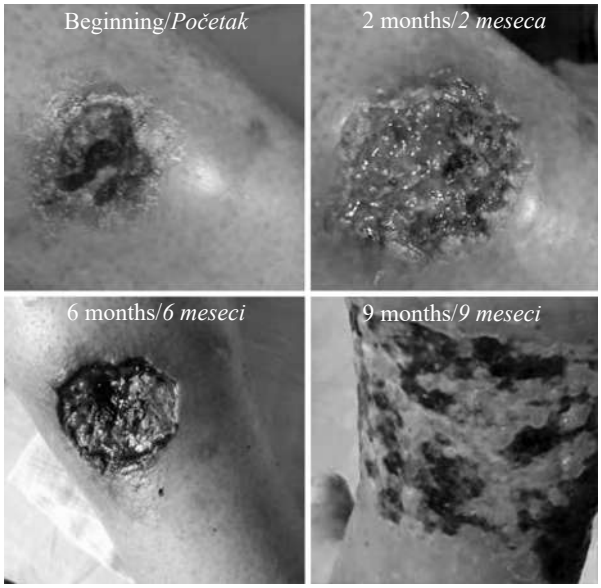

Figure 1. Gradual progression of the ulcer
Slika 1. *Postepena progresija ulceracije*

rectly diagnosing a leg ulcer in each patient and its proper management [5].

Hypertensive ischemic leg ulcer was first described by Fernandes Martorell in 1945 in Barcelona, among the obese female population with arterial hypertension [1]. The first one, as well as further reports [6, 7] showed specific clinical and histopathological characteristics of HYTILU. It occurs almost exclusively in patients with arterial hypertension. It is more common in women and in patients with type 2 diabetes. Localization on the latero-dorsal distal third of the lower leg is specific for this type of ulcer. These ulcers are extremely painful. The clinical features may resemble pyoderma gangrenosum very much.

Case Report

We are presenting a case of a 40-year-old obese male with a body mass index 34.1. He has been treated for high blood pressure since the age of 14. His medical record showed good regulation of blood pressure levels most of the times. The ulcer appeared spontaneously on the lateral aspect of the lower right leg, and progressed gradually **(Figure 1)**. From its very onset the ulcer was extremely painful. During the first 7 months, the patient did not seek medical help. Then, he was referred to our clinic for the first time, and our first (clinical) diagnosis was HYTILU. At that time, a skin biopsy was performed. The histopathological analysis was consistent with the diagnosis of pyoderma gangrenosum (dense inflammatory infiltrate of the entire dermis and hypodermis, thickened septa of the subcutaneous fat). Detailed laboratory tests were performed, including blood glucose level, immunological findings, serum calprotectin and fecal occult blood test that were within normal ranges, except for elevated inflammatory markers. The duplex ultrasound scans of the leg veins were inconclusive. The ankle brachial pressure index was within normal ranges.

In accordance with the obtained findings, methylprednisolone treatment (initial dose 1 mg/kg, with gradual decrease), a standard for pyoderma gangrenosum, was initiated. After the introduction of this therapy, only partial improvement of the ulcer was achieved. During the following 4 months, the patient did not keep the scheduled follow up appointments and stopped taking all the medications prescribed for ulcer. However, due to further ulcer deterioration, that affected the whole circumference of the lower leg, he was again admitted to our clinic. A combination therapy with methylprednisolone and methotrexate was initiated. Since there was no improvement during the next 8 weeks, cyclosporine was introduced to the existing treatment instead of methotrexate. The therapy was conducted regularly in hospital conditions, so there was no doubt that the patient was using the prescribed medications, unlike before. During this period, we observed no improvement of the ulcer, but several complications emerged **(Figure 2)**. The ulcer pain was worse, and local infections of the ulcer repeatedly occurred resulting in necessary repetitive administration of several antibiotics, and everyday use of painkillers. A bleeding peptic ulcer also appeared.

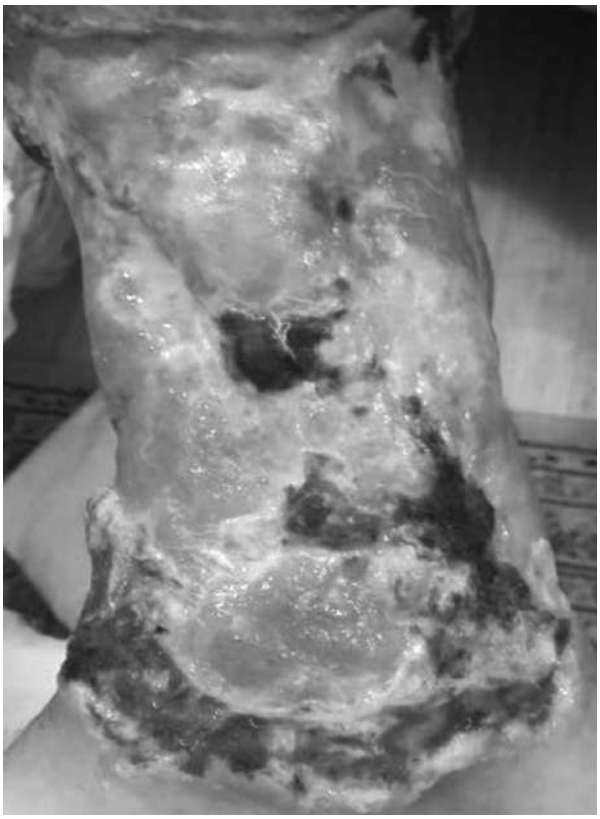

Figure 2. Ulcer deterioration - 13 months since onset
Slika 2. *Pogoršanje ulceracije – 13 meseci od početka*

