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Risk factor-based point-based scoring system - CHA ₂ DS ₂ -VASc	
Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age \geq 75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65-74	1
Sex category (i.e. female sex)	1
Maximum score	9

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.



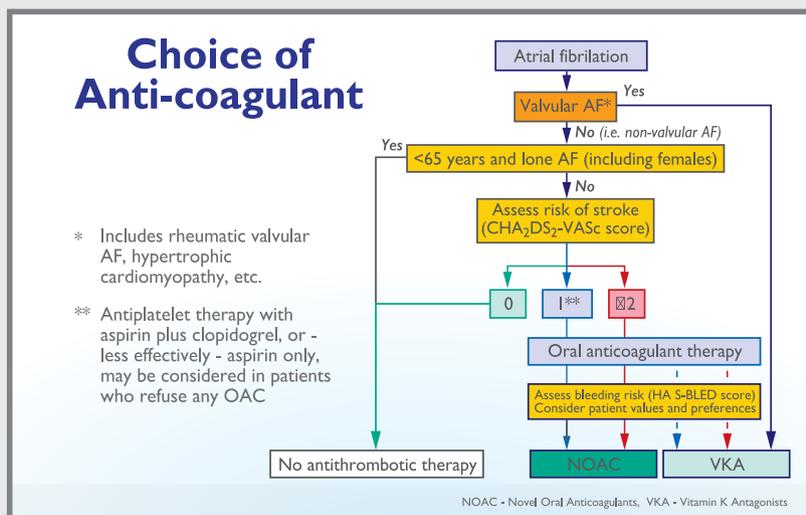
Major i non-major riziko faktori za procjenu tromboembolizma kod A Fib!

Risk factors for stroke and thrombo-embolism in non-valvular AF	
Major risk factors	Clinically relevant non-major risk factors
Previous stroke	CHF or moderate to severe LV systolic dysfunction [e.g. LV EF \leq 40%]
TIA or systemic embolism	Hypertension
Age \geq 75 years	Diabetes mellitus
	Age 65-74 years
	Female sex
	Vascular disease

AF = atrial fibrillation; EF = ejection fraction (as documented by echocardiography, radio nuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left ventricular; TIA = transient ischaemic attack.



Algoritam antikoagulantne terapije nakon procjene CHA₂DS₂VASc i major risk faktora!



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Cosmetic otoplasty techniques in relation to age distribution and types of postoperative complications

Tehnike kozmetske otoplastike u odnosu na dobnu distribuciju i tipove postoperativnih komplikacija

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ABSTRACT

Introduction: correction of prominent ears is a very common operative procedure in aesthetic plastic surgery with indication often at younger age due to the potential impact of deformity on psychophysical development and social integration. Operative techniques may be more or less invasive, which is related to correction of auricular cartilage, with or without excisions, which are associated with known, but relatively rare, postoperative complications. Aim: evaluate age and gender distribution in the assessed group with indication for cosmetic otoplasty, determine the representation of bilateral in relation to unilateral otoplasty, evaluate the types of operative techniques with occurrence of potential complications. Materials and methods: we assessed 88 patients with indication for cosmetic otoplasty patients treated at the Clinic of Reconstructive and Plastic Surgery, Clinical Center University of Sarajevo, in the period from 2014 to 2018, with evaluation of gender and age distribution, representation of the different operative techniques, and incidence of potential postoperative complications. Statistical data processing was done through IBM SPSS (version 21.0, SPSS) and Microsoft Excell (version 11). Significance of data evaluated by Hi-Square and Fischer test. Values of p below 0.05 ($p < 0.05$) were considered statistically significant as presented in figures. Results: statistically significant difference in gender distribution was not evaluated in the study group ($p > 0.05$). The median age was 12.7 years (men 12.6 years and women 12.4 years). Surgical procedures up to 18 years and in older age showed a statistically significant difference ($p < 0.05$). The correlation of bilateral and unilateral otoplasty confirmed a significant statistical difference in terms of predominance of bilateral otoplasty ($p < 0.05$). Surgical techniques of auricular cartilage excision applied in 39 cases (44.3%), auricular cartilage modeling techniques in 37 cases (42%) and combinations of these operative techniques in 12 cases (13.7%). The prevalence of early and late complications in our estimated group of patients was very low (1 patient; 1.1%), with statistically significant difference ($p < 0.05$) regarding otoplasty without complications. Conclusion: modalities of cosmetic otoplasty depends on the preferences and experience of the surgeon. Unilateral correction of otoplastosis is rarely indicated, due to impossibility of achieving the ideal symmetry, even in cases of clinically evident unilateral deformity, in such cases bilateral correction is the best option. Cosmetic otoplasty

is associated with a low incidence of postoperative complications, due to precision surgical techniques and predictable results. Modern trends of cosmetic otoplasty move in the direction of minimally invasive procedures development, with a fast recovery and on the one-day surgery basis. The importance of otoplasty is reflected in the indication at a younger age, unlike other cosmetic procedures, because a satisfactory postoperative result has an unquestionable effect on mental development and self-esteem.

Key words: cosmetic otoplasty, cartilage excision, cartilage modeling, complications

SAŽETAK

Uvod: kozmetska otoplastika je vrlo čest operativni postupak u estetskoj plastičnoj kirurgiji s indikacijom koja se postavlja najčešće u maldoj životnoj dobi, zbog potencijalnog utjecaja deformiteta na psihofizički razvoj i socijalnu integraciju. Operativne tehnike mogu biti više ili manje invazivne, što se odnosi na korekciju aurikularne hrskavice sa ili bez ekscizija, koje su povezane s poznatim, ali relativno rijetkim postoperativnim komplikacijama. Cilj: procijeniti dobnu i polnu distribuciju u našoj ispitivanoj grupi pacijenata, evaluirati zastupljenost obostrane u odnosu na jednostranu kozmetsku otoplastiku, utvrditi vrste primjenjenih operativnih tehnika, kao i pojavu potencijalnih komplikacija. Materijali i metode: procijenili smo 88 slučajeva sa indikacijom za kozmetsku otoplastiku, Klinici za rekonstruktivnu i plastičnu hirurgiju Kliničkog centra Univerziteta u Sarajevu, u periodu od 2014 do 2018. godine, sa evaluacijom polne i dobne distribucije, zastupljenosti različitih operativnih tehnika i učestalosti postoperativnih komplikacija. Statistička obrada podataka izvršena je putem IBM SPSS (verzija 21.0) i Microsoft Excell (verzija 11). Statistička signifikantnost podataka procijenjenih vrijednostima Hi-kvadrat i Fischerovog testa. Vrijednosti p ispod 0,05 ($p < 0,05$) smatrane su statistički značajnim. Rezultati su prikazani u grafikonima. Rezultati: statistički signifikantna razlika u polnoj distribuciji nije evaluirana u ispitivanoj skupini pacijenata ($p > 0,05$). Srednja životna dob je iznosila 12.7 godina (muškarci 12.6 godina; žene 12.4 godine). Operativni zahvati indikovani do 18 godina starosti i u starijoj životnoj dobi pokazuju statistički značajnu razliku ($p < 0,05$). Odnos bilateralne prema unilateralnoj otoplastici je potvrdio značajnu statističku razliku u smislu predominantnosti

bilateralne otoplastike ($p < 0.05$). Hirurške tehnike ekscizije aurikularne hrskavice primjenjene su u 39 slučajeva (44.3%), tehnike modeliranja aurikularne hrskavice u 37 slučajeva (42%) i kombinacije ovih operativnih tehnika u 12 slučajeva (13.7%). Zastupljenost ranih i kasnih komplikacija u našoj procijenjenoj skupini pacijenata je bila vrlo niska (1 slučaj; 1.1%), sa statističkom značajnošću ($p < 0.05$). Zaključak: modalitet kozmetičke otoplastike ovisi o preferencijama i iskustvu kirurga. Unilateralne korekcija otapostaze se rijetko indicira, jer je gotovo nemoguće postići idealnu simetrizaciju i u slučajevima postojanja klinički evidentnog jednostranog deformiteta, te je obostrana korekcija najbolja opcija. Kozmetička otoplastika je povezana

sa niskom incidencom postoperativnih komplikacija zbog preciznosti hirurških tehnika i predvidljivosti rezultata. Moderni trendovi kozmetičke otoplastike idu u pravcu razvoja minimalno invazivnih procedura, sa brzim oporavkom i na bazi jednodnevne hirurgije. Otoplastika ima značaj zbog indikacije u mlađoj životnoj dobi za razliku od ostalih estetskih operacija, jer zadovoljavajući postoperativni rezultat ima neupitan efekat na psihički razvoj i samopostovanje.

Ključne riječi: kozmetička otoplastika, ekscizija hrskavice, modeliranje hrskavice, komplikacije otoplastike

INTRODUCTION

Prominent ears affect approximately 5% of the population and can have a significant psychological impact on patients. A wide variety of otoplasty techniques have been described, all sharing the goal of re-creating the normal appearance of the ear and achieving symmetry between the 2 sides. Recent trends in otoplasty techniques have consistently moved toward less invasive options, ranging from nonsurgical newborn ear molding to cartilage-sparing surgical techniques and even incisionless, office-based procedures (1). Otoplasty for prominent ears is a rewarding yet exacting surgery that demands the precise application of anatomic knowledge, anthropometric norms, and surgical creativity. The practitioner must be able to use a variety of different techniques to provide durable and acceptable cosmetic results to patients (2). Pediatric otoplasty is generally considered to be a "simple" procedure, but an astute surgeon recognizes the challenges of this operation and is mindful of the degree of detail involved in its planning and execution. The vast number of described otoplasty methods, which are ever evolving, is a testament to the complexity of this procedure (3). Adopting an effective and safe technique should be based on proven efficacy and effectiveness to avoid early disappointments (4). Ear prominence is a relatively common cosmetic deformity with no associated functional deficits, but with profound psychosocial impact, especially in young patients. Both cosmetic and reconstructive perspectives should be entertained when addressing this anatomical deformity (5). Prominent ears can have a significant psychological impact especially in children. It is often the subject of negative remarks among classmates. Prominent ears are the result of one or more congenital anomalies that may be associated together in various degrees. Absence of antihelical fold, opening the cephalo-conchal angle and conchal hypertrophy are the most common. The surgery aims to correct these anomalies, by reshaping the cartilage in order to obtain well-shaped ears that is normally positioned and oriented with natural size and appearance (6).

AIM

To evaluate age and gender distribution in the assessed group with indication for cosmetic otoplasty, determine the representation of bilateral in relation to unilateral otoplasty, evaluate types of operative techniques with occurrence of potential complications.

MATERIALS AND METHODS

We assessed 88 patients with indication for cosmetic otoplasty, with evaluation of gender and age distribution, representation of the different operative techniques, and incidence of potential postoperative complications in 88 patients treated at the Clinic of

Reconstructive and Plastic Surgery, Clinical Center of the University of Sarajevo, in the period from 2014 to 2018. Statistical data processing was done through IBM SPSS (version 21.0, SPSS Inc, Chicago, Illinois, USA) and Microsoft Excell (version 11, Microsoft Corporation, Redmond, WA, USA). Descriptive processing of statistical data was also carried out within the framework of the survey. Significance of data evaluated by Hi-Square and Fischer test Values of p below 0.05 ($p < 0.05$) were considered statistically significant. The results are presented in graphs and tables.

Study inclusion criteria: patients of all ages and genders with prominent ears, patients undergoing cartilage excision surgery, patients undergoing cartilage modeling surgery and patients treated by combination of these two techniques.

Study exclusion criteria from the study: patients treated in other hospital centers, patients treated with incisionless techniques.

RESULTS

The assesment of the gender distribution (Figure 1) showed no significant difference in the gender distribution in our study group, 45 patients were male (51.1%), while 43 patients were female (48.9%). No statistically significant difference was found in the gender representation ($p > 0.05$).

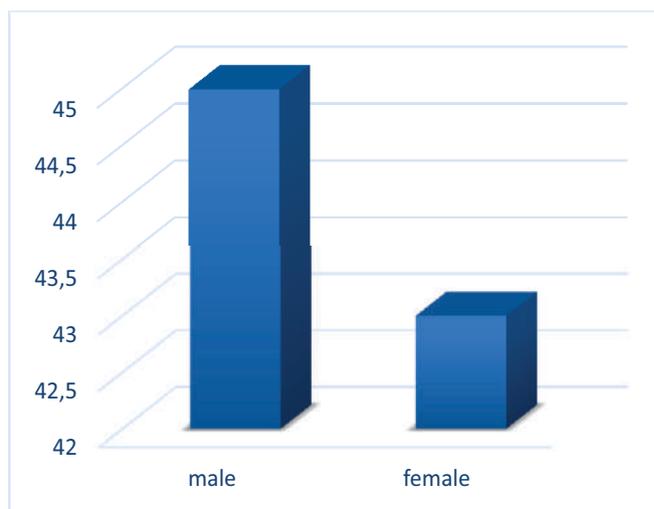


Figure 1 Gender distribution.

The median age of evaluated group of 88 patients was 12.7 years (Figure 2). The youngest male patient was 6 years old and the oldest was 65. The youngest female patient was also 6 years old, while the oldest female patient was 27 years old. The average age of male patients was 12.6 years, whereas for women it was 12.4 years.

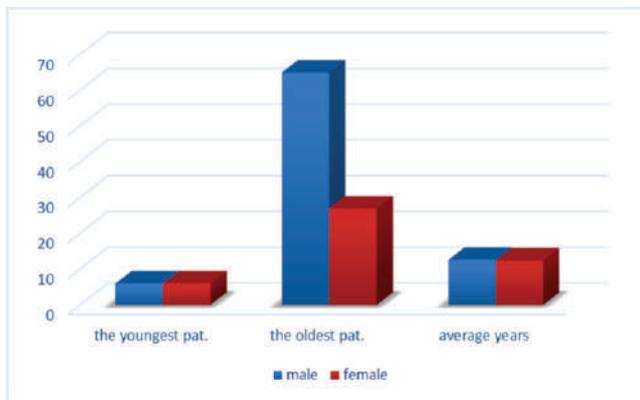


Figure 2 Age distribution.

The underage patients undergone cosmetic ear correction in the majority of cases (84 patients; 95.5%). Adult patients were represented in a much smaller percentage (4 patients, 4.5%). A statistically significant difference ($p < 0.05$) was found in the proportion of patients undergoing cosmetic ear correction after 18 years of age. Data is presented numerically and in percentages (Figure 3).



Figure 3 Age distribution presented numerically and in percentages.

Bilateral otoplasty (Figure 4) was indicated in the majority of cases (86 patients; 97.7%), unlike unilateral otoplasty indicated in 2 evaluated cases (2.3%). The statistically significant difference was found between the representation of bilateral and unilateral otoplasty ($p < 0.05$).