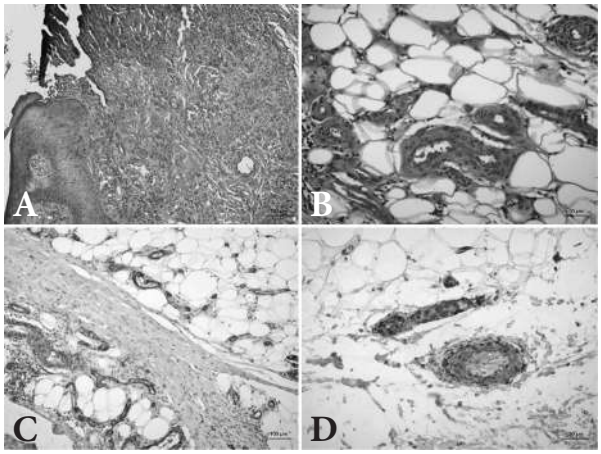

Figure 3. Histopatholoic findings
Slika 3. *Histopatološki nalaz*
A: ulcerated epidermis, with necrotic material on the ulcer base which is located deep into the dermis (HEx100) **B**: margin between dermis and subcutaneous adipose tissue with numerous blood vessels with thickened wall (HEx200) **C**: margin between dermis and subcutaneous adipose tissue with numerous blood vessels with thickened muscle wall (SMAx100) **D**: thickened muscle wall of the blood vessels in the subcutaneous adipose tissue (SMAx200) ***A****: epidermis je ulcerisan, dno defekta je prekriveno sa nekrotičnim masama i prostire se duboko u dermis (HEx100)* ***B****: granica dermisa i potkožnog masnog tkiva sa umnoženim krvnim sudovima zadebljalog zida (HEx200)* ***C****: granica dermisa i potkožnog masnog tkiva sa umnoženim krvnim sudovima zadebljalog mišićnog zida (SMAx100)* ***D****: zadebljali mišićni zid krvnog suda potkožnog masnog tkiva (SMA x200)*

After a month of unsatisfactory response to therapy, a revision of the histopathology was performed., Beside ulcerated and necrotic epidermis, the pathologist noticed concentrically thickened walls and narrow lumens of arterioles in the dermis and hypodermis. Fresh thrombi were observed in the lumen of arterioles located near the ulcer. These findings were in agreement with HYTILU diagnosis **(Figure 3)**.

As soon as the new histopathology report was issued, the immunosuppressive therapy was discontinued. The beta-blocker, which was previously used as an antihypertensive drug, was replaced with a calcium channel blocker. Low molecular weight heparin was introduced into the therapy. A plastic surgeon was included in the team. He performed a complete surgical debridement of the devitalized tissue **(Figure 4)**. Local

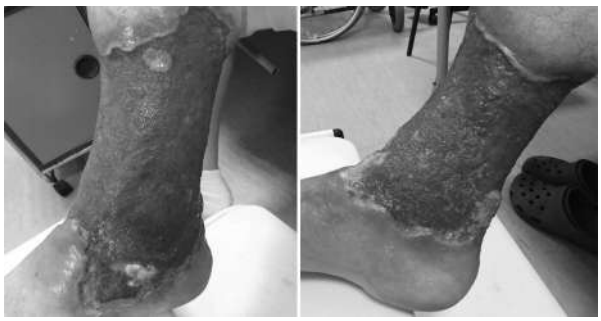

Figure 4. Ulcer after surgical debridement
Slika 4. *Ulkus posle hirurškog debridmana*

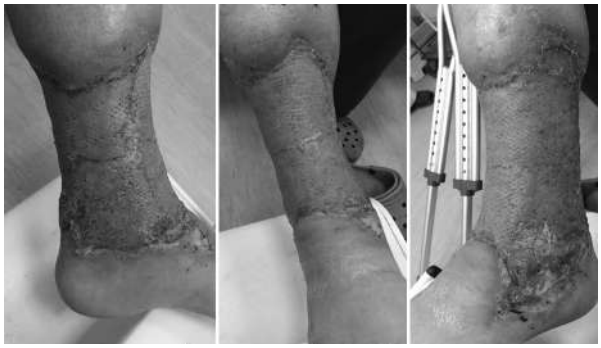

Figure 5. Healed ulcer two weeks after skin grafting
Slika 5. *Zarasla ulceracija, dve nedelje posle postavljanja kožnog grafta*

negative pressure treatment was started thereafter in order to improve the wound bed. Two weeks after the beginning of this treatment, a surgical intervention was performed. It included excochleation of granulation tissue and covering the skin defect of 3% total body surface with split-thickness skin grafting taken from the opposite thigh. After applying the skin graft, a very fast improvement of the ulcer was noticed and the pain almost completely disappeared. Two weeks after skin grafting, complete epithelization was achieved **(Figure 5)**. There were no relapses of the ulcer during the one-year follow-up period. Currently, the patient uses maintenance therapy – clopidogrel, antihypertensive therapy, emollient creams and a compression stocking.

Discussion

First reports of the association of ischemic ulcers and arterial hypertension date back to the 1940s [1, 6, 7]. From the earliest reports, the following characteristics of Martorell ulcer were noted: strong association with arterial hypertension; localization on anterolateral aspect of the lower leg; intense pain with deterioration in the horizontal position; no signs of arterial calcification or venous insufficiency; it is more frequent in females, aged 50 to 70 years.

Since that time, little has changed, considering clinical and epidemiological characteristics. It is known that HYTILU occurs exclusively in patients with arterial hypertension; in up to 58% of the cases there is also a simultaneous presence of diabetes mellitus [8]. Women between 50 and 70 years of age are predominantly affected, but there is a growing number of cases described in males, and younger patients as well [8–11].

Martorell ulcer may be a late complication of arterial hypertension, even if it is well controlled [12]. Although the presented patient is younger than most of the previously reported cases, he has a history of arterial hypertension treated over 25 years. As mentioned, his hypertension was generally well regulated, and was not accompanied by other cardiovascular complications.

The main histopathological factors responsible for the appearance of HYTILU are related to microvascular changes and do not involve large blood ves-

Table 1. Comparative characteristics of Martorell ulcer and pyoderma gangrenosum
Tabela 1. *Komparativne karakteristike Martorelovog ulkusa i Pyoderma gangrenosum*

Martorell ulcer/*Martorelov ulkus*	Pyoderma gangrenosum/*Pyoderma gangrenosum*
Associated diseases/*Pridružene bolesti:* Arterial hypertension/*Arterijska hipertenzija* Diabetes type II/*Dijabetes tip II*	Associated diseases/*Pridružene bolesti:* Inflammatory bowel disease/*Inflamatorne bolesti creva* Rheumatoid arthritis/*Reumatoidni artritis* Myeloproliferative disorders/*Mijeloproliferativne bolesti*
Location at laterodorsal leg or Achilles tendon/*Lokalizacija na latero-dorzalnom delu potkolenice ili predelu Ahilove tetive*	Any location (legs) *Bilo koja lokalizacija (noge)*
Bilateral occurrence, often sequential (weeks to years) *Bilateralna pojava, često sekvencijalna (od nekoliko nedelja do više godina)*	Pathergy *Patergija*
Excruciating pain/*Izuzetno jak bol*	Intense pain/*Jak bol*
Histology: subcutaneous arteriolosclerosis; thickened arteriolar walls associated with a narrow vessel lumen *Histologija: supkutana ateroskleroza; zadebljanje arteriolarnog zida, sa suženjem lumena krvnog suda*	Histology: not specific; massive neutrophilic infiltration; often around and within the vessel walls *Histologija: nije specifična; masivan infiltrat neutrofila; često okolo i unutar zida krvnih sudova*
Treatment: conservative wound treatment; wound surgery *Lečenje: konzervativno lečenje ulceracije; hirurška terapija*	Treatment: topical steroids; systemic steroids, other immunosuppressive agents/*Lečenje: lokalni kortikosteroidi; sistemski kortikosteroidi, drugi imunosupresivi*

sels, as is the case with the most of peripheral vascular diseases. Patients with Martorell ulcers usually have a normal ankle brachial pressure index, but vascular resistance is increased. It suggests that there is a narrowing of arterioles, which not only results in reduced tissue perfusion, but also in a diminished effectiveness of compensatory mechanism that usually occurs below the arterial narrowing or occlusion sites [13]. It is known that even slight trauma can be a triggering factor for HYTILU. However, half of the ulcers arise spontaneously [14].

Martorell ulcers are very painful wounds on the lateral-dorsal aspect of the calf or in the Achilles tendon region. In about 50% of all the cases there is a bilateral involvement. Usually the first symptom is a painful red blister, which soon becomes purpuric and finally ulcerates. In most cases the ulcer is superficial with necrotic base and purple-reddish edges, but sometimes it may be quite deep. In further course, there is a gradual increase in the size of the ulcer, sometimes with satellite lesions [8].

Pain is an important clinical sign in Martorell ulcer. There is a great disproportion in the size and clinical appearance of the ulcer. Rest or elevation of the limb does not relieve the pain; horizontal leg position can even aggravate it. In 75% of cases patient's night rest is significantly disturbed because of the pain [15]. Consequently, patients develop a heavy dependence on painkillers [10, 16].

The diagnosis of HYTILU is based on the typical history and clinical presentation, but final confirmation can be made only after histological analysis. Histological presentation of Martorell ulcer is rather characteristic. The most important point is the presence of thickened subcutaneous arteriolar walls associated with a narrow vessel lumen. The increase in the size of the arteriolar wall is due to hypertrophy of the media musculature and intimal hyperplasia. The ratio of lumen/wall thickness in the vessels is significantly reduced. Periarteritis is frequently found, but should be regarded as a non-specific cellular response to the skin necrosis [8, 10, 14].

Martorell HYTILU can easily be misdiagnosed as some other painful ulcerative condition of the lower leg. Martorell ulcer may very much resemble pyoderma gangrenosum, especially if the ulcer is deep. In both conditions the ulcers progress rapidly, their edges are livid and elevated, and both conditions can be extremely painful. There are some clinical characteristics that can help distinguish between the two, but histopathological findings should confirm the exact diagnosis **(Table 1)** [10, 17].

In a large series of HYTILU cases from Zurich, 52% (16/31 patients) were referred with an erroneous diagnosis of pyoderma gangrenosum, and another 19% (6/31 patients) with an erroneous diagnosis of necrotizing vasculitis [8]. This was also the case with our patient, who was initially diagnosed with pyoderma gangrenosum, and only after the revision of the histological finding, HYTILU was diagnosed. It was rather a long time until the right diagnosis was made, which is partly a consequence of the fact that it was a so-called "difficult to treat patient" that reported for check-ups irregularly and refused hospital treatment for a long time.

The most important step of the treatment is the detection of the disease. One always must bear in mind that wound healing is an extremely slow process and clinical response to standard treatment takes considerable time.

There are few recommended therapeutic approaches:

Surgical treatment: debridement of devitalized tissue is the first step. For wound bed conditioning, localized negative pressure therapy may be used. It can improve the take rate of the subsequent mesh grafts [17]. After removing the necrotic tissue, skin grafts are applied. Autologous mesh skin grafts are

usually used. Surgical closure of lesions > 4 cm^2 is recommended [18]. In smaller ulcers it is reasonable to try conservative therapy measures first. If the appropriate therapeutic effect is not achieved, lumbar sympathectomy should be considered, in order to promote vasodilatation [10].

Anticoagulation therapy: in all patients with HYTILU, anticoagulants like heparin or coumarin should be given, and antiplatelets should be introduced in maintenance therapy [10].

Blood pressure control: the drugs of choice are calcium channel blockers and angiotensin-converting enzyme inhibitors. Nonselective beta-blockers are contraindicated, because they are known to worsen the skin perfusion pressure [14, 19, 20].

Pain control: is of great importance for such extremely painful ulcers. Mild or moderate pain can be controlled with oral, non-steroidal anti-inflammatory drugs, while narcotic analgesics are usually required for extremely painful ulcers. It was noted in many cases that pain almost completely disappears during the first few postoperative days after applying grafts on the wound surface [12, 21, 22]. Our patient, who was taking narcotic analgesics for many months, no longer required any pain medications, just a couple of days after surgery.

Conclusion

In conclusion, we can once again highlight the importance of considering Martorell ulcer in hypertensive patients with extremely painful ulcers of the lower legs. In order to establish the appropriate diagnosis, it is not enough to rely solely on clinical features. It is essential to take a deep skin biopsy, in order to establish the thickening of the subcutaneous arteriolar walls. That is the only way not to confuse hypertensive ischemic leg ulcer with pyoderma gangrenosum, since the management of the two conditions is completely different.