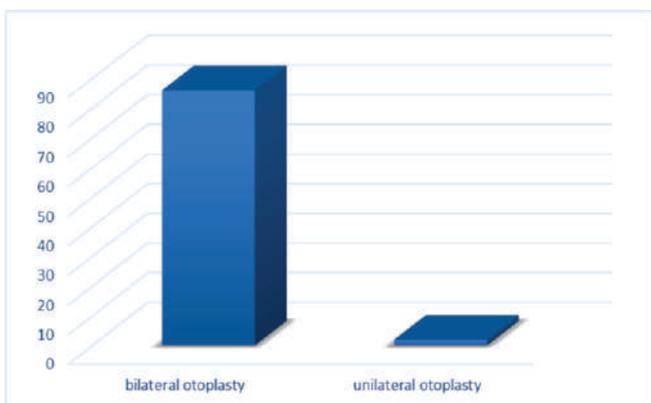


Figure 4 Representation of bilateral in relation to unilateral otoplasty.

In the assessed group we evaluated three types of available surgical techniques (Figure 5). Pitanguy and Converse techniques of cartilage excision were applied in 39 cases (44.3%), Furnas and Mustarde techniques of cartilage modeling were applied in slight smaller percentage (37 patients; 42%) and combination of presented techniques in 12 cases (13.7%).

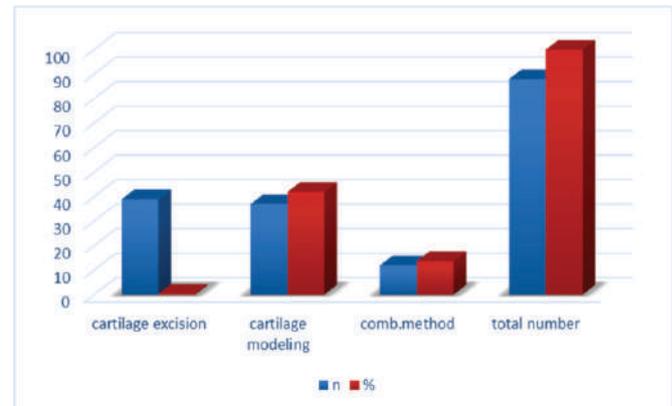


Figure 5 Numerical and percentage representation of otoplasty modalities.

Statistically significant difference ($p < 0.05$) was evaluated in patients undergoing cosmetic otoplasty without postoperative complications (87 patients; 98.9%) compared to patients with postoperative complications (1 patient; 1.1%). The type of cosmetic otoplasty technique was found not to be correlated with the incidence of postoperative complications. One case of complication in terms of recurrence of prominent ears was related to the application of Furnas technique of cartilage.

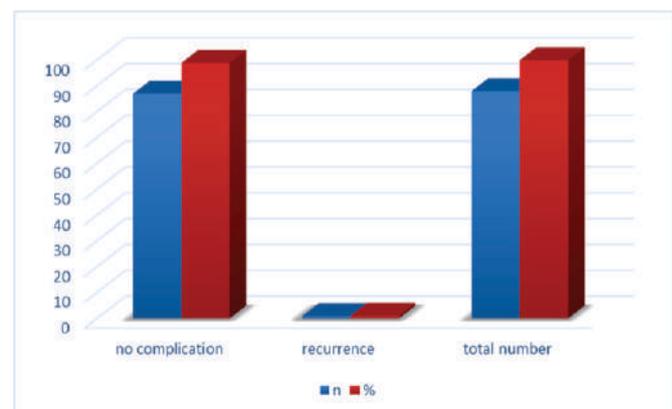


Figure 6 Recurrence of otoplasty presented in relation to cases without complications and according to total number of evaluated cases.

DISCUSSION

Otoplasty is one of the first procedures learned during residency. Recurrence rates are low for most techniques. Recurrence rates are low for most techniques (7). Many techniques have been described using one or a combination of 3 basic methods: cartilage cutting, cartilage weakening and pure cartilage shaping techniques. The ideal otoplasty technique should yield a natural correction of the deformity,

with low recurrence rates and with little risk of complications (8). Aesthetic correction of the ears requires thorough diagnosis and subsequent treatment of the affected areas. Correction of the eventual discrepancy between cartilage height and the skin envelope is particularly observed and addressed by means of scaphal reduction. Restoration of facial harmony through aesthetic correction of the ears is a highly satisfying procedure for both patients and surgeons (9). However, the best technique is one that is reproducible, simple, and versatile. Modern otoplasty techniques consist of two main surgical categories, cartilage sparing and cartilage cutting, along with many variations (10). In otoplasty surgery the antihelical fold is frequently created using Mustarde sutures. When using the Mustarde suture technique it is important to insert the needle through the cartilage at right angles. No other complications, such as bowstringing of the internal sutures, haematoma, or infection, were observed. The patients expressed a high degree of satisfaction with their results. The risk of technical error is minimal. It is easy to perform and not time-consuming (11). The role of cartilage-cutting and cartilage-sparing techniques as well as individual preferred otoplasty techniques are thoroughly covered. Postoperative management of these patients was presented by the individual surgeons (12). Prominent ears are a fairly common and emotionally charged facial variation. Both children and adults may suffer a damaged psyche secondary to outside ridicule and self-criticism from ears that "stick out." The external ear anatomy is intricate, with thin skin and resilient cartilage. These underlying characteristics make the ears prone to the overt display of surgical correction. (13). No specific otoplasty method has been considered as the absolute standard in patients with prominent ears showing thick and strong auricular cartilage (14).

CONCLUSION

Otoplasty is a cosmetic surgery indicated mainly in childhood, with significance in terms of improving integration into social life and overall psychophysical health. Requirements for this type of cosmetic surgery are not uncommon in adulthood, but communication with the patient, assessment of the psychological profile and the existence of realistic expectations regarding the possibilities of the procedure are the task of the cosmetic surgeon. The modality of cosmetic otoplasty depends on the surgeon's preference and experience, which is related to the possibility to predict the course and postoperative results of surgery, as well as preventing and solving potential complications. Modern tendencies go towards such procedures to be performed on the basis of the daily surgery principle of one-day surgery for a fast return to daily activities. Careful examination of the patient, assessment of each individual case, as well as the psychological profile, are important components of the balance between the patient's wishes and the possibilities of aesthetic plastic surgery.

REFERENCE

1. Pawar SS, Koch CA, Murakami C. Treatment of Prominent Ears and Otoplasty: A Contemporary Review. *JAMA Facial Plast Surg*. 2015;17(6):449-54.
2. Schneider AL, Sidle DM. Cosmetic Otoplasty. *Facial Plast Surg Clin North Am*. 2018;26(1):19-29.
3. Sands NB, Adamson PA. Pediatric esthetic otoplasty. *Facial Plast Surg Clin North Am*. 2014 Nov;22(4):611-2.
4. Stewart KJ, Lancerotto L. Surgical Otoplasty: An Evidence-Based Approach to Prominent Ears Correction. *Facial Plast Surg Clin North Am*. 2018;26(1):9-18.
5. Ali K, Meaie JD, Maricevich RS, Olshinka A. The Protruding Ear: Cosmetic and Reconstruction. *Semin Plast Surg*. 2017;31(3):152-60.
6. Ellart J, Guerreschi P, Pasquesoone L, Duquennoy-Martinet V. Otoplasty. *Ann Chir Plast Esthet*. 2016;61(5):703-12.
7. Stewart KJ, Lancerotto L. Surgical Otoplasty: An Evidence-Based Approach to Prominent Ears Correction. *Facial Plast Surg Clin North Am*. 2018;26(1):9-18.
8. Hendrickx BIMM, Hamdi M, Zeltzer A, Greensmith A. The 'WiFi' otoplasty: Combined concentric posterior microchondrectomies and sutures for correction of prominent ears. *J Plast Reconstr Aesthet Surg*. 2018;71(6):900-90.
9. de la Fuente A, Sordo G. Minimally invasive otoplasty: technical details and long-term results. *Aesthetic Plast Surg*. 2012;36(1):77-82.
10. Sevin K, Sevin A. Otoplasty with Mustarde suture, cartilage rasping, and scratching. *Aesthetic Plast Surg*. 2006;30(4):437-41.
11. Eryilmaz T, Ozmen S, Cukurluoglu O, Sezgin B. External Mustarde suture technique in otoplasty revisited: a report of 82 cases. *J Plast Surg Hand Surg*. 2013;47(4):324-7.
12. Gantous A, Tasman A, Neves JC. Management of the Prominent Ear. *Facial Plast Surg Clin North Am*. 2018;26(2):181-92.
13. Handler EB, Song T, Shih C. Complications of Otoplasty. *Facial Plast Surg Clin North Am*. 2013;21(4):653-62.
14. Park C, Jeong TW. Antihelical shaping of prominent ears using conchal cartilage-grafting adhesion. *Laryngoscope*. 2012;122(6):1238-45.

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Quality management of healthcare in the function of improving nursing clinical practice

Upravljanje kvalitetom zdravstvene njege u funkciji unaprijeđenja sestrinske kliničke prakse

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ABSTRACT

Introduction: improving the quality of health services is nowadays an imperative of every health system. The overall health system should be focused on the health needs of the individual and the community. Health services should be effective, recognizable in the market, economical, accessible and safe. Clinical healthcare is a very important segment of healthcare and deserves special attention in reform of healthcare systems. Standards and criteria have been established within clinical health care, quality indicators serving as basis for implementation and evaluation of nursing practice. Aim: to determine the methods of quality implementation in the clinical healthcare process; to examine the practice of nurses-technicians in the process of healthcare risk management; healthcare process evaluation; level of nurses-technicians satisfaction with the healthcare process outcomes. Materials and methods: the study was conducted among the nurses-technicians employed in the Clinical Center University of Sarajevo hospital units. A total of 182 respondents was included in the study. For the purpose of this descriptive study, an original author's anonymous survey questionnaire was used. Results: the majority of respondents consider that quality healthcare facilitates patients' healing, as well as the existence of standardized documents, such as nursing procedures or documentation. Healthcare planning is mainly done by assessing the patient's condition and providing written or oral instructions. Risk and incident situations are regularly monitored, most commonly hospital infections/colonization and adverse drug reactions, for all categories of employees equally. Conclusion: the implementation of quality programs in clinical healthcare ensures safety of patients and nurses. The application of standardized quality documents reduces the possibility of risks and adverse events in the healthcare process, monitors the efficiency of nursing services, and ensure continuity in the practice improvement process.

Key words: nursing, quality of healthcare, safety, standards, indicators

SAŽETAK

Uvod: poboljšanje kvalitete zdravstvenih usluga danas je imperativ svakog zdravstvenog sistema. Cjelokupan zdravstveni sistem trebao bi biti fokusiran na zdravstvene potrebe pojedinca i zajednice. Zdravstvene usluge trebaju biti kvalitetne, prepoznatljive na tržištu, ekonomične, dostupne i sigurne. Klinička zdravstvena njega vrlo je važan segment zdravstvene zaštite i zaslužuje posebnu pažnju u okviru reformi zdravstvenih sistema. U okviru kliničke zdravstvene njege uspostavljeni su standardi i kriteriji, indikatori kvaliteta na osnovu kojih se implementira i evaluiira sestrinska praksa. Cilj: utvrditi način implementacije kvaliteta u procesu kliničke zdravstvene njege; ispitati praksu medicinskih sestara-tehničara u procesu upravljanja rizicima u zdravstvenoj njezi; ispitati način provođenja evaluacije procesa zdravstvene njege; utvrditi stepen zadovoljstva medicinskih sestara-tehničara ishodima u procesu zdravstvene njege. Materijali i metode: istraživanje je provedeno među medicinskim sestrama-tehničarima zaposlenim u hospitalnim jedinicama Kliničkog centra Univerziteta u Sarajevu. Ukupan broj ispitanika uključenih u studiju bio je 182. Za potrebe ovog deskriptivnog istraživanja, korišten je originalni autorski upitnik za anonimno anketiranje. Rezultati: većina ispitanika smatra da kvalitetna zdravstvena njega pomaže izlječenju pacijenata, kao i da posjeduju standardizirane dokumente, kao što su sestrinske procedure ili dokumentacija. Planiranje zdravstvene njege se u najvećoj mjeri vrši procjenom stanja pacijenta te davanjem pismenih ili usmenih uputstava. Rizične i incidentne situacije se redovno prate, a najčešće se provjeravaju bolničke infekcije/kolonizacije i neželjene reakcije na lijek, podjednako za sve kategorije uposlenika. Zaključak: implementacija programa kvaliteta u kliničkoj zdravstvenoj njezi osigurava sigurnost za pacijente i medicinske sestre-tehničare. Primjenom standardiziranih dokumenata kvaliteta smanjuje se mogućnost rizika i neželjenih događaja u procesu zdravstvene njege, prati efikasnost sestrinskih usluga, te postiže kontinuitet u procesu unaprijeđenja prakse.

Ključne riječi: sestinstvo, kvalitet zdravstvene njege, sigurnost, standardi, indikatori

INTRODUCTION

Nursing is a dynamic profession, which through application of new research methods finds new answers related to healthcare changes aiming at satisfying the health needs of the individual and the community. In satisfying the health needs, nursing clinical practice has two distinguished healthcare principles: the principle of benefit (achieving good results) and the principle of harmlessness (do no harm) (1,2).

The key components of all main functions of the nurse and precondition for responsibility of nurses for their own work are the development and application of generally accepted and appropriate ethical, cultural and professional standards. In order to provide adequate and quality healthcare to patients the nurse must have ability to identify principles for all the implemented activities. Also, it is necessary to establish standards which healthcare professionals and nurses, respectively will follow to evaluate the implemented healthcare quality (3,4).

In the healthcare process nurses use the adopted nursing clinical practice standards and guidelines based on scientific evidence in healthcare and good nursing practice. The standards are created in accordance with competences of nurses and their professional achievements (5,6).

The quality of patients' healthcare involves physical approach to patients which fulfills their psychosocial needs, satisfaction with the provided care, and is considered as overall and multidimensional responsibility of the nurse for the intended activities, protection and trust of patients (7).

The concept involves the assessment and evaluation of the healthcare quality, identification of a problem or any shortcoming in the implementation of the healthcare process, planning of the activities aimed at overcoming the said problems or shortcomings and monitoring or supervising in order to ensure efficiency of the implemented activities (corrective steps) (8).

Quality in the healthcare process can be integrated in several ways: legal provisions or regulations, requirements for more rational and more comprehensive and quality approach and care to the patient, application of information and communication technologies, and continuous promotion of the healthcare quality process (9).

Management clinical healthcare functions directed at quality promotion include: planning, organization, communication, monitoring, staff monitoring, guidance or leadership, coordination and similar (10).