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PRIMARY AORTODUODENAL FISTULA WITHOUT AN ABDOMINAL AORTIC ANEURYSM – A CASE REPORT

PRIMARNA AORTODUODENALNA FISTULA BEZ PRISUSTVA ANEURIZME ABDOMINALNE AORTE – PRIKAZ SLUČAJA

Slobodan TORBICA

Summary

Introduction. Aortoenteric fistula is a communication between the aorta and segments of the gastrointestinal tract. Primary aortoduodenal fistula is an extremely rare cause of gastrointestinal bleeding associated with a high mortality rate. **Case Report.** We report a case of a 63-year-old man admitted due to abdominal pain lasting for a week. Abdominal ultrasound and computed tomography angiography revealed an aortoduodenal fistula without an aortic aneurysm. **Conclusion.** This case is an example of a rare cause of gastrointestinal bleeding, as well as presentation of aortoduodenal fistula that was not caused by an abdominal aortic aneurysm.

Key words: Intestinal Fistula; Aorta, Abdominal; Computed Tomography Angiography; Ultrasonography; Atherosclerosis; Gastrointestinal Hemorrhage; Abdominal Pain; Surgical Procedures, Operative

Sažetak

Uvod. Aortoenterična fistula predstavlja komunikaciju između aorte i nekog segmenta gastrointestinalnog trakta. Primarna aortoduodenalna fistula izuzetno je redak uzrok gastrointestinalnog krvarenja i prati visoka stopa smrtnosti. **Prikaz slučaja.** Predstavljamo slučaj 63-godišnjeg muškarca sa bolovima u abdomenu koji traju nedelju dana. Ultrazvukom i kompjuterizovanom tomografskom angiografijom uočena je aortoduodenalna fistula, bez aneurizme abdominalne aorte. **Zaključak.** Ovaj slučaj je primer izuzetno retkog uzroka gastrointestinalnog krvarenja, kao i prezentacija aortoduodenalne fistule, koja nije uzrokovana aneurizmom abdominalne aorte.

Ključne reči: intestinalna fistula; abdominalna aorta; kompjuterizovana tomografska angiografija; ultrasonografija; ateroskleroza; gastrointestinalno krvarenje; abdominalni bol; operativne hirurške procedure

Introduction

Aortoenteric fistula (AEF) is a pathological direct communication between the aorta and segments of gastrointestinal tract. The AEFs are classified into primary and secondary. Primary AEFs are most commonly caused by erosions of abdominal aortic aneurysms and extravasation of blood into a segment of the gastrointestinal tract. Secondary AEFs represent complications of abdominal aortic surgeries [1].

According to the autopsy series data, the incidence of primary AEF in general population ranges from 0.04 to 0.07% [2–5]. They are most common in patients between 60 and 63 years of age and they are three times more common in men than women [6–8].

Despite all the available modern diagnostic and surgical techniques, AEFs are still associated with a high mortality rate. According to the literature data, the mortality due to primary AEF ranges from 65 to 100% [9, 10].

Case Report

A 63-year-old man was admitted to the Hospital Emergency Department with a severe abdominal pain lasting for a week. On admission, the patient was somnolent, with flaccid limbs, blood pressure non-measurable, heart rate of 100 beats per minute, the abdomen diffusely tender to palpation, without palpable masses. Hetero-anamnestic data revealed the following: the patient was a smoker, occasionally consumed alcohol, he was treated for chronic obstructive pulmonary disease, his left kidney was surgically removed due to carcinoma, and he was previously treated for abdominal pain. The pertinent laboratory tests included white blood cell count 18,5 x 10^9, red blood cell count 2.93 x 10^{12}, hemoglobin 87 g/l, and hematocrit 0.27 L/l. The abdominal ultrasound (US) showed dilated loops of small bowel filled with hyperechogenic content. Retroperitoneum was not visualized due to dilated bowel loops and intestinal meteorism. The computed tomography angiography (CTA) was performed immediately after confirmation of dilated loops of small intestine

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Abbreviations

AEF – aortoenteric fistula
ADF – aortoduodenal fistula
US – ultrasound
CTA – computed tomography angiography
EGD – esophagogastroduodenoscopy

filled with hyperdense material with an average density of 60 HU, consistent with fresh blood. The non-dilated abdominal aorta, measuring up to 24 mm in diameter, had distinct atherosclerotic wall lesions. In the infrarenal segment of the abdominal aorta, at about 50 mm below the renal arteries, contrast media extravasation was noticed between the third and the fourth segment of the duodenum. Also, there was severe chronic periaortitis **(Figure 1)**. Free fluid was detected neither by US nor by CTA.

During immediately performed emergency laparotomy, distended loops filled with coagulated blood, without free fluid in the peritoneal cavity, were observed. Access to retroperitoneum revealed inflammation with duodenal edema and the first jejunal loop. The D3 to D4 duodenal segments were identified in the front wall of the aorta. Further preparation confirmed an aortoduodenal fistula (ADF), about 20 mm in diameter. Due to the poor general condition of the patient, we opted for "dam-

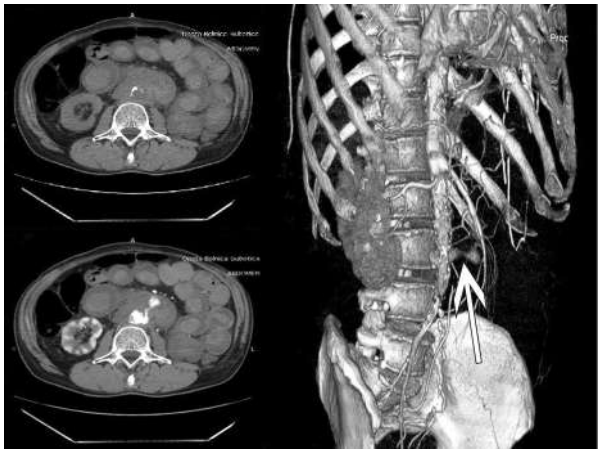

Figure 1. Axial view of non-enhanced phase of CTA showing dilated small bowel loops filled with hyperdense material - fresh blood; Distinct atherosclerotic abdominal aorta wall lesions; CTA showing active extravasation of the aortic contrast between the third and the fourth segment of the duodenum; 3D reconstructed image of CTA showing non-dilated abdominal aorta and confirmed contrast extravasation (red arrow)

Slika 1. *Aksijalni presek nativne faze kompjuterizovane tomografske angiografije (KTA), na kojoj se vide proširene vijuge tankih creva ispunjene hiperdenznim sadržajem, koji odgovara svežoj krvi. Takođe, u ovoj fazi se može videti izrazito aterosklerotski izmenjen zid trbušne aorte. KTA prikazuje aktivnu ekstravazaciju kontrasta iz trbušne aorte u treći/četvrti segment duodenuma. 3D rekonstruisana slika KTA prikazuje nedilatiranu trbušnu aortu i potvrđuje ekstravazaciju kontrasta (crvena strelica)*

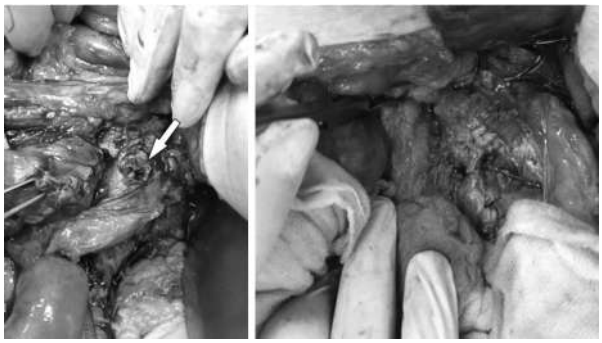

Figure 2. Emergency laparotomy finding shows an aortoduodenal fistula, 20 mm in diameter (white arrow); Surgical reconstruction of the duodenal defect was done by continuous stitches, and the abdominal aortic tear was closed by Dacron patch

Slika 2. *Nalaz hitne laparotomije prikazuje aortoduodenalnu fistulu prečnika 20 mm (bela strelica). Hirurška rekonstrukcija duodenalnog defekta produžnim šavom i trbušne aorte Dacron zakrpom*

age control" surgical treatment, and the duodenal defect was closed by continuous stitches. On the aortic segment affected by the fistula, wall debridement to the healthy tissue was performed and the defect was closed by Dacron® patch **(Figure 2)**. Since we opted for "damage control" surgical treatment, histopathological analysis was not performed. The patient was postoperatively placed in the intensive care unit. Four hours after the surgery the patient passed away due to the multiorgan failure.

Discussion

Although primary AEF was first described by Sir Astley Paston Cooper way back in 1829, it continues to be a great diagnostic and therapeutic challenge [11]. In approximately 73% of cases, abdominal aortic aneurysms are the cause of primary AEFs. Atherosclerotic aortic wall exerts a long-lasting compressive-pulsatile effect on the bowel wall that develops ischemia, which is followed by bowel wall necrosis and perforation. Subsequent contamination of the aortic aneurysm wall by the intestinal contents leads to aortic rupture and fistula development [12]. In approximately 26% of cases, the aneurysms are traumatic and mycotic in etiology, but their effects are the same as in atherosclerotic aneurysms. Around 1% of primary AEF causes are non-specific arthritis, peptic ulcer disease, cholelithiasis, diverticulosis, appendicitis, malignant abdominal neoplasms, foreign bodies, and others [12].

According to the literature, as much as 83% of primary AEFs are located between the aorta and duodenum, usually D3 segment (57%) [13, 14], because of the close anatomical relationship of the two structures. Clinical findings most commonly include a triad of gastrointestinal bleeding/hematemesis, or melena (64%), abdominal pain (32%) and pulsatile masses (25%) [10, 14, 15].

Three diagnostic procedures are used in making the diagnosis of primary AEF: esophagogastroduodenoscopy (EGD), CTA and digital subtraction angiography. Although many authors initially propose EGD when ADF is suspected, CTA is the modality of choice, with a sensitivity of 94% and a specificity of 83% [16], which is far above the two other modes with respect to specificity and sensitivity.

Two possible therapeutic approaches for primary ADF are open surgery or endovascular repair [17–20]. Open surgery techniques include aortic resection followed by axillo-bifemoral bypass, aortic reconstruction using a prosthetic graft, and autogenous femoral vein graft. Endovascular aortic repair is a good option in hemodynamically unstable patients.

The most common causes of primary AEF are abdominal aortic aneurysms, defined as dilatations of abdominal aorta greater than 30 mm in diameter. In the case presented here, there was no dilatation of the abdominal aorta. We can assume that AEF most likely occurred due to severe atherosclerosis of the aortic wall and chronic periaortitis, as well as earlier left nephrectomy due to kidney cancer. All of these led to the weakness of the aortic wall and duodenum and subsequent primary aortoduodenal fistula development.

Conclusion

The incidence of primary aortoenteric fistulas in the general population is most likely greater than recorded. Their clinical presentation is very dramatic and includes massive gastrointestinal bleeding that often causes hemodynamic instability. The diagnosis can be confirmed by computed tomography angiography which is generally immediately followed by a surgical intervention, because surgical management is the only therapeutic option, despite a generally poor prognosis.

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UNDIFFERENTIATED PLEOMORPHIC RETROPERITONEAL SARCOMA – A CASE REPORT

NEDIFERENCIRANI PLEOMORFNI RETROPERITONEALNI SARKOM – PRIKAZ SLUČAJA

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Summary

Introduction. Undifferentiated pleomorphic sarcoma, previously known as malignant fibrous histiocytoma, is the most common soft tissue sarcoma in adults, and retroperitoneum is the second most common location. **Case Report.** We present a case of a 60-year-old female patient with a painless mass in the left hemiabdomen. Computed tomography revealed a well defined retroperitoneal mass, while magnetic resonance showed a lobulated hypointense mass on T1-weighted and heterogeneous on T2-weighted images 180 x 230 x 250 mm in size, with intense peripheral enhancement. The patient underwent complete tumor excision, as well as reoperation after local recurrence. After histopathological and immunohistochemical analysis of the operating material, the diagnosis of malignant fibrous histiocytoma (giant cell type) was made. **Conclusion.** Radiological imaging has a limited diagnostic accuracy in undifferentiated pleomorphic sarcomas and definitive diagnosis relies on histopathological confirmation.