Clinical healthcare also includes a number of specific tasks, where nurses are expected to have advanced knowledge, skills and abilities for clinical healthcare management (11).

In their practice, clinical nurses are on a daily bases faced with a number of challenges in the treatment of patients, especially patients with more severe clinical manifestations, unclear conditions and new illnesses of different etiology. Accordingly, it is expected that nurses must be subjected to continuous training in their practice in order to achieve expected results in healthcare and final satisfaction of the patient (11,12).

Improvement of the clinical healthcare quality depends on degree of involvement of nurses in the work processes. Certainly, all hospitalized patients require an individual approach due to different health needs and medical conditions.

However, nurses should therefore be committed to finding the best solutions aiming at achieving their satisfaction. That can be achieved through good team cooperation, involvement of patients as partners, using experiences of other experts, and through application of previously adopted standard treatment methods (13).

In order to meet standards and criteria in the healthcare process it is necessary to implement the quality documents defining the work process expectations. Quality documents in the field of clinical healthcare include Policies and Procedures, Clinical Guidelines, Checklists and Algorithms. These documents provide human, professional, legal and ethical protection in the process of nurses' work. Thus, nurses improve their practice and professional identity in health system and the quality implementation has multiple benefits for both patients and healthcare providers (14).

Documenting healthcare is also one of the important segments in the field of quality, as it recognizes importance, efficiency and effectiveness of services in the healthcare process, as well as the importance of the nursing profession in the health team. The documenting has a special importance in the process of quality indicators monitoring and safety of health services. All healthcare services can be measured and improved based on the results. Clinical healthcare indicators may point to the treatment outcomes, unfavorable events, complications, satisfaction with services and similar (15,16).

In the process of improving quality and safety of the nursing clinical practice, clinical audit has an important role as it assists nurses to systematically analyze and review previously taken activities and thus improve the work processes quality (17).

The improvement of clinical nursing practice is one of the aims in the development of new health policy and health system oriented to the benefits of patients.

AIM

To determine the methods of quality implementation in the clinical healthcare process; to examine the practice of nurses-technicians in the process of healthcare risk management; healthcare process evaluation; level of nurses-technicians satisfaction with the healthcare process outcomes.

MATERIALS AND METHODS

The study was conducted among nurses-technicians employed in the Clinical Center University of Sarajevo (CCUS) hospital units. A total of 182 nurses-technicians was included in the study, which was 11.3% of the total number of nurses-technicians employed in the CCUS. The survey was design as an open access Google forms link, which was distributed to all the nurses working at the CCUS, and who can participate solely on voluntary basis. The study included the following respondents: charge nurse-technician of the Clinic, charge nurses-technicians of the wards and five nurses-technicians engaged in the healthcare process at wards (nurses-technicians working in shifts, with no functions).

For the purpose of the study an author's anonymous survey questionnaire was used. The questionnaire was created in an electronic program „Google forms“ and via link (sent by electronic mail) was accessible to nurses-technicians working in organizational units of the CCUS (personal e-mail, e-mail of the organizational unit).

The questionnaire was anonymous and respondents' identity could not be revealed based on the provided answers, and full anonymity was guaranteed during filling out the forms (the forms were filled out in a separate intimate space, without the possibility to influence persons in providing their answers).

The study was descriptive and it also used the induction, deduction and compilation methodology.

Data analysis was performed using the SPSS Windows software package (version 23.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft

Excel (version 11 of Microsoft Corporation, Redmond, WA, USA). Results of descriptive analysis are shown in frequencies and percentages.

RESULTS

The sample consisted of 19 or 10.7% male and 159 or 89.3% female respondents.

According to the age distribution the majority of nurses was at the age group 35-54 years – 68.8% with the significant difference according to gender (Pearson's chi-square test, $p = 0.001$).

The majority of nurses is working between 11 and 30 years – 128 or 70.3% and the least for up to 10 years – 19 or 10.0%. There was a significant difference between the genders (Pearson's chi-square test, $p = 0.001$).

According to the education there was just more graduated nurses with college or master's degree – 98 or 53.8%, but there were significantly more graduated nurses among female respondents (Fisher's exact test, $p = 0.031$).

The sample consisted of 84 or 47.2% head/chief nurses and 94 or 52.8% of ward nurses. There was a significant difference among genders (Fisher's exact test, $p = 0.026$) (Table 1).

Table 1 Representation of respondents by age, years of employment, education and workplace according to gender.

		Male		Female		Total	
		n	%	n	%	n	%
Age	18-34	8	40.0	16	9.9	24	13.0
	35-54	9	45.0	116	71.6	125	68.8
	>54	3	15.0	30	18.5	33	18.1
Years of employment	0-10	8	40.0	11	6.8	19	10.0
	11-20	5	25.0	54	33.3	59	32.4
	21-30	2	10.0	67	41.4	69	37.9
	>30	5	25.0	30	18.5	35	19.2
Education	High school	14	70.0	70	43.2	84	46.2
	College or master	6	30.0	92	56.8	98	53.8
Workplace	Head nurse	4	21.1	80	50.3	84	47.2
	Nurse	15	78.9	79	49.7	94	52.8
Total		19	10.7	159	89.3	178	100.0

There was a significant difference in the answers provided from various disciplines of the CCUS. The staff of the Internal Medicine Discipline to a large extent implement the healthcare process together with patients (Pearson χ^2 test, $p < 0.001$) (Figure 1).

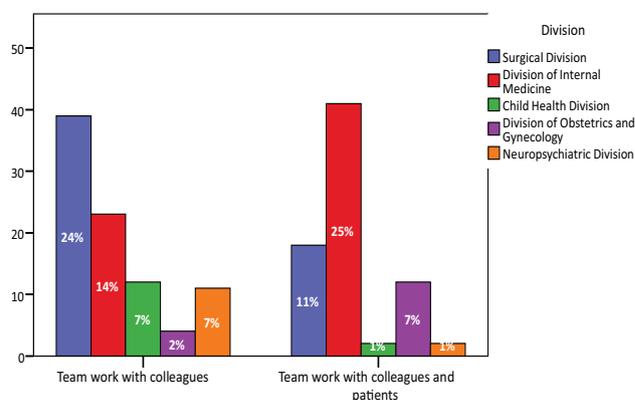


Figure 1 Implementation of healthcare by medical disciplines.

Younger staff more often only partially have standardized documents or use them less often in practice (Pearson's chi-square test, $p = 0.021$) (Figure 2).

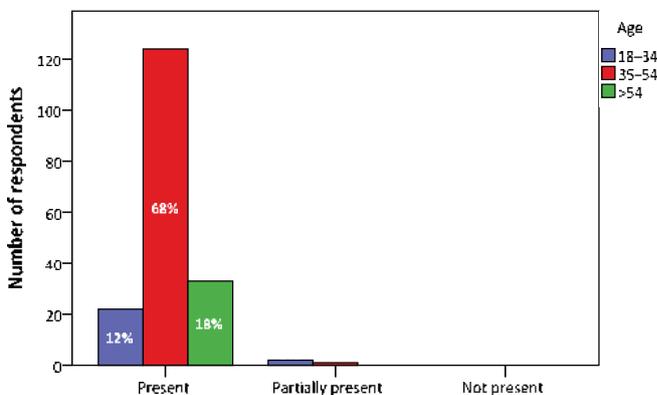


Figure 2 Knowledge of adopted standardized quality documents and their use in practice.

Younger staff more often only partially have standardized documents or use them less often in practice (Pearson's chi-square test, $p = 0.021$) (Figure 3).

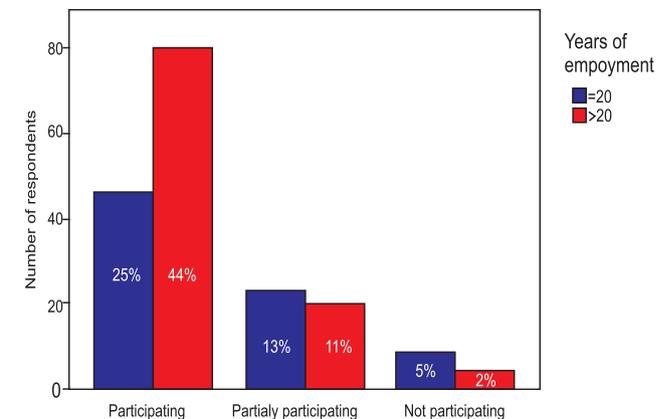


Figure 3 Participation of respondents in quality planning and adopting healthcare regulations in respect to years of service.

Staff over 20 years of service more often participate in quality planning and adopting regulations on patients' healthcare (Pearson's chi-square test, $p = 0.021$) (Table 5).

Table 5 Practice of respondents regarding methods of planning and evaluation of healthcare process.

		No. of answers		Share in the no. of respondents
		n	%	
The method of healthcare planning	Assessing the state of the patient, providing written instructions	118	40.4%	65.2%
	Providing oral instructions and assignments to nurses-technicians	102	34.9%	56.4%
	Providing oral instructions during nursing rounds	70	24.0%	38.7%
	No healthcare planning	2	0.7%	1.1%
Total		292	100.0%	161.3%
The method of healthcare evaluation	Group overview	65	24.2%	36.5%
	Statistic overview	51	19.0%	28.7%
	Documenting in absence of the patient	151	56.1%	84.8%
	No healthcare evaluation	2	0.7%	1.1%
Total		269	100.0%	151.1%

Analysis of individual answers shows that the staff of the Internal Medicine Discipline usually provides written instructions (Pearson's chi-square test, $p < 0.001$). On the other hand, oral instruction and assignments to nurses-technicians are common in the Gynecology and Obstetrics Discipline (Pearson's chi-square test, $p = 0.001$), as presented in figures.

With regard to the healthcare evaluation method, the answers are to a large extent uniformed among different groups of respondents. It is interesting that „group overview“ is not significant in the Gynecology and Obstetrics and Neuropsychiatric Discipline (Pearson's chi-square test, $p < 0.001$) (Table 6, Table 7).

Table 6 Overview of respondents in the process of clinical healthcare risk prevention.

Do you regularly perform nursing rounds?	Yes	175	96.7%
	Partially	5	2.8%
	No	1	0.6%
Do you categorize patients for healthcare?	Yes	178	97.8%
	Partially	4	2.2%
	No	0	0.0%
Do you monitor risks of hospital on patients?	Yes	176	97.2%
	Partially	5	2.8%
	No	0	0.0%
Do you report unwanted and incidental situations in the healthcare process?	Yes	178	97.8%
	Partially	4	2.2%
	No	0	0.0%

Table 7 Management of unfavorable events in the clinical healthcare process.

Overview of unfavorable events monitored in the field of clinical healthcare	Decubitus ulcer	150	20.1%	82.4%
	Hospital infections/colonization	173	23.2%	95.1%
	Fall	147	19.7%	80.8%
	Adverse drug reaction	153	20.5%	84.1%
	Inadequate communication with patients	115	15.4%	63.2%
Other	8	1.1%	4.4%	
Total		746	100.0%	409.9%
Nursing practice in cases of unfavorable events in the healthcare process	Reconstruction of events	105	25.0%	58.0%
	Approach to risk elimination	155	36.9%	85.6%
	Recording only	16	3.8%	8.8%
	Education of nursing staff on risk prevention	144	34.3%	79.6%
	Total		420	100.0%

As expected, decubitus ulcer is less frequently monitored in the Gynecology and Obstetrics Discipline, where patients do not spend much time or where patients are mobile (Pearson's chi-square test, $p < 0.001$). On the other hand, fall monitoring is more significant in both Internal Medicine and Gynecology and Obstetrics Discipline (Pearson's chi-square test, $p = 0.001$), but also in other CCUS disciplines.

Table 8 Satisfaction of respondents with the outcome of provided healthcare.

Role	Satisfied	Partially or not satisfied
Participating	94%	6%
Partially or not participating	88%	12%

Majority of the respondents (167 or 91.8%) was satisfied with the healthcare outcome. There was not significant difference among the survey participating groups (Table 8).

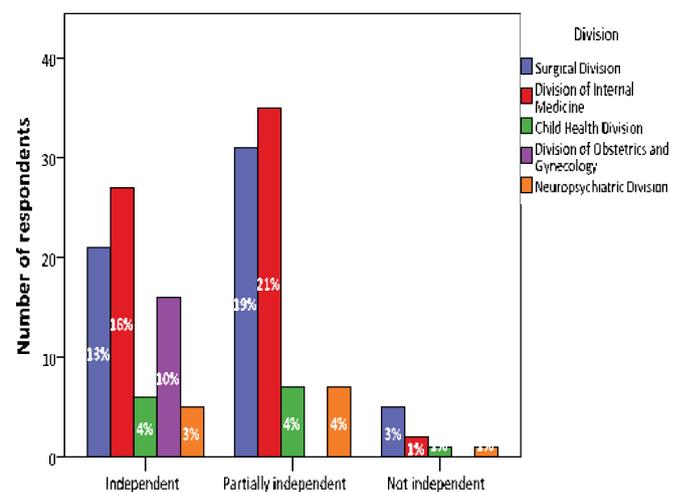


Figure 4 Position of the respondents in the healthcare decision-making process.

Independence in decision making was expressed among respondents of the Gynecology and Obstetrics Discipline (Pearson's chi-square test, $p = 0.003$) (Figure 4). Also, the staff engaged in the process of quality planning and adopting healthcare regulations was more independent in decision-making (Fisher's exact test, $p < 0.001$) (Table 9).

Table 9 Proposals of nurses-technicians for healthcare improvement.

How do you think you can improve healthcare?	Greater commitment of all nurses - technicians in the work process	152	28.7%	84.0%
	Introducing quality at all levels of healthcare	146	27.6%	80.7%
	Organizing number of trainings for nurses-technicians	144	27.2%	79.6%
	Greater independence in decision making process	64	12.1%	35.4%
	Involving patients and their careers in decisions	23	4.3%	12.7%
Total		529	100.0%	292.3%

DISCUSSION

The most important dimension of healthcare and priority of each and every health system is patient's safety and the patient in its center. Thus, we must invest efforts to make the system as safe as possible for both patients and all those providing healthcare.

Implementing healthcare process in the Clinical Center University of Sarajevo is a team work, with significant participation of patients. That is especially emphasized in the Internal Medicine Discipline, most probably due to more cooperative staff attitude. The staff with completed secondary education more often cooperates with patients in the field of healthcare.

Large majority of respondents consider that more quality healthcare facilitates healing of patients, and they also claim to have standardized documents, such as nursing procedures or documentation. As expected, quality planning and adopting healthcare regulations is not in the scope of all employees, especially those with less than 10 years of service. Nevertheless, two thirds of respondents participated in the process, somewhat more in the Internal Medicine Discipline.

Based on the provided answers, regular nursing rounds are common practice in the CCUS. They were performed by large majority of respondents and there was no significant difference in any groups of employees participating in the survey.