Key words: Sarcoma; Retroperitoneal Neoplasms; Histiocytoma, Malignant Fibrous; Soft Tissue Neoplasms; Magnetic Resonance Imaging; Tomography, Spiral Computed

Sažetak

Uvod. Nediferencirani pleomorfni sarkom, prethodno poznat pod nazivom maligni fibrozni histiocitom, najčešći je maligni tumor mekih tkiva kod odraslih, a retroperitoneum je druga najčešća lokalizacija. **Prikaz slučaja.** U ovom radu prikazan je slučaj pacijentkinje starosti 60 godina, sa bezbolnom masom u levom hemiabdomenu. Kompjuterizovana tomografija pokazala je jasno ograničenu retroperitonealnu masu, koja je na magnetnoj rezonanci u T1W sekvenci opisana kao policiklična hipointenzna masa, dok se u T2W sekvenci uočava kao heterogena masa sa intenzivnim perifernim postkontrastnim pojačanjem, veličine 180 x 230 x 250 mm. Izvršena je potpuna ekscizija retroperitonealno lokalizovanog tumora, kao i ponovna operacija nakon lokalnog recidiva. Na operativnom materijalu, nakon patohistološke i imunohistohemijske analize, postavljena je dijagnoza malignog fibroznog histiocitoma (*giant cell type*). **Zaključak.** Radiološki imidžing ima ograničene mogućnosti u dijagnostici nediferenciranih plaomorfnih sarkoma, te je za postavljanje definitivne dijagnoze neophodna patohistološka potvrda.

Ključne reči: Nediferencirani pleomorfni sarkom, maligni fibrozni histiocitom, retroperitoneum, kompjuterizovana tomografija, magnetna rezonanca

Introduction

Undifferentiated pleomorphic sarcoma (UPS), previously known as malignant fibrous histiocytoma (MFH), is the most common soft tissue sarcoma in adults predominantly affecting the male population [1]. The UPS arises from primitive mesenchymal elements, predominantly in the muscles of the extremities, retroperitoneum and abdominal cavity [2]. It may also occur within the bone tissue, in which case it mostly involves the femur and tibia. This report describes a case of UPS arising from the retroperitoneal space.

Case Report

A 60-year-old woman was referred to our hospital by her general practitioner for evaluation of a substantial, palpable and painless mass in her left iliac fossa. The patient had a history of hypertension, arrhythmias and total abdominal hysterectomy with bilateral adnexectomy that was performed 15 years earlier.

Abdominal and pelvic computed tomography (CT) revealed a well defined retroperitoneal mass, 180 x 160 x 150 mm in size, demarcated from other organs, except psoas muscle, descending colon, and left ureter. The colonoscopy was incomplete mostly due to the angulation of the bowel loops, external compression at 20 cm from the anocutaneous line, discomfort and intolerance. Magnetic resonance imaging (MRI) of the pelvis showed an extensive supravesical abdominal mass, 180 x 230 x 250 mm in size, that extended from the anterior abdominal wall to the great vessels posteriorly, and to the vascular structures of the left kidney and the pancreas tail cranially. The mass was lobulated hypointense on T1-weighted and heterogeneous on T2-weighted

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Abbreviations

UPS – undifferentiated pleomorphic sarcoma
MFH – malignant fibrous histiocytoma
CT – computed tomography
MRI – magnetic resonance imaging
ESR – erythrocyte sedimentation rate
CRP – C-reactive protein

images. Contrast-enhanced T1W images showed intense peripheral enhancement in comparison to the hypointense hypovascular necrotic center **(Figures 1 and 2)**. The colon was shifted up and to the right, the left pyelon showed dilatation, due to compression of the left ureter. It was not possible to determine the exact origin of the mass, intraperitoneal or retroperitoneal.

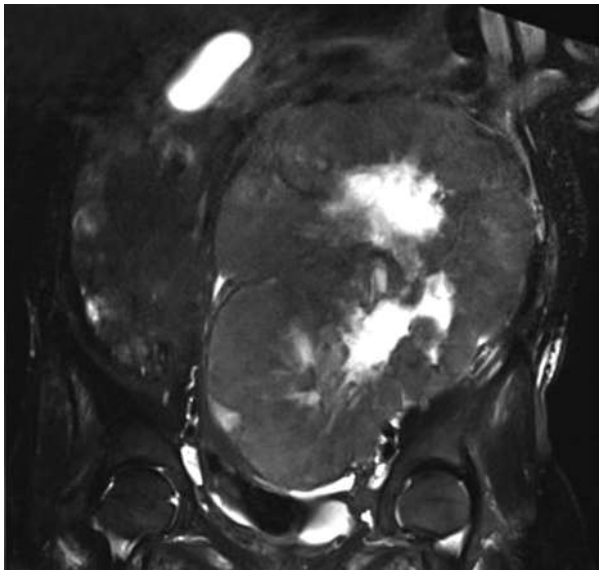

Figure 1. T2-weighted fat-saturated tomogram shows a large lobulated mass in the left hemiabdomen with central necrosis of unknown origin
Slika 1. *T2W FS koronalni tomogram pokazuje veliku lobuliranu centralno nekrotičnu masu u levom hemiabdomenu, nepoznatog porekla*

After thorough investigation, the patient was urgently admitted due to her overall bad condition and ileus caused by the mass in the left hemiabdomen. The patient presented with abdominal pain, distention and rigidity, while peristalsis was absent on physical examination. There was edema of the left leg and right ankle due to compression of the vascular structures. Routine laboratory tests were performed, including biochemical parameters, blood count, erythrocyte sedimentation rate (ESR), that revealed normal results, except elevation of leukocytes 11,3 x 10^3/mm^3, C-reactive protein (CRP) 132 mg/l and procalcitonin (PCT) 0,23 ng/ml. Chest X-ray showed only a slightly blunt right costophrenic angle.

The patient underwent laparotomy. After opening the abdomen, it was confirmed that the tumor

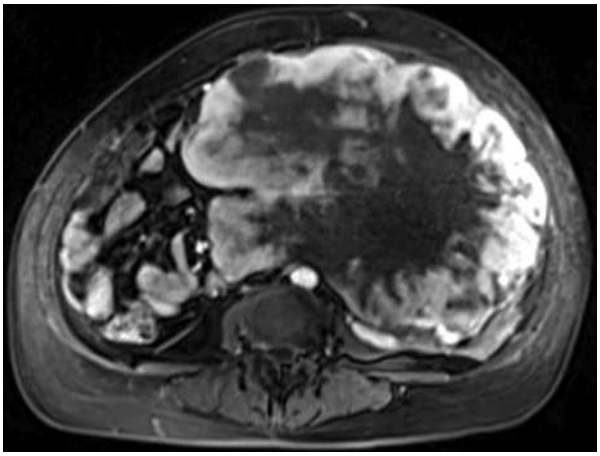

Figure 2. T1-weighted axial tomograms after contrast admission of a large lobulated mass in the left hemiabdomen with central necrosis
Slika 2. *T1W transverzalni tomogrami nakon aplikacije kontrasta pokazuju veliku lobuliranu centralno nekrotičnu masu u levom hemiabdomenu*

originated from the retroperitoneum. The retroperitoneal mass extended to the pelvis, abdominal cavity and invaded the left colon, part of the small intestine and the parietal peritoneum of the anterior abdominal wall. The whole mass was excised; left hemicolectomy and permanent colostomy were performed. The parietal peritoneum was partially resected, and adhesiolysis of the small bowel with cuneiform resection was performed.

Macroscopically, the resected retroperitoneal tumor was lobulated, with smooth shiny capsule on the surface, weighing 5,770 g **(Figure 3)**. On serial section the tumor was white and pinkish, partly solid, cystic and friable with areas of necrosis and hemorrhage.

Histopathological examination showed atypical, fibroblast-like and spindle cells with prominent cytoplasm, pleomorphic and bizarre nuclei, arranged

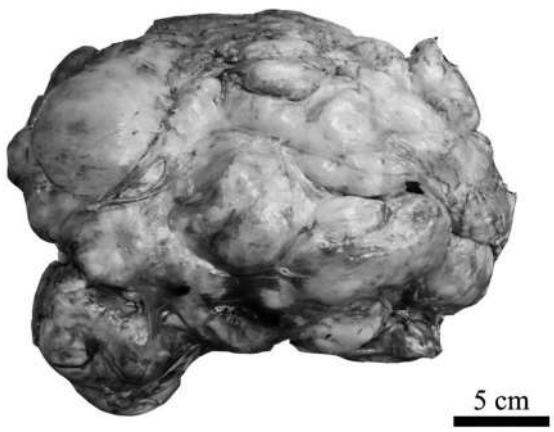

Figure 3. Gross appearance of the lobulated tumor from the retroperitoneum, scale bar: 5 cm
Slika 3. *Makroskopski izgled lobuliranog retroperitonealnog tumora, skala 5 cm*

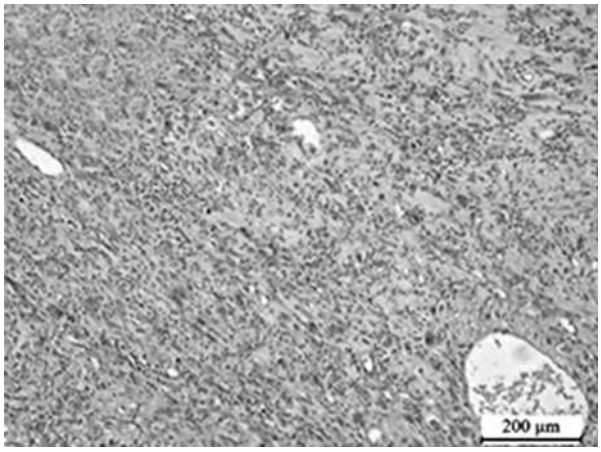

Figure 4. Histopathological characteristics of undifferentiated pleomorphic sarcoma: Hematoxylin-eosin, x 10
Slika 4. *Histološke karakteristike nediferentovanog pleomorfnog sarkoma: Hematoksilin-eozin, x 10*

in fascicles, surrounded by scarce collagenous stroma. Multinucleated cells (giant cells), rare bizarre mitotic figures and low mitotic activity (3/10 high-power fields (HPF)) were present **(Figure 4)**. The area of necrosis was less than 50%. Immunohistochemical staining was performed and the tumor cells were positive for vimentin **(Figure 5)**, CD68 **(Figure 6)**, CD99

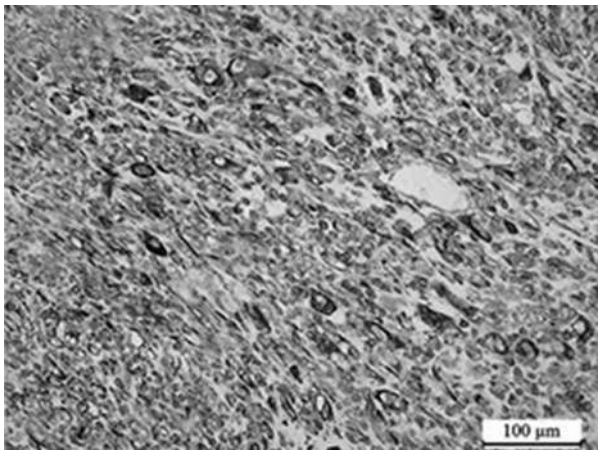

Figure 5. Histopathological characteristics of undifferentiated pleomorphic sarcoma: vimentin, x 20
Slika 5. *Histološke karakteristike nediferentovanog pleomorfnog sarkoma: vimentin, x 20*

and PDGFRA. The immunohistochemical techniques proved negative for Pan-CK pan, Bcl-2, actin, caldesmon, S-100 protein, DOG-1, and CD117 antigen. The CD34 antigen was positive in the endothelial cells of blood vessels and negative in the tumor. Based on the histomorphological features and immunophenotype of tumor cells, definitive diagnosis of UPS of giant cell subtype was confirmed.