Healthcare planning is mostly performed by assessing patients' condition and providing written or oral instructions. At Internal Medicine Disciplines, where communication with patients is easier, written instructions are more common. On the other hand, in places where instructions should be provided quickly and indirectly, communication is often oral, as is the case in the Gynecology and Obstetrics Discipline.

Risk and incident situations are regularly monitored, and hospital infections/colonization and adverse drug reactions are most often checked, for all categories of employees equally. As expected, there were differences in priorities among different medicine disciplines.

Nursing staff is independent in the healthcare decision-making process, especially in the Gynecology and Obstetrics Discipline.

Healthcare evaluation is most commonly performed at the patient's discharge from hospital, and rarely in the group or statistic overview.

Majority of respondents was satisfied with the outcome of healthcare, which was equally confirmed by all categories of respondents. The research also examined the connection between the outcome and the fact whether anyone participated in the quality improvement process or not. The difference was not significant.

Majority of respondents considered that better quality could be achieved by larger efforts of all nurses-technicians, and by introducing quality at all levels of healthcare or by organizing number of trainings. The employees considered that quality could be improved by mutual respect among colleagues, better organization of the collective and increasing number of nurses-technicians.

Previous studies on establishing quality in the healthcare process were mainly based on general and methodological approach to healthcare quality establishing.

In her master's thesis, defended in 2017 at the Medical School in Zagreb, author Kljaić M, emphasized the need and importance of introducing quality in the field of nursing. She also highlighted the importance of laws and bylaws defining the nursing quality management and also pointed to the importance of the healthcare quality indicators and treatment outcomes monitoring (10).

In his work entitled „Monitoring clinical healthcare indicators as an indication of quality and safety of health services“, Ovčina, et al. pointed to the importance of introducing quality into nursing practice, and monitoring health condition of patients during treatment and evaluating the healthcare outcome. He considers it to be important in monitoring quality of nursing services, work evaluation and planning actual needs for nurses-technicians in the work process (16).

The aim of the research entitled „Significance of healthcare standards in intensive care units“ conducted by Miličević in 2014, was to show to which extent there existed standards of medical care applicable in intensive care and therapy units of the Clinical Center University of Sarajevo. Besides this primary aim, the research also assessed the level of satisfaction of employed nurses, specifically how the respondents evaluated work environment and what they considered was the cause of poor work environment. Results of this research showed that it was necessary to work on the development of nursing standards and nursing operative procedures (18).

In 2017, Mate Čikeš conducted a research on establishing needs for categorization of patients, emphasizing the need of applying standardized nursing documentation aimed at assessing the healthcare needs. The research showed importance of introducing quality into nursing practice given that it set clear standards both in work processes and in nursing staff planning (19).

In his work from 2008, Biščan, et al., defined healthcare standards with a special reference to the importance of keeping nursing documentation (4).

In 2010, the Croatian Nurses Chamber published a book entitled „Standardized procedures in healthcare“ which defined particular work processes in the field of healthcare (20).

In 2017, working group of the Ministry of Health of the Federation of Bosnia and Herzegovina in cooperation with the Consortium of Foundation FAMI for support and strengthening nursing in BiH, published a book entitled „Standard operative

procedures for nurses-technicians in primary healthcare" which included standard work processes at the primary healthcare level.

CONCLUSION

The implementation of quality programs in clinical healthcare ensures safety of patients and nurses. The application of standardized quality documents reduces the possibility of risks and adverse events in the healthcare process, monitors the efficiency of nursing services, and ensure continuity in the practice improvement process. Improvement of healthcare process is possible through a through team work with an active participation of patients. Since the staff involved in quality management in clinical nursing practice contributes more independently in decision making and thus contributing to the strengthening and autonomy of nursing profession, standardization of the clinical healthcare process, safety and general satisfaction of health care users.

REFERENCES

1. Lemon. Udžbenik za medicinske sestre. Prevodi publikacija, Sarajevo: 1999.
2. Čukljek S. Teorija i organizacija u zdravstvenoj njezi - nastavni tekstovi. Zagreb: Zdravstveno veleučilište u Zagrebu; 2008.
3. Kalauz S. Upravljanje kvalitetom u zdravstvenoj njezi. Zagreb: Visoka zdravstvena škola; 2010.
4. Biščan J. Standardi u sestrijskoj njezi. Zagreb: Hrvatski časopis za javno zdravstvo; 2008;7.
5. Ivanuš A, Železnik D. Standardi aktivne zdravstvene njege. 2. dopunjeno izdanje. Maribor; 2008.
6. Australian Council on Healthcare Standards. Clinical Indicators. A user's manual surgery indicators. Fitzroy: ACHS; 1997.
7. Henderson V. Osnovna načela zdravstvene njege. Zagreb: Hrvatska udruga za sestrijsku edukaciju; 1994.
8. Mojsović Z, et al. Sestrinstvo u zajednici. Zagreb: Visoka zdravstvena škola; 2005.
9. Halilović-Gunić L. Kvalitet komunikacije i modeli zdravstvene njege u bolničkom okruženju; magistarski rad. Sarajevo: Medicinski fakultet; 2013.
10. Kljaić M. Upravljanje kvalitetom u zdravstvenoj njezi: diplomski rad. Zagreb: Sveučilište u Zagrebu, Medicinski fakultet; 2017.
11. Ovčina A, et al. Menadžment standardizacije zdravstvene njege i značaj za reformске procese u zdravstvu. Naučno stručna konferencija Fakulteta zdravstvenih studija. Sarajevo: Univerzitet u Sarajevu; 2018.
12. Tijanić M, et al. Zdravstvena nega i savremeno sestriinstvo. Beograd: Naučna KMD; 2004.
13. Pričić N. Opća načela zdravlja i njege. Zagreb: Školska knjiga; 2014.
14. Nuhić M. Uspostava internog sistema poboljšanja kvaliteta i sigurnosti u zdravstvenim ustanovama. Sarajevo: Klinički centar Univerziteta u Sarajevu (KCUS), Agencija za kvalitet i akreditaciju u zdravstvu Federacije Bosne i Hercegovine (AKAZ); 2011.
15. Akreditacijski standardi za bolnice. Sarajevo: Agencija za kvalitet i akreditaciju u zdravstvu (AKAZ); 2010.
16. Ovčina A, Izetbegović S, Eminović E. Implementation of patient categorization model based on their need for medical care as an indicator of efficiency and effectiveness of nursing clinical practice. Acta Med Croatica. 2018;72(4):453-556.
17. Akreditacijski standardi za bolnice. Sarajevo: Agencija za kvalitet i akreditaciju u zdravstvu (AKAZ); 2010.
18. Milićević D. Značaj standarda za zdravstvenu njegu u jedinicama za intenzivno liječenje. Mostar: Rauche; 2015:6.
19. Čikeš M. Utvrđivanje potreba za zdravstvenom njegom primjenom kategorizacije pacijenta: diplomski rad. Dubrovnik: Sveučilište u Dubrovniku, Odjel za stručne studije, Dubrovnik; 2017.
20. Šepec S, et al. Standardizirani postupci u zdravstvenoj njezi. Zagreb: Hrvatska komora medicinskih sestara; 2010.

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Peripheral blood as alternative source to bone marrow in detection of minimal residual disease by flow cytometry in acute myeloid leukemia

Periferna krv kao alternativa koštanoj srži u detekciji minimalne rezidualne bolesti protočnom citometrijom u akutnoj mijeloidnoj leukemiji

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ABSTRACT

Minimal residual disease (MRD) in acute myeloid leukemia (AML) is term used for leukemic cells that remain after treatment and they are undetectable by conventional cytomorphic criteria. Detection of MRD by flow cytometry helps to distinguish patients with AML in prognostic groups with different outcomes. MRD percentage was found to be an independent prognostic factor in AML when assessed in a postinduction or postconsolidation setting. The principle of immunophenotyping is to identify leukaemia-associated phenotypes (LAPs). Conventional MRD measurement is carried out in bone marrow. This study aimed to investigate does peripheral blood can replace bone marrow as source for detection MRD in AML. MRD was measured in bone marrow and peripheral blood of 40 AML patients from Clinical Center University of Sarajevo, Clinic of Hematology between March 2013. and June 2015. who achieved complete remission after induction chemotherapy. Percentage of MRD in peripheral blood (PB MRD) compared with level of MRD in bone marrow (BM MRD). A significant correlation was found between PB MRD and BM MRD ($\rho(38) = 0.856, p < 0.001$). This study demonstrates that peripheral blood can replace bone marrow and can be used as non-invasive method for detection of MRD in postinduction AML.

Key words: acute myeloid leukemia (AML), minimal residual disease (MRD), leukaemia-associated phenotypes (LAPs)

INTRODUCTION

A high complete remission rate is currently achieved in patients with acute myeloid leukemia. However, many AML patients eventually relapse due to the persistence of low numbers of residual leukemic cells that are undetectable by conventional cytomorphic criteria. This condition is known as minimal residual disease (MRD). Among the techniques suitable for MRD detection, flow cytometry is the most commonly used.

MRD detection by flow cytometry is a strong, independent prognostic marker of increased risk of relapse and shorter survival in

SAŽETAK

Minimalna rezidualna bolest (MRD) u akutne mijeloidne leukemije (AML) je termin za leukemijske ćelije koje zaostaju nakon terapije i koje nisu detektabilne citomorfološki. Detekcija MRD protočnom citometrijom pomaže klasifikaciji pacijenata sa AML u prognostičke grupe sa različitim ishodima. Utvrđeno je da je procenat MRD neovisan prognostički faktor u AML kada se procjenjuje u postindukcionom ili postkonsolidacionom okruženju. Princip imunofenotipizacije je identifikovati leukemija asocirane fenotipove (LAPs). Konvencionalno se MRD mjeri iz uzorka koštane srži. Ova studija je imala za cilj da istraži da li periferna krv može zamijeniti koštanoj srži kao izvor određivanja MRD u AML. MRD je mjerena u koštanoj srži i perifernoj krvi 40 AML pacijenata Klinike za hematologiju KCUS u periodu od marta 2013. do juna 2015. godine, a koji su postigli kompletnu remisiju nakon indukcione kemoterapije. Procenat MRD perifernoj krvi (PB MRD) kompariran je sa MRD koštane srži (BM MRD). Nađena je signifikantna korelacija između PB MRD i BM MRD ($\rho(38) = 0.856, p < 0.001$). Ova studija ukazuje da periferna krv može zamijeniti koštanoj srži te se kao kao neinvazivna metoda može primjeniti u detekciji MRD u postindukcionoj fazi AML.

Ključne riječi: akutna mijeloidna leukemija (AML), minimalna rezidualna bolest (MRD), leukemija asocirani fenotipovi (LAPs)

patients with AML and can be used to refine risk-stratification and treatment response assessment (1). The presence of any disease detected by this methodology after treatment is associated with a worse prognosis (2).

The principle of immunophenotyping is to identify leukaemia-associated phenotypes (LAPs) when leukemic cells differ from the large majority of healthy hematopoiesis bone marrow or blood cells. LAPs can be divided into four different types: 1. cross-lineage expression, 2. overexpression, 3. lack of expression, 4. asynchronous expression. This LAPs approach for measuring MRD in AML defines LAPs at diagnosis and tracks these in subsequent samples.

In virtually, LAPs are detectable with multiparameter flow cytometry in all AML patients. These can be targeted with high sensitivity ranging up to 10 (-4) during the course of disease. Finding a LAPs to all AML patients requires an extensive panel of antibodies. However, 80–90% of patients can be followed using a reasonably sized panel (3).

For diagnostic LAPs, peripheral blood can be used because high percentages of blasts are often present in the peripheral blood at the time of diagnosis. However, for follow-up and MRD assessment, bone marrow is preferred because the frequency of leukemic cells is usually lower in peripheral blood compared to bone marrow (4). Nevertheless, usage of peripheral blood would be an attractive alternative source because bone marrow acquisition is relatively invasive and time consuming.

MATERIALS AND METHODS

The study included 40 AML patients from Clinical Center University of Sarajevo, Clinic of Hematology from March 2013 and June 2015 who achieved complete remission (CR) after one or two of induction courses. The follow up was 18 months. The diagnoses of AML were based on morphologic findings, immunophenotyping, and cytogenetics (5). Complete remission defined using the criteria developed by an International Working Group (6). All patients provided written informed consent, and study was approved by the CCUS Ethics Committee.

Inclusion criteria: AML patients who achieved cytomorphology complete remission after one or two cycles of induction.

Exclusion criteria: Patients who did not achieve complete remission after second cycle of induction.

Induction involved one or two cycles of chemotherapy with cytarabine 5 or 7 days and an anthracycline drug / daunorubicin or idarubicin / 2 or 3 days/.

Bone marrow was collected for LAPs identification at diagnosis. For MRD detection peripheral blood and bone marrow were used. The blood and bone marrow samples of each patient for MRD detection were obtained at the same day.

Identification of LAPs at diagnosis and MRD detection at postinduction complete remission have been performed by BD four-color flow cytometry using BD FACSDiva software. Immunophenotypic analysis was performed on erythrocyte-lysed whole samples with directly conjugated monoclonal antibodies. Two monoclonal antibodies panels were used in the study: screening and secondary panels. The screening panel is our standard diagnostic panel used to distinguish acute lymphoblastic leukemia from AML. Subsequently, in AML, the secondary panel was used to identify LAPs and MRD. Blasts were identified by using a CD45/SSC log gating strategy. Panel of monoclonal antibodies consisted:

1. G2/G1/CD45/G1;
2. HLADR/CD33/CD45/CD2;
3. CD7/CD13/CD45/CD2
4. CD10/CD19/CD45/CD34;
5. CD34/CD56/CD45/CD38;
6. CD61/CD64/CD45/CD14;
7. CD15/CD117/CD45/CD11b;
8. CD5/CD22/CD45/CD3;
9. CD79a/MPO/CD3/CD34.

Data were analyzed using descriptive statistics methods and presented in tables. Log-rank tests (7) was used to determine the optimal cut-off for BM MRD who distinguish AML patients in two groups: MRD positive (MRD⁺) and MRD negative (MRD⁻). The

Spearman correlation (*r*) used to summarise the strength and direction of a relationship between BM MRD and PB MRD. Kaplan-Meier estimate used to measure OS and RFS.

RESULTS

Out of the total of 40 AML patients 19 (47.5 %) were female and 21 (52.5 %) male. 30 (75%) patients were under 60 years of age and 10 (30 %) were over 60. 30 (75%) AML patients achieved complete remission after one course of induction and 10 (25 %) after second cycle.

LAPs were observed in all 40 cases (100 %), total 62 LAPs, median: 1.5 LAPs per case. The most frequent identified LAP was asynchronous antigen expression, followed by cross-lineage expression (Table 1).

Table 1 Leukaemia-associated phenotypes (LAPs).

Leukaemia-associated phenotypes (LAPs)	n(62)
Cross-lineage expression	22
Over expression	6
Asynchronous expression	30
Lack of expression	4

The average level of MRD in bone marrow in postinduction complete remission was 1.98% (range: 0.10 – 4.30), the average level of MRD in peripheral blood in postinduction complete remission was 1.54 % (range: 0.00-4.00) (Table 2).

Table 2 MRD in postinduction CR of AML patients.

Variable	M	sd	I quartile	Median	III quartile	Min	Max	Skewness (st. gr. = 0.37)	Kurtosis (st. gr. = 0.73)
MRD in bone marrow	1.98	1.38	0.80	1.75	3.15	0.10	4.30	0.21	-1.49
MRD in peripheral blood	1.54	1.33	0.23	1.25	2.73	0.00	4.00	0.39	-1.25

BM MRD cut-off used in this study was 0.9% with maximally selected rank statistics $M= 5.567$, $p<0.0001$.

24 (60 %) patients was MRD⁺, 16 (40 %) MRD⁻ (Table 3).

Table 3 MRD groups.

MRD group	n	%
MRD ⁺	24	60
MRD ⁻	16	40
Total	40	100

After a median follow-up of 18 months median RFS was 11 months, OS 12.51 months (Table 4).

Table 4 Outcomes of patients.

Variable	M	sd	I quartile	Median	III quartile	Min	Max	Skewness (st. gr. =0.37)	Kurtosis (st. gr. =0.73)
RFS (month)	11.01	6.60	5.25	11.00	18.00	0	18	-0.21	-1.54
OS (month)	12.51	6.69	6.25	17.00	18.00	0	18	-0.69	-1.24

In MRD⁻ group 15 patients had no relaps while 23 patients in MRD⁺ group relapsed during 18 months of follow up. Adjusted analyses confirmed significant relapse free survival (RFS) differences between MRD⁺ and MRD⁻ grupes, Mann-Whitney U=10.000; Z=5.199; p<0.0001 (Table 5).

Table 5 RFS in MRD- and MRD+ group.

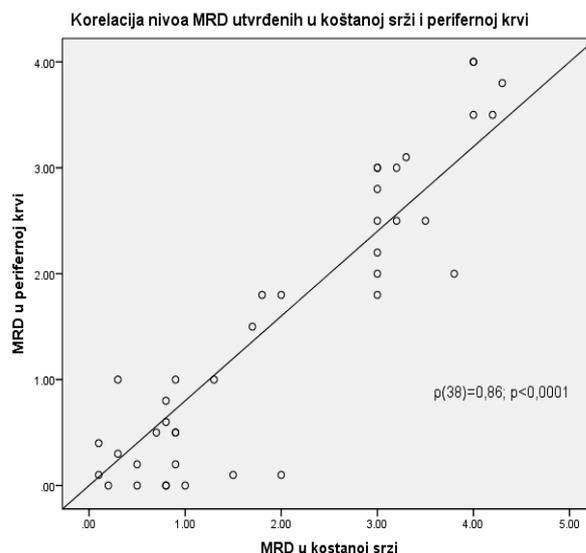
MRD group	RFS		Total
	No relapse	Relapse	
MRD ⁻	15	1	16
MRD ⁺	1	23	24
Total	16	24	40

In MRD⁻ group 16 patients stayed alive, in MRD⁺ group only 4 patients during 18 months of follow up. Adjusted analyses confirmed significant overall survival (OS) differences between MRD⁺ and MRD⁻ grupes: $\chi^2(1)=23.438$; p<0.0001 (in χ^2 test included Yates correction for continuity) (Table 6).

Table 6 OS in MRD- and MRD+ group.

MRD group	OS		Total
	Alive	Death	
MRD ⁻	16	0	16
MRD ⁺	4	20	24
Total	20	20	40

After induction, the findings in bone marrow and peripheral blood were significantly concordant, Spearmanov rho: $\rho(38) = 0.856$, p<0.001 (Figure 1)



MRD peripheral blood had a positive correlation to MRD bone marrow in postinduction complete remission of AML. Higher levels of MRD bone marrow was associated with higher levels of MRD peripheral blood.

DISCUSSION

The current prognostic assessment of AML patients relies on a variety of factors reviewed in detail elsewhere. Since molecular and cytogenetic analysis lack the precision to distinguish the individual AML patients likely to be cured with conventional therapy from those destined to relapse, there has been considerable interest in development of multiparameter flow cytometry to provide a more precise measure of minimal residual disease.

MRD monitoring has been shown to be a powerful independent prognostic factor and is now routinely used to guide therapy in AML patients. MRD states may be essential for assigning patients to therapy-dependent risk categories.

Flow cytometry becomes an obvious MRD measuring tool based on the high-throughput nature of the technique and the possibility for very exact cell characterization offered by multicolor protocols. The principle is to identify leukaemia-associated phenotypes. Finding a LAPs to all AMLs requires an extensive panel of antibodies (8).

Immunophenotypical investigation of MRD of AML patients in complete remission obtained after induction therapy provides important information for risk assessment.

The study of Terwijn, et al. showed that after all courses of AML therapy, low MRD values distinguished patients with relatively favorable outcome from those with high relapse rate and adverse relapse-free and overall survival. In the whole patient group and in the subgroup with intermediate-risk cytogenetics, MRD was an independent prognostic factor (9).

Conventional MRD measurement is carried out in bone marrow. The information about peripheral blood blast dynamics is obtained easily using standard clinical laboratory measures and is available earlier than other methods of response assessment. It is non-invasive method for monitoring of remission or relapse.

In our study, we were able to detect MRD in peripheral blood of all patients enrolled in study. The level of MRD in peripheral blood significantly reflected that observed in bone marrow. In fact, a significant correlation between MRD in the two cell sources was found at postinduction complete remission.

Usage of peripheral blood would be an attractive alternative source because bone marrow acquisition is relatively invasive and time consuming but technical recommendations for MRD detection and its clinical use by the European LeukemiaNet are also expected shortly (10).

CONCLUSION

Minimal residual disease in bone marrow evaluated by flow cytometry in postinduction complete remission of AML impacted relapse free survival and overall survival. MRD status post-induction is adversely associated with relapse free survival and overall survival and proved an independent prognostic factor in AML. Peripheral blood minimal residual disease may replace bone marrow minimal residual disease as an immunophenotypic biomarker. MRD peripheral blood is a non-invasive method for monitoring of residual leukemic cells.

REFERENCES

1. Ravandi F, Walter RB, Freeman DS. Evaluating measurable residual disease in acute myeloid leukemia. *Blood Adv.* 2018;2(11):1356-66.
2. Percival ME, Lai C, Estey E, Hourigan CS. Bone marrow evaluation for diagnosis and monitoring of acute myeloid leukemia. *Blood Rev.* 2017;31(4):185-192.
3. Freeman SD, Virgo P, Couzens S, Grimwade D, Russell N, Hills RK, Burnett AK. Prognostic relevance of treatment response measured by flow cytometric residual disease detection in older patients with acute myeloid leukemia. *J Clin Oncol.* 2013;31(32):4123-31.
4. Zeijlemaker W, Kelder A, Oussoren-Brockhoff YJ, Scholten WJ, Snel AN, Veldhuizen D, Cloos J, et al. Peripheral blood minimal residual disease may replace bone marrow minimal residual disease as an immunophenotypic biomarker for impending relapse in acute myeloid leukemia. *Leukemia.* 2016;30(3):708-15.
5. O'Donnell MR, Tallman MS, Abboud CN, Altman JK, Appelbaum FR, Arber DA, et al. Acute myeloid leukemia. Version 2.2013. *J. Natl. Compr. Cancer Netw.* 2013;11(9):1047-55.

6. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol.* 2003;21(24):4642-9.
7. Hothorn T, Lausen B. On the exact distribution of maximally selected rank statistics. *Computational Statistics & Data Analysis.* 2003;43(2):121-37.
8. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 217 ELN recommendations from an international expert panel. *Blood.* 2017;129(4):424-47.
9. Terwijn M, van Putten WL, Kelder A, van der Velden VH, Brooimans RA, Pabst T, et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. *J Clin Oncol.* 2013;31(31):3889-97.
10. Hourigan CS, Gale RP, Gormley NJ, Ossenkopppele GJ, Walter RB. Measurable residual disease testing in acute myeloid leukemia. *Leukemia.* 2017;31(7):1482-90.

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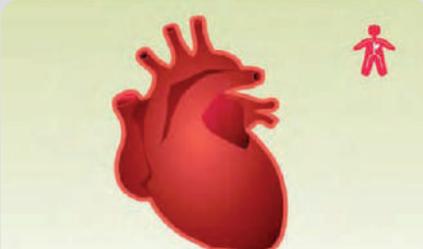
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**DEBLJINA - POVEĆANA
TJELESNA TEŽINA**

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životnih navika

Povećana tjelesna težina uzrokuje brojne zdravstvene komplikacije, oštećuje vaše srce i krvne sudove, smanjuje kvalitetu života i skraćuje životni vijek.



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POVEĆAN KRVNI PRITISAK**

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Povišeni krvni pritisak, hipertenzija, jedan je od riziko faktora koji značajno pridonosi nastanku bolesti srca i krvnih sudova, vodećih uzroka smrtnosti i glavnog javnozdravstvenog problema svuda u svijetu.

Importance of introducing sentinel lymph node biopsy as a procedure of choice in patients with early stage breast cancer

Značaj uvođenja biopsije aksilarnog sentinel limfnog čvora kao metode izbora kod pacijentica sa ranim stadijem karcinoma dojke

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ABSTRACT

Introduction: breast cancer as a malignant neoplasm number one in female population, is under huge attention of health professionals, as well as of healthcare system as a whole. therefore, introducing sentinel lymph node biopsy in patients with early stage breast cancer is of utmost value in disease prognosis thus reducing morbidity and acute complications occurring upon axillar dissection, as well as for its financial benefit. Aim: to confirm the influence of introducing axillar sentinel lymph node biopsy as a method of choice in patients with early stage of breast cancer. Materials and methods: we retrospectively analyzed 226 patients subjected to surgical treatment of breast cancer and axillary lymph nodes dissection. data was retrospectively gathered from patients' medical histories, with pathohistological diagnosis and preoperatively confirmed disease. Results: the study included 226 patients, with average age of 59.25 ± 11.26 years. In 57.1% patients breast cancer was localized in the right breast, while in 42.9% of breast cancer types we established that the most represented type was ductal cancer (72.6%), followed by lobular (11.1%) and papillary cancer (4.9%). Analysis of molecular subtypes of breast cancer revealed that the most common was lobular a (62.8%), followed by triple negative (16.8%). Out of the total number of examinees, grade II had 54.4% of patients, grade I 10.2% of patients and grade III 35.4% of patients. The pathohistological analysis revealed that 49.1% of patients had positive pathologic finding of axillar lymph node dissection, whereas 50.9% of patients had negative pathologic finding of axillar lymph node dissection. The most common positive finding following axillary lymph node dissection was observed in luminal b her 2 positive breast cancer, followed by triple negative breast cancer. The study revealed significant relation between positive axillary lymph nodes and cancer grade. Positive findings after dissection were registered in only 13% of grade I patients, in 47.2% of grade II patients and in 62.5% of grade III patients. Conclusion: based on the above said we can, without any doubt, confirm the importance of sentinel lymph node biopsy, as a method of choice in patients with early-stage breast cancer. Considering the fact that 50.9% of patients had negative pathological finding following axillary lymph node dissection, and having in mind that this procedure has a high specificity

and sensitivity, we can state that axillary sentinel lymph node biopsy presents the golden standard in early breast cancer treatment.

Key words: breast cancer, SLN biopsy, axillar lymph nodes

SAŽETAK

Uvod: karcinom dojke kao maligna neoplazma broj jedan kod žena, zaokuplja ogromnu pažnju zdravstvenih radnika, kao i cjelokupnog sistema zdravstvene zaštite. Samim tim, uvođenje biopsije sentinel limfnog čvora kod pacijentica sa ranim stadijem karcinoma dojke je od značaja i u prognozi bolesti, smanjenju morbiditeta i akutnih komplikacija koje bi bile praćene disekcijom aksile kao i sama finansijska korist. Cilj istraživanja: da se potvrdi značaj uvođenja biopsije aksilarnog sentinel limfnog čvora kao metode izbora kod pacijentica sa ranim stadijem karcinoma dojke. Materijali i metode: retrospektivno smo analizirali 226 pacijentica koje su podvrgnute hirurškoj terapiji karcinoma dojke i disekciji aksilarnih limfnih čvorova. Podaci su retrospektivnom analizom dobiveni iz dostupnih historija bolesti, sa patohistološkim nalazom i preoperativno potvrđenom dijagnozom. Rezultati: u istraživanju je učestvovalo 226 pacijentica, čije je prosječna dob iznosila 59,25 ± 11,26 godina. Kod 57,1% pacijentica karcinom dojke je bio lokalizovan u desnoj dojci, a u lijevoj u 42,9% slučajeva. Analizom histološkog tipa karcinoma dojke ustanovljeno je da dominira duktalni tip karcinoma dojke i to čak u 72,6% ispitanica, zatim lobularni sa 11,1% i papilarni tip karcinoma dojke u 4,9% slučajeva. Analizom molekularnog podtipa karcinoma dojke najzastupljeniji je bio Luminalni A tip karcinoma koji se javio u čak 62,8% slučajeva, te Triple negativni u 16,8% slučajeva. Od ukupnog broja ispitanica Grade II je imalo 54,4% pacijentica, Grade I je bio u 10,2% pacijentica i Grade III u 35,4% pacijentica. Patohistološkom analizom je ustanovljeno da je 49,1% ispitanica imalo pozitivan nalaz disekcije aksilarnog limfnog čvora, dok je 50,9% ispitanica imalo negativan nalaz nakon disekcije aksilarnog limfnog čvora. Najučestaliji pozitivni nalaz nakon disekcije aksilarnih limfnih čvorova se vidao kod Luminalnog B HER 2 pozitivnog karcinoma, a zatim kod Triple negativnog tipa karcinoma dojke. U istraživanju je utvrđena i značajna veza između pozitivnih aksilarnih

nalaza i Gradea karcinoma. Ispitanice sa Gradeom I su samo u 13% slučajeva imale pozitivan nalaz nakon disekcije aksilarnih limfnih čvorova, kod Gradea II 47,2% pacijentica je imalo pozitivan nalaz, te kod Gradea III čak 62,5% pacijentica je imalo pozitivan nalaz. Zaključak: na osnovu gore navedenog možemo bez imalo sumnje potvrditi značaj biopsije sentinel limfnog čvora kao metode izbora kod pacijentica sa ranim stadijem karcinoma dojke. Imajući u vidu činjenicu da je 50,9%

pacijentica imalo negativan nalaz nakon disekcije aksilarnih limfnih čvorova, te ako se uzme u obzir i visoka specifičnost i senzitivnost same dijagnostičke procedure, onda možemo reći da biopsija sentinel limfnog čvora predstavlja zlatni standard u tretmanu ranog stadija karcinoma dojke.

Ključne riječi: karcinom dojke, SLN biopsija, aksilarni limfni čvorovi

INTRODUCTION

The sentinel node (SN) concept is predicated by the idea that a single lymph node can reflect the tumor status of an entire lymphatic basin (1). Axillary lymph node status is one of the most important prognostic factors in patients with breast cancer (2). Each year 183 thousand new women suffering from breast cancer have been diagnosed, while in 41 thousand women it is the cause of death (3). Breast cancer represents most common type of cancer in female population worldwide, while in Europe 30% of all newly diagnosed cancer in female population is breast cancer (4). In 2006 Breast cancer incidence in European Union was 110.3/100000 women, while annual mortality rate was 25/100000 women (5). Unfortunately, breast cancer is the cause of death in 15% of women dying from malignant disease in female population in Europe (6). A huge number of studies since 1970 have shown that size of tumor and status of regional lymph nodes are the most important prognostic factors in breast cancer (7).

AIM

To confirm the influence of introducing axillar sentinel lymph node biopsy as a choice method in patients with early-stage breast cancer.

MATERIALS AND METHODS

This is a retrospective study conducted at the Clinic of Oncology and Glandular Surgery of the Clinical Center University of Sarajevo (CCUS) based on the existing data obtained from patients' medical records and pathos histology findings obtained from the CCUS Institute for Pathology. Data was gathered in accordance with ethic and bio-ethic principles of the latest Helsinki Declaration. The study included 226 patients surgically treated at the Clinic of Oncology and Glandular Surgery of the CCUS in the period from 2011 to 2013. We analyzed medical documentation of patients surgically treated at the Clinic of Oncology and Glandular Surgery of the CCUS with histopathological diagnosis confirming breast cancer by using the following statistical methods: number of cases (n), percentage (%), arithmetic mean (X) with standard deviation (SD) and standard error (X) SEM as well as median. The study excluded patients with incomplete data in disease history, patients without pathohistology findings, patients with benign breast diseases, patients with pathology status equals 0 (carcinoma in situ), patients with egulcerrated (T4) breast cancer and patients treated with neoadjuvant oncology therapy (chemotherapy or irradiation).

RESULTS

The average age of the study patients was 59.25 ± 11.26 . In 57.1% of patients breast cancer was localized in the right breast

whereas in 42.9% of patients breast cancer was localized in the left breast. Analysis of histology type of the breast cancer revealed domination of ductal breast cancer in 72.6 % of patients followed by lobular cancer registered in 11.1% of patients and papillary type of cancer in 4.9 % of patients. Analysis of molecular sub-type of the breast cancer showed that Luminal A type of carcinoma was the most frequent appearing in 62.8% cases, followed by Triple negative in 16.8% cases. Out of the total number of examinees Grade II was registered in 54.4% of patients, Grade I in 10.2% of patients and Grade III in 35.4% of patients. Patho-histology analysis showed that 49.1% of examinees had positive finding of the dissection of axilla lymph node whereas 50.9% of examinees had negative finding after axilla lymph node dissection. The most frequent positive finding after dissection of axilla lymph nodes was at Luminal B HER 2 positive carcinoma followed by Triple negative type of the breast cancer. In our research, we noticed an important connection between positive axilla findings and carcinoma Grade. Positive findings after dissection were registered in only 13% of Grade I patients, in 47.2% of Grade II patients and in 62.5% of Grade III patients.

Table I Review of examinees according to age groups.

		N	%	Valid %	Cumulative %
Age Groups	30 -39	11	4.9	4.9	4.9
	40 -49	41	18.1	18.1	23.0
	50 -59	66	29.2	29.2	52.2
	60 -69	57	25.2	25.2	77.4
	70 -79	43	19.0	19.0	96.5
	80 -89	8	3.5	3.5	100.0
	Total	226	100.0	100.0	
X		59.25			
SD		11.96			
MIN		30			
MAX		87			

The average age was of patients was $59, 25 \pm 11.96$. The youngest examinee was 30 years of age and the oldest was 87. Examinees were divided into groups based on their age structure. The majority of examinees were in the 50-59 age group (29.2%), and the lowest number in the 80-89 age group (3.5%). Number of examinees had linear growth up to the 50-59 age group, and then their number declined.

Table 2 Review of breast cancer according to histology type.

Histology carcinoma type	N	%	Valid %	Cumulative
Ductal	164	72.6	72.6	72.6
Papillary	11	4.9	4.9	77.4
Medullar	2	.9	.9	78.3
Lobular	25	11.1	11.1	89.4
Lobular-Ductal	7	3.1	3.1	92.5
Tubular	1	.4	.4	92.9
Mucinoze	4	1.8	1.8	94.7
Tubulo-lobular	6	2.7	2.7	97.3
Apocrini	1	.4	.4	97.8
Meta-plastic	3	1.3	1.3	99.1
Mucopapilar	2	.9	.9	100.0
Total	226	100.0	100.0	
$\chi^2=1125.24; p=0.001$				

Analysis of the histology type of cancer showed that ductal breast cancer was dominant in 72.6% of examinees, followed by lobular in 11.1% and papillary in 4.9%. Other histology types were present in less than 3% of examinees. Chi-square test showed statistically important difference in the presence of certain histology types, $\chi^2=1125, 48; p=0.001$.

Table 3 Review of breast cancer according to molecular type.

	N	%	Valid %	Cumulative %
Luminal A	142	62.8	62.8	62.8
Luminal B	29	12.8	12.8	75.7
Luminal B HER 2 positive	6	2.7	2.7	78.3
Non-luminal HER 2 positive	11	4.9	4.9	83.2
Triple negative	38	16.8	16.8	100.0
Total	226	100.0	100.0	
$\chi^2=274.13; p=0.001$				

Dominant type of carcinoma was luminal A type registered in 62.8% of examinees, followed by triple negative type in 16.8% of examinees. Luminal B carcinoma type was present in 12.8% of cases, whereas non-luminal HER 2 was present in 4.9% of examinees. The lowest presence was that of luminal B HER 2 positive type of carcinoma in 2.7%, and the application of square test showed statistically important difference in the frequency of different molecular types of breast carcinoma, $\chi^2=274, 13; p=0.001$.

Table 4 Review of breast cancer according to grade.

	N	%	Valid %	Cumulative %
Grade I	23	10.2	10.2	10.2
Grade II	123	54.4	54.4	64.6
Grade III	80	35.4	35.4	100.0
Total	226	100.0	100.0	
$\chi^2=274.13; p=0.001$				

Out of the total number of examinees included into the study, Grade II was registered in 54.4% of examinees, which was statistically significant in relation to Grade I and Grade III registered in 10.2% and 35.4% of examinees respectively.

Table 5 Frequency of positive axilla finding upon surgical treatment.

	N	%	Valid %	Cumulative %
Positive axilla finding	111	49.1	49.1	49.1
Negative axilla finding	115	50.9	50.9	100.0
Total	226	100.0	100.0	

Following surgical treatment of examinees and pathohistology analysis of axilla lymph nodes, it was concluded that positive findings were registered in 49.1% of examinees whereas negative findings were recorded in 50.9% of examinees.

Table 6 Frequency of positive axilla findings in relation to molecular type of carcinoma.

Molecular type of carcinoma		AXILLA		Total
		Positive	Negative	
Luminal A	Number	69	73	142
	%	48.6%	51.4%	100.0%
Luminal B	Number	7	22	29
	%	24.1%	75.9%	100.0%
Luminal B HER 2 positive	Number	5	1	6
	%	83.3%	16.7%	100.0%
Non-luminal HER 2 positive	Number	6	5	11
	%	54.5%	45.5%	100.0%
Triple negative	Number	24	14	38
	%	63.2%	36.8%	100.0%
Total	Number	111	115	226
	%	49.1%	50.9%	100.0%

In relation to molecular type of carcinoma, statistically significant difference was found between positive and negative axilla findings. The most frequent positive findings related to luminal B HER 2 positive molecular type of carcinoma followed by Triple negative, $p=0.011$.

In relation to molecular type of carcinoma, statistically significant difference was found between positive and negative axilla findings. The most frequent positive findings related to luminal B HER 2 positive molecular type of carcinoma followed by Triple negative, $p=0.011$.

Table 7 Frequency of positive axilla findings in relation to grade.

		AXILLA		Total	
		Positive	Negative		
GRADE	I	Number	3	20	23
		%	13.0%	87.0%	100.0%
	II	Number	58	65	123
		%	47.2%	52.8%	100.0%
	III	Number	50	30	80
		%	62.5%	37.5%	100.0%
Total		Number	111	115	226
		%	49.1%	50.9%	100.0%

The Chi-Square Test showed statistically significant difference in the frequency of positive axilla findings and clinical status of disease. Among Grade I patients only 13% had positive axilla finding, 47.2% of Grade II patients had positive axilla finding, whereas 62.5% of Grade III patients had positive axilla finding, $p=0.001$.

DISCUSSION

The study included 226 examinees with average age structure $59, 25 \pm 11.96$. The youngest examinee was 30 years of age and the oldest was 87. Number of examinees had linear growth up to the 50-59 age group and then the number declined. This is also supported by the fact that the risk of breast cancer increases with age, meaning that the lowest incidence is under the age of 30 then being doubled each 10 years until menopause.

Research of the British Institute of Cancer indicates that the incidence of breast cancer increases in between the 30-34 years of age, facing afterward a significant growth in women in their fifties reaching climax in the age between 65 and 69. The incidence declines in women in the 70-74 age group reaching plateau in the 85-89 age group (8).

Analysis of histology type of the breast carcinoma established that ductal breast carcinoma was dominant in 72.6% of examinees followed by lobular in 11.1% and papillary in 4.9% of examinees. Other histology types of breast cancer were present in less than 3% of examinees. According to data, ductal breast cancer is the most common type, occurring in 68% of cases (9).

Our results are in correlation with general representation of molecular types quoting that the most represented is Luminal A with 30-70% cases, followed by Triple negative with 15 to 20%, Luminal B with 10-20% cases so as its subgroup Luminal B HER 2 provided the similar results were among 56 cases of breast cancer, the most represented was Luminal A with 34% and Triple negative with 25% of cases (10).

Following surgical treatment and axilla lymph node dissection, samples were sent to patho-histology analysis. Patho-histology analysis revealed that 49.1% of examinees had positive finding whereas 50.9% of them had negative findings. Research by Veronesi et al., from 2003, compared a biopsy of sentinel lymph node and routine axilla dissection. In their research, out of representing 32.3% even 174 examinees had negative findings or 67.7%. 257 patients subjected to axilla dissection, 83 had positive lymph nodes. Out of 259 patients being subjected to the biopsy of sentinel lymph nodes, 92 (35.5%) had positive findings and 167 (64.5%) had negative biopsy findings (11). In both, ours and Veronesi researches, majority of patients subjected to axilla dissection had negative pathohistology findings, although, percentages are slightly higher in the Veronesi, et al. research.

Giuliano, et al., in their randomized study from 2011, compared five-year survival at patients with axilla dissection with patients subjected only to dissection of sentinel lymph nodes. Mid number of removed lymph nodes at complete axilla resection was 17, and only 2 lymph nodes at dissection of sentinel lymph nodes. Lower number of removed lymph nodes lowers the possibility of eventual complications. With the follow up time period of 6.3 years (the last checkup was on March 4, 2010), five year survival was 91.8% at complete axilla dissection and 92.5% at dissection of sentinel lymph nodes; five year survival with no signs of disease was 82.2% at complete axilla dissection and 83.9% at dissection of sentinel lymph nodes. Their conclusion stated that among the patients with limited metastases in sentinel lymph nodes at breast cancer cured by conservative surgical treatment and systemic therapy, using a dissection of sentinel lymph nodes in comparison to complete axilla dissection, did not show lower survival (12).

Petrelli, Lonati and Barni performed meta-analysis of four randomized studies comparing dissection of axilla lymph nodes and biopsy of sentinel lymph nodes at patients with early stage of carcinoma. Meta-analysis was performed for survival and repeated occurrence of disease. Combined analysis of those four studies did not find significant difference in survival (relative risk RR 1.5; $P=0.16$; 95% CI: 0.95-1.39), specific characteristics of breast cancer (RR 1.03; $P=0.85$; 95% CI: 0.75-1.43), survival with no signs of disease (RR 1.07; $P=0.3$; 95% CI: 0.94-1.21), distant metastases (RR 1; $P=0.98$; 95% CI: 0.76-1.32) and relapses in the ipsilateral breast (RR 1.64; $P=0.34$; 95% CI: 0.60-4.47) connected with biopsy of sentinel lymph node (13). Many other studies did not find differences in the total survivals and local relapses of disease at patients being subjected exclusively to the biopsy of sentinel lymph node and those patients who also had dissection of axilla lymph nodes (14, 15, 16, 17, 18).

In relation to molecular type of carcinoma, statistically significant difference was established between positive and negative axilla findings. The most frequent positive finding was recorded in relation to luminal B HER 2 positive molecular type of carcinoma followed by triple negative, $p=0.011$. The research from 2014, showed that Luminal B (HER 2 positive and negative) molecular type of carcinoma is connected to higher probability of spreading to axillar lymph nodes than other molecular types of breast cancer (19). Luminal B HER 2 positive tumors are often diagnosed in later stadium thus more often give metastasis into axilla lymph nodes.

The Chi-square test revealed statistically significant difference in the incidence of positive axilla findings and carcinoma grade. Higher grade of breast carcinoma increases the incidence of metastasis in sentinel axilla lymph nodes. Very classification of stadium III breast cancer in majority of sub-types has positive metastasis in ipsilateral lymph nodes. Research by Kumara, et al., from 2015, showed that the highest percentage of patients had grade II breast carcinoma in the moment of diagnostics, even 54% (8).

CONCLUSION

Based on the above said, and without any doubt, we can confirm the importance of the sentinel lymph node biopsy as the method of choice in patients with early stage of breast cancer. Having in mind the fact that 50.9% of patients had negative finding after axilla lymph nodes dissection, and taking into account high specificity and sensitivity of the very diagnostic procedure, we can say that the biopsy of sentinel lymph node represents a golden standard in the early stadium of breast cancer treatment.

REFERENCES

- Henry M. Kruer: *Kruer's Breast Surgical Oncology*, China: The McGraw-Hill Companies Inc; 2010: 669.
- Sasanpour P, Sandoughdaran S, Mosavi-Jarrahi A, Malekzadeh M. Predictors of Pathological Complete Response to Neoadjuvant Chemotherapy in Iranian Breast Cancer Patients. *Asian Pacific Journal of Cancer Prevention: APJCP*. 2018;19(9):2423-7.
- Greenlee RT, Murray T, Bolden S, Winago PA: *Cancer statistics*. *CA Cancer J Clin*; 2000; 50:7-33.
- Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2000. *Int J Cancer*. 2010;127(12): 2893-2917.
- Anghel R. Ghid de management al cancerului mamar. Order No. 1059/2009, Annex 9, Ministry of Health.
- Bešlija Semir, Vrbancic Damir. *Medicine/intern oncology*. Sarajevo: Medicinski fakultet; 2014: 213-323.
- Trocha SD, Giuliano AE. Sentinel node in the era of neoadjuvant therapy and locally advanced breast cancer. *Surg Oncol*. 2003;12(4):271-6.
- Data were provided by the Cancer Research UK, April 2020. Similar data can be found here: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-One>
- Berg JW, Hutter RV. Breast cancer. *Cancer*. 1995;75: 257-69.
- Kumar N, Patni P, Agarwal A, Khan MA, Parashar N. Prevalence of molecular subtypes of invasive breast cancer: A retrospective study. *Med J Armed Forces India*. 2015;71(3):254-8.
- Veronesi U, Paganelli G, Viale G, Luini A, Zurrada S, Galimberti V, et al. A Randomized Comparison of Sentinel-Node Biopsy with Routine Axillary Dissection in Breast Cancer. *N Engl J Med*. 2003;349:546-553.
- Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumentcranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305(6):569-75.
- Petrelli F, Lonati V, Barni S. Axillary dissection compared to sentinel node biopsy for the treatment of pathologically node-negative breast cancer: a meta-analysis of four randomized trials with long-term follow up. *Oncol Rev*. 2012;6(2):e20.
- Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer. *J Natl Cancer Inst*. 2006;98(9):599-609.
- Del Bianco P, Zavagno G, Burelli P, Scalco G, Barutta L, Carraro P, et al. Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the Sentinella-GIVOM Italian randomised clinical trial. *Eur J Surg Oncol*. 2008;34(5):508-13.
- Zavagno G, De Salvo GL, Scalco G, Bozza F, Barutta L, Del Bianco P, et al. A randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. *Ann Surg*. 2008;247(2):207-13.
- National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: Breast Cancer Guidelines*. 2010;2
- George R, Quan ML, McCready D, et al. Sentinel Lymph Node Biopsy in Early-stage Breast Cancer: Guideline Recommendations. A Quality Initiative of Cancer Care Ontario's Surgical Oncology Program (SOP) and Cancer Care Ontario's Program in Evidence-Based Care (PEBC). Report Date: July 14, 2009.
- Chengshuai Si, Yiting Jin, Hongying Wang, Qiang Zou. Association between molecular subtypes and lymph node status in invasive breast cancer. *Int J Clin Exp Pathol*. 2014;7(10): 6800-06.

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Algorithm of melanoma treatment in relation to pathohistological characteristics and surgical modalities

Algoritam tretmana melanoma u odnosu na patohistološke karakteristike i hirurške modalitete

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ABSTRACT

Introduction: melanoma mortality rates are very high among cancer patients. It is life threatening disease which survival rate is correlated with many, mainly pathohistological factors, although some macroscopic forms of melanoma are associated with poorer prognosis. Aim: to evaluate the exiting correlation between melanoma thickness according to Breslow index and the degree of anatomical invasion according to Clark regarding positive sentinel biopsy and indication for radical lymphadenectomy, and the existence of distant and dermal metastases, according to pathohistological characteristics of the tumor. Materials and methods: the research included 213 melanoma patients treated at our Clinic using Microsoft Excel program and IBM statistics SPSS v 21 or 22. Results: the correlation between the degree of anatomical invasion with positive sentinel node was evaluated by χ^2 -test = 26.9, with statistically significant difference ($P < 0.00001$). Statistical significance was confirmed between Breslow index and results of the sentinel node biopsy (χ^2 -test = 82.5, $P < 0.00001$). The degree of the melanoma anatomical invasion and indication for radical lymphadenectomy after positive sentinel node biopsy had statistically significant correlation according to Clark (χ^2 -test=26.9, $P < 0.00001$). The relation between invasiveness according to Clark classification and the occurrence of metastases also showed statistical significance (χ^2 -test=9.4, $p = 0.0022$). Statistical significance was confirmed (χ^2 -test = 47.1; $p = < 0.00001$) by group integration (Clark I-III, Clark IV-V). The correlation between the incidence of cutaneous and distant metastases referring to Breslow index is presented by group classification of the anatomical invasion of melanoma (χ^2 -test=19.6, $P < 0.00001$). The results are presented in tables and figures. Conclusion: the existence of clear correlation was confirmed among the pathohistological characteristics of melanoma, resulting positive sentinel node biopsy and consequent indication for radical lymphadenectomy, as well as the existence of distant and dermal metastasis. The algorithm of melanoma treatment facilitates the surgical and oncological treatment in everyday clinical practice.

Key words: melanoma, pathohistological characteristics, treatment, algorithm

SAŽETAK

Uvod: mortalitet pacijenta oboljelih od melanoma je načelno visok među onkološkim pacijentima. To je životno ugrožavajuće oboljenje, čiji je procenat preživljavanja koreliran sa mnogobrojnim, uglavnom patohistološkim faktorima, iako su neke makroskopske forme melanoma povezane sa lošijom prognozom. Debljina melanoma prema Breslow indeksu je važan prediktor petogodišnjeg preživljavanja. Cilj: evaluacija postojanja korelacije između debljine melanoma prema Breslow indeksu i stepena anatomske invazije po Clark klasifikaciji, u odnosu na pozitivne rezultate sentinel biopsije sa indikacijom za limfadenektomiju, kao i postojanja udaljenih i kutanih metastaza u odnosu na patohistološke karakteristike tumora. Materijali i metode: evaluiran je postojeći protokol tretmana 213 pacijenata sa dijagnosticiranim melanomom, tretiranih na našoj Klinici korištenjem Microsoft Excel program i IBM statistics SPSS v 21 ili 22. Rezultati: korelacija između stepena anatomske invazije i pozitivnog sentinel nodusa je evaluirana putem χ^2 -testa=26.9, sa statistički signifikantno razlikom ($P < 0.00001$). Statistička signifikantnost je potvrđena između Breslow indeksa i rezultata sentinel biopsije (χ^2 -test=82.5, $P < 0.00001$). Potvrđena je statistička korelacija između stepena anatomske invazije prema Clark klasifikaciji u odnosu na postavljenu indikaciju za radikalnu limfadenektomiju nakon pozitivnih rezultata sentinel biopsije (χ^2 -test=26.9, $P < 0.00001$). Korelacija između Breslow indeksa i indicirane radikalne limfadenektomije je takođe evaluirana putem χ^2 -testa=82.5, sa statistički signifikantnom razlikom ($P < 0.00001$). Odnos između invazivnosti prema Clark klasifikaciji i pojave metastaza (Tis, T1, T2, T3 i T4) takođe pokazuje statističku signifikantnost (χ^2 -testa = 9.4, $P = 0.0022$). Statistička signifikantnost je potvrđena (χ^2 -test = 47.1; $P = < 0.00001$) integracijom grupa (Clark I-III, Clark IV-V). Korelacija između pojave kutanih i udaljenih metastaza u odnosu na Breslow indeks prezentirana je putem integracije stepena anatomske invazije melanoma (χ^2 -test=19.6, $P < 0.00001$). Rezultati su prezentirani tabelarno i putem dijagrama. Zaključak: potvrđeno je postojanje jasne korelacije između patohistoloških karakteristika tumora sa rezultatima sentinel biopsije, posljedičnom indikacijom za radikalnu limfadenektomiju i vjerovatnosti udaljenih i kutanih metastaza. Postojanje algoritma tretmana melanoma znatno olakšava hirurški i onkološki tretman u svakodnevnoj praksi kao kliničke smjernice.

Ključne riječi: melanoma, patohistološke karakteristike, algoritam, tretman

INTRODUCTION

Melanoma is malignant tumor with melanocytes cells which originate from the neural crest. The incidence of melanoma has been increasing. It can grow anywhere on the skin (1), but more common on the trunk in men and lower limb in women. Also, it can be formed in other parts such as the eyes (retinal pigment epithelium, mouth and other mucosal organs). Diagnosis can be confirmed by pathohistological biopsy (2).

There are major types of melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma and acral lentiginous melanoma. Staging the tumor helps us to develop a prognosis and a treatment plan for patients (3). The classification system was primarily Breslow classification which mainly depends on measuring the depth of the invading melanoma, and Clark classification, which is a staging system which describes the depth of anatomical invasion of melanoma as it grows in the skin with five grades. Grade I melanoma is confined to the epidermis (melanoma in situ), Grade II has invaded the papillary dermis, Grade III is invasion of the papillary dermis and with contact with the reticular dermis, Grade IV is invasion of the papillary reticular dermis and Grade V presents the invasion of subdermal tissue (4).

Nowadays, the most prognostic system developed by the American Joint Committee on Cancer (AJCC), relies upon assessments of the primary tumor (T) and the presence of ulceration, regional lymph nodes (N), and distant metastatic sites (M) (5).

Surgery remains the treatment modality for melanoma. Principles in surgical treatments start with elliptical excision, with a small amount of normal skin, at the 2-3 mm edges in healthy tissue with safe margins and possibility of subsequent re-excision and direct reparation of defects. Careful handling of the sample with intraoperative rough manipulation creates the possibility of dissipation of cells.

The incidence of primary cutaneous melanoma continues to increase each year. Melanoma accounts for the majority of skin cancer-related deaths, but treatment is usually curative following early detection of disease. In the American Academy of Dermatology Clinical Practice Guideline, updated treatment recommendations are provided for patients with primary cutaneous melanoma (American Joint Committee on Cancer stages 0-II C and pathologic stage III by virtue of a positive sentinel lymph node biopsy). Biopsy techniques for a lesion that is clinically suggestive of melanoma are reviewed, as are recommendations for the histopathologic interpretation of cutaneous melanoma (6). Excisional biopsy remains the gold standard for diagnosis, although there is no evidence that use of other biopsy types alters survival or recurrence. Wide local excisions should be carried out with margins as recommended by National Comprehensive Cancer Network guidelines according to lesion Breslow depth, with sentinel lymph node biopsy being offered to all medically suitable candidates with intermediate thickness melanomas (1.0 to 4.0 mm), and with sentinel lymph node biopsy being considered for high-risk lesions (ulceration and/or high mitotic figures) with melanomas of 0.75 to 1.0 mm (7).

AIM

This study was based on findings and it evaluated the connection between melanoma thickness concerning Breslow index and the degree of anatomical invasion according to Clark classification regarding positive sentinel biopsy and indication for radical lymphadenectomy with presence of distant and dermal metastases.

MATERIALS AND METHODS

The surgical protocol of melanoma treatment was evaluated in respect of pathohistological results of sentinel biopsies and radical lymphadenectomies in 213 patients with pathohistologically verified melanoma treated at Clinic of Reconstructive and Plastic Surgery of the Clinical Center University of Sarajevo in the period from 2015 to 2018. There was a variable degree of melanoma invasion and different localization. The analysis was carried out in Microsoft Excel program and IBM statistics SPSS v21 or 22. Significance of data has been determined by Chi Squared method and Fishers' test.

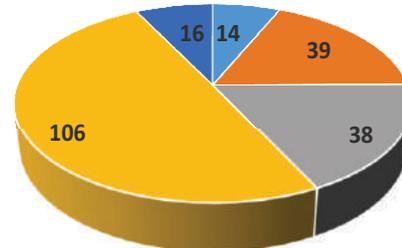
Study Inclusion criteria: cases with primary melanoma subjected to primary excision, sentinel biopsies and, in the case of positive sentinel node biopsy, to radical lymphadenectomy at the Clinic of Reconstructive and Plastic Surgery of the Clinical Center University of Sarajevo. Study exclusion criteria: patients subjected to sentinel biopsies and radical lymphadenectomy in other hospital centers.

RESULTS

There was a variable degree of melanoma localization among the patients.

Chest wall was the most common site (91 patients, 43%), followed by abdomen and lumbal area (28 patients, 13%), shoulder, arms, legs and feet (26 patients, 12%), followed by localization in the other areas in the smaller percentages, such as thigh (19.9%) head and neck (17 patients, 8%) and hands forearm (6 patients, 3%).

Results also show variable degree of melanoma invasion among patients according to Clark Classification (Figure 1). Clark IV was the most common percentage (106 patients; 50%) followed by Clark II and III (39 patients; 18% and 38 patients; 18%), followed by Clark V (16 patients; 7%) and Clark I (31 patients; 14.7%).



- CLARK I (melanoma in situ)
- CLARK II (invasion of papillary dermis)
- CLARK III (invasion of papillary-reticular dermal junction)
- CLARK IV (invasion of reticular dermis)
- CLARK V (invasion of subcutaneous tissue)

Figure 1 Degree of anatomical invasion according to Clark.

According to AJCC classification (Figure 2), in our clinical sample we evaluated percentage representation of the primary tumor thickness by Breslow index. In the majority of cases the tumor thickness was T1 (80 patients; 37.5%), followed by T4 (78 patients; 36.6%), T3 (10 patient; 4.69%) and Tis- tumor in situ (8 patients; 3.75%).

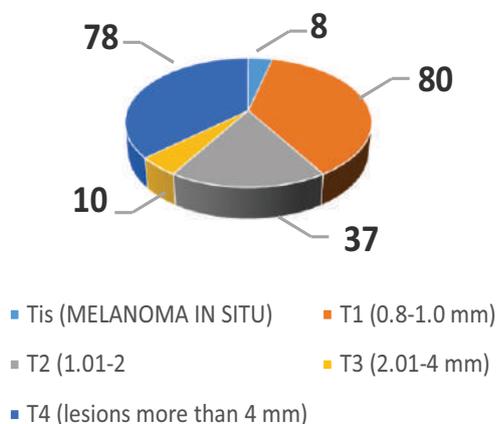


Figure 2 Primary tumor thickness according to AJCC, Breslow index.

During the follow up period, sentinel biopsy was indicated in 159 cases (74.6%). The results show positive sentinel node in 79 patients (37%) with indication for radical lymphadenectomy, according to algorithm of melanoma treatment. In 66 cases pathohistology confirmed positive lymphogenous dissemination after radical lymphadenectomy. The systemic dissemination and dermal metastases was evaluated in 16 cases.

There was statistically significant correlation (Table 1) between positive sentinel node and the degree of anatomical invasion according to Clark classification (Chi-squared test 26.9; $p < 0.00001$).

Table 1 Correlation between positive sentinel node and degree of anatomical invasion of the tumor according to Clark classification.

Sentinel Node	Clark I,II	Clark III	Clark IV,V
Positive	7	11	65
Negative	46	27	57
Total	53	38	122

The correlation between positive sentinel node and thickness of the primary tumor is presented in Table 2, with statistical significance (Chi-squared test= 82.5; $p < 0.00001$).

Table 2 Correlation between positive sentinel node and melanoma thickness according to Breslow.

Sentinel Node	Tis	T1	T2	T3	T4
Positive	1	5	13	8	56
Negative	55	27	24	2	22
Total	56	32	37	10	78

The degree of the anatomical invasion (Table 3) and the indication for radical lymphadenectomy after positive sentinel node confirmed statistically significant correlation (Chi-squared test = 26.9; $p < 0.00001$). The higher degree of melanoma invasiveness was

associated with greater number of the radical lymphadenectomies-regrouped stages.

Table 3 Correlation between radical lymphadenectomy patients and the degree of the anatomical invasion according to Clark Classification.

Radical lymphadenectomy	Clark I,II	Clark III	Clark IV,V
Yes	7	11	65
No	46	27	57
Total	53	38	122

The statistically significant correlation between radical lymphadenectomy and Breslow index is presented in Table 4 (Chi-squared test = 82.5; $p < 0.00001$).

Table 4 Correlation between the indication for radical lymphadenectomy and Breslow index.

Radical lymphadenectomy	Tis	T1 (≤ 1 mm)	T2 (1.01-2mm)	T3 (2.01-4.0 mm)	T4 (> 4 mm)
Yes	1	5	13	8	28
No	55	27	24	2	22
Total	56	32	37	10	78

According to our clinical results, there was significant correlation between the onset of distant and dermal metastases (Table 5) and the degree of the anatomical invasion (Chi-squared test = 9.4; $p = 0.0022$). Statistical significance was confirmed by integration of Clark I-III, Clark IV and Clark V groups (Chi-squared test = 47.1; $p < 0.00001$).

Table 5 Correlation between onset of metastases and degree of the anatomical invasion according to Clark classification.

Distant and dermal metastases	Clark I,II,III	Clark IV,V
Positive	1	15
Negative	90	107
Total	91	122

We presented (Table 6) statistically significant correlation between distant and dermal metastases and Breslow index evaluated by stage integration (Chi-square test= 19.6; $p < 0.00001$).

Table 6 The correlation between distant and dermal metastases and Breslow index.

Distant and dermal metastases	Tis, T1, T2	T3, T4
Positive	1	15
Negative	124	73
Total	125	88

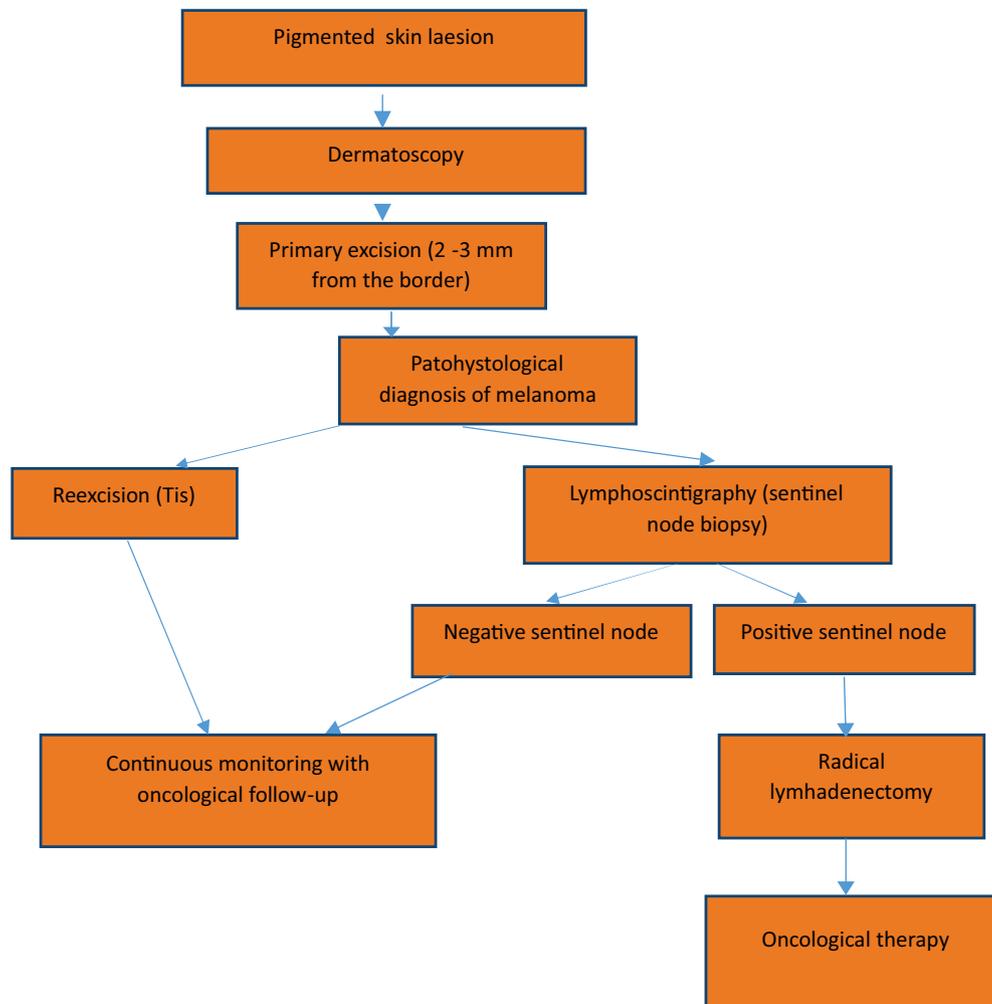


Figure 3 Algorithm of melanoma treatment - Clinic of Reconstructive and Plastic Surgery, Clinical Center University of Sarajevo.

DISCUSSION

The survival rate of melanoma patients depends on histological invasiveness according to the AJCC classification. There is significant relationship between positive sentinel node and Clark classification, although it represents the degree of anatomical invasion and depends on skin thickness which is variable with respect to age and localization, so it is not reliable for overall survival rate.

The clinical status of melanoma, as one of the most malignant tumors in human pathology, is difficult to predict. The importance of early diagnosis through continuous dermatological examinations and excisions of all clinically and dermatoscopically suspected lesions is a significant factor in the system of early detection and overall survival.

The Breslow index is correlated directly with positive sentinel biopsy results. According to the recommendations of the AJCC, sentinel biopsy is not indicated for lesions below 0.8 mm thickness. According to the experience of our clinic, such cases are presented at the oncology consulate, and in thin melanomas cases, reexcision with further dermatological monitoring is recommended.

Routine SLN biopsy is not recommended for patients with thin melanomas that are T1a (non-ulcerated lesions < 0.8 mm in Breslow thickness). SLN biopsy may be considered for thin melanomas that are T1b (0.8 to 1.0 mm Breslow thickness or <0.8 mm Breslow thickness with ulceration) after a thorough discussion with the patient of the

potential benefits and risk of harms associated with the procedure. SLN biopsy is recommended for patients with intermediate-thickness melanomas (T2 or T3; Breslow thickness of >1.0 to 4.0 mm). SLN biopsy may be recommended for patients with thick melanomas (T4; > 4.0 mm in Breslow thickness), after a discussion of the potential benefits and risks of harm. In the case of a positive SLN biopsy, CLND or careful observation are options for patients with low-risk micrometastatic disease, with due consideration of clinicopathological factors (8).

According to the recommendations of the oncology consult at our clinic, any positive sentinel node is an indication for radical lymph node dissection. Given that sentinel biopsy is a diagnostic rather than a therapeutic procedure, radical lymph node dissection is indicated in patients with a positive sentinel nodus but without clinically and diagnostically confirmed distant metastases. Such a treatment protocol is in line with standard procedures of this type in other centers.

Systematic review of current evidence supports a selective, individualized approach to CLND for SLN-positive melanoma. For low-risk, low-volume micrometastatic disease, SLN biopsy may be both diagnostic and therapeutic, and close clinical follow-up with imaging or CLND are reasonable options for appropriately selected patients. For higher-risk patients, omission of CLND requires careful consideration of risks versus benefits, relevant histopathology, and individualized patient discussion. This should address patient comorbidities and life expectancy, the predicted likelihood of

additional positive nodes, availability of imaging surveillance, likelihood of adherence to imaging and clinical follow-up, consequences of regional recurrence, and the prognostic value of complete nodal staging and its impact on adjuvant therapy recommendations or clinical trial participation (9).

Justification of radical dissection of regional lymph nodes could also be questioned in patients with histopathologically confirmed metastasis to sentinel lymph node. According to the results presented above, there is a certain percentage of patients with confirmed metastasis to regional lymph nodes even after negative sentinel biopsy results, which confirms the fact that sentinel biopsy is a diagnostic rather than a therapeutic procedure.

Recently the 8th version of the American Joint Committee on Cancer (AJCC) classification has been introduced, and has attempted to define a more accurate and precise definition of prognosis in line with the major progresses in understanding the biology and pathogenesis of melanoma. This new staging system introduces major stages in the stage III staging system. Indeed, surgical practice is changing in stage III patients, since, according to recent evidence, there is no survival benefit in radical lymph node dissection following a positive sentinel lymph node dissection. Therefore, some patients currently staged IIIB-C after dissection could be downgraded to III A (as in the case of patients with metastatic non-sentinel lymph nodes) since many completion lymph node dissections will no longer be performed (10).

Creating a unique treatment protocol for melanoma, including the stages of treatment of a pigmented lesion, which is pathohistologically diagnosed as melanoma, is a useful tool in daily practice and in anticipation.

Each patient diagnosed with melanoma is presented at the Oncology Board, where, in collaboration with oncologists, radiologists and plastic surgeons, the most optimal guidelines for further treatment are established.

CONCLUSION

Determining the melanoma treatment algorithm is an important guideline from clinician's point of view, although the clinical behavior of this type of malignant tumor cannot be predicted. It has been observed that in a certain percentage of deeply invasive melanoma, after sentinel biopsies and radical lymphadenectomy, reoccurrence of distant metastases and relapse of the disease were not recorded after years of follow-up, compared to low-invasive melanomas which resulted in dissemination and recurrence, which was not expected in relation to the pathohistological characteristics and sentinel diagnostic results. The application of the algorithm determines sentinel biopsies in all pathohistologically confirmed melanomas, regardless of the Breslow index, without clinical and radiological confirmation of metastasis to regional lymph nodes. In the case of diagnostic confirmation of enlarged regional lymph nodes, sentinel biopsy is contraindicated. It is important to emphasize that sentinel biopsy is a diagnostic, not therapeutic procedure, important for melanoma staging.

REFERENCES

1. Bandarchi B, Ma L, Navab R, Seth A, Rasty G. From melanocyte to metastatic malignant melanoma. *Dermatol Res Pract.* 2010;2010:583748.
2. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology.* 2011;118(9):1881-5.
3. Kozovska Z, Gabrisova V, Kucerova L. Malignant melanoma: diagnosis, treatment and cancer stem cells. *Neoplasma.* 2016;63(4):510-7.
4. Dickson PV, Gershenwald JE. Staging and Prognosis of Cutaneous Melanoma. *Surg Oncol Clin N Am.* 2011;20(1):1-17.
5. Amin MB, Edge SB, Greene FL, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin.* 2017;67(2):93-9.
6. Liu Y, Sheikh MS. Melanoma: Molecular Pathogenesis and Therapeutic Management. *Mol Cell Pharmacol.* 2014;6(3):228.
7. Pavri SN, Clune J, Ariyan S, Narayan D. Malignant Melanoma: Beyond the Basics. *Plast Reconstr Surg.* 2016;138(2):330e-40e.
8. Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Ariyan C, et al. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2018;36(4):399-413.
9. Tchernev G, Chokoeva A, Popova LV. Primary Solitary Melanoma of the Lymphatic Nodes Or a Single Metastasis of Unknown Melanoma: Do We Need a New Staging System?. *Open Access Maced J Med Sci.* 2017;5(7):970-973.
10. Romano E, Scordo M, Dusza SW, Coit DG, Chapman PB. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2010;28(18):3042-3047.

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„Crash-clamping” liver resection - our experience

„Crash-clamping” resekcija jetre - naše iskustvo

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ABSTRACT

Introduction: liver resection is an operative procedure that carries a significant risk of intraoperative bleeding which is correlated with postoperative morbidity, mortality and long-term survival. Hepatic pedicle clamping performed with this technique increases the potential risk of liver disease. Great efforts are being made worldwide to improve the outcome of treatment in patients undergoing liver resection, and we want to present our observations in the use of the CC-LR method in this paper. **Aim:** to present our results in patients treated with classical methods of liver resection (CC-LR), with special emphasis on the clinical significance of intraoperative blood loss on the course and outcome of treatment in these patients. **Materials and methods:** this clinical study was conducted on patients undergoing classical hepatic resection (CC-LR). The study included thirty patients operated by the same team of surgeons with practically the same experience. **Results:** by Pearson correlation test between the examined variables in the sample, we found that there was a positive significant correlation between blood loss and length of hospitalization ($r = ,392$ $p = 0,032$). It was also found that there was a negative significant correlation between blood loss and postoperative hemoglobin values. **Conclusion:** the classic CC-LR technique remains a reliable method of liver resection, especially for pathological changes of larger size, and the effectiveness of this technique depends most on the experience of the surgeon. We believe that liver resection techniques should be combined to maximize their potential.

Key words: liver, surgery, hemorrhage, complications, hospitalization, prognosis

INTRODUCTION

Liver resection is an operative procedure that carries a significant risk of intraoperative bleeding, which is correlated with postoperative morbidity, mortality and long-term survival. The advancement of surgical and anesthesiology techniques as well as the development of new technical aids result in minimal blood loss. Surgical hemorrhage due to the liver resection can be divided into intraoperative and postoperative. Intraoperative blood loss, or more precisely inadequate hemostasis during resection is a major complication in liver surgery. This can be indicated by the large amounts of blood given to patients during surgery (1). Bleeding is the root cause of intraoperative mortality, most commonly occurring during hepatic vein preparation. Profuse bleeding can also occur during transection of the liver parenchyma. Postoperative bleeding is the result of inadequate

SAŽETAK

Uvod: resekcija jetre predstavlja operativnu proceduru koja nosi značajan rizik od intraoperativnog krvarenja, a koje je u korelaciji sa postoperativnim morbiditetom, mortalitetom i dugoročnim preživljavanjem. Klemovanje hepatičkog pedikla koje se radi kod ove