The patient was discharged three weeks after the operation, with scheduled follow-up imaging. The

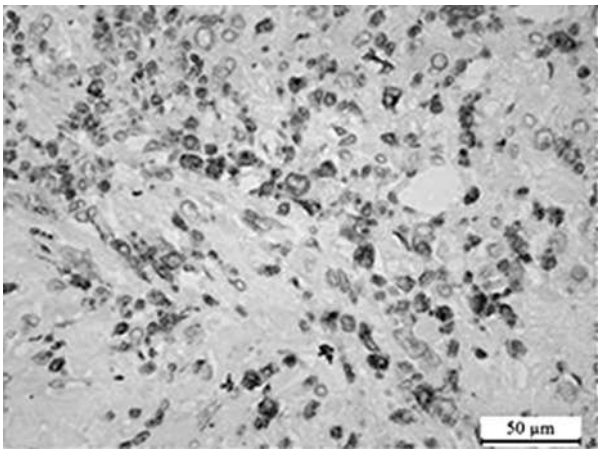

Figure 6. Histopathological characteristics of undifferentiated pleomorphic sarcoma: cd68, x 40
Slika 6. *Histološke karakteristike nediferentovanog pleomorfnog sarkoma: cd68, x 40*

subsequent MRI showed focal nodular lesions in the left side of the retroperitoneal space, a single lesion cranially 2 mm in size with a tendency to form conglomerates inferiorly with the maximum transverse diameter of 10 cm. Nodular lesions showed intensive postcontrast enhancement, diffusion restriction and represented evidence of tumor recurrence. The tumor invaded the left anterior renal fascia, perirenal space, left psoas muscle fascia anteriorly, posteriorly and laterally, and surrounded the external iliac vessels. The inferior part of the psoas muscle and the anterior iliacus muscle showed infiltrations, as well. Due to local recurrence, 8 months after the first surgery, the patient underwent reoperation, with partial resection of the partly necrotic and hemorrhagic tumor. Tumor infiltrated the left iliac vessels and part of the small bowel and it was resected with end to end anastomosis. Histopathologically, a giant cell subtype of UPS was found, and a local recurrent tumor was confirmed. Follow-up CT imaging was scheduled in 6 months.

Discussion

Retroperitoneal sarcomas represent 10–20% of all sarcomas [3, 4]. After liposarcoma and leiomyosarcoma, UPS is the third most common sarcoma with retroperitoneal location. UPS occurs most frequently in lower extremities 50%, in upper extremities 20%, followed by 16% in retroperitoneum and 5–10% in the abdominal cavity. The thigh presents the most commonly affected site in the extremities accounting for 30% of tumors [2]. UPS is an adult malignancy, with a peak incidence in the fifth and sixth decades of life, more common in males, with a 2 to 1 male to female ratio.

Sarcomas can arise due to mutations of tumor suppressor genes [5], but the most common etiologic factor is radiation treatment for another malignancy. However, they can also evolve after trauma, burn scars,

xeroderma pigmentosum, Hodgkin's lymphoma, multiple myeloma and malignant histiocytosis [6, 7].

Retroperitoneal sarcomas may have vast dimensions, and they are often detected because of an enlarged, palpable mass without any present symptoms. If the symptoms appear, they are not specific and can be misdiagnosed, as a benign process [8]. Symptoms include abdominal pain, fever, palpable mass, weight loss and mass effect. The mass effect depends on the location of the tumor: increased intra-abdominal pressure, including abdominal distension, varicocele and hernia are characteristic for tumors located in the abdomen or retroperitoneal space [2].

Undiferrentiated pleomorphic sarcoma in the retroperitoneum may cause hyperglycemia, hyperinsulinemia, due to the production of an insulin-like substance [9]. Blood tests reveal leukocytosis, with elevated ESR and CRP levels, particularly in patients with an inflammatory response [10].

In our case, the patient had a painless, enlarged soft tissue mass for months, elevated leukocytes, CRP, and PCT and developed abdominal pain with abdominal distension.

The embryological origin is thought to be from primitive mesenchymal stem cells, primitive fibroblast or histiocytes. Differentiation of the subtypes of UPS from other malignant tumors is very difficult. UPS can be classified into five histological subtypes a) storiform-pleomorphic type, b) myxoid type (myxofibrosarcoma), c) inflammatory type, d) giant cell type, e) and angiomatoid type. Our patient's histology showed a giant cell subtype that accounts for 5–10% of all such tumors, while storiform-pleomorphic type is the most common accounting for 50–60% [11]. UPS was shown to frequently express vimentin, CD68, actin, alpha-1-antitrypsin and alpha-1-antichymotrypsin, also CD10 and CD99. Other antigens such as smooth muscle actin, desmin, cytokeratin, epithelial membrane antigen, and S100 protein are not always present in MFH [12]. The immunohistochemical staining of vimentin, CD68, CD99 and PDGFRA in the present retroperitoneal MFH were positively stained, while other markers for establishing the line of differentiation were negative.

For tumors that are located within the retroperitoneum, it is very complex to determine whether the tumor originates from the retroperitoneal space or some major organ in this space. If none of the signs that suggest an organ of origin is present, then the tumor probably originates from the retroperitoneal space. The radiologic signs that are used are "beak sign", the "phantom (invisible) organ sign", the "embedded organ sign", and the "prominent feeding artery sign" [13]. In our case, the precise localization was possible only after surgery, due to the fact that the CT showed retroperitoneal location but it could not be determined on MRI.

Magnetic resonance imaging showed low or equal signal on T1-weighted images, heterogeneous high signal intensity on T2-weighted images, and heterogeneous postcontrast enhancement [14, 15]. Moreover, in our case, the T1-weighted images presented low-intensity signal and on T2-weighted images the mass was heterogeneous, while Romano F, et al. described a hypointense lesion on both T1W and T2W images [16]. Typical CT findings include a large infiltrative mass with ill-defined borders and density similar to that of muscle tissue [17]. Heterogeneity and uneven enhancement on CT and MRI are due to the presence of hemorrhage, necrosis, calcification, or myxoid material [18].

The main choice of treatment is radical surgery. Radiotherapy and chemotherapy are other modalities that are used to treat UPS. Adjuvant radiotherapy reduces mortality and metastatic spread of the disease [19].

Conclusion

The diagnostic value of radiologic imaging is limited and even location of retroperitoneal neoplasms is usually challenging, but it is useful to determine relations with the surrounding structures and the extent of their invasion, if present. Definitive diagnosis relies on histopathology and immunohistochemistry after surgery, which is the treatment of choice. The patient in this review showed tumor recurrence and was reoperated after 8 months, with recommendation for further follow-up.

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∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG*, *GIF*, *TIFF*, *EPS*.

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– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

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All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

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6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

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Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

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The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

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The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

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The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

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The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

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Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

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– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

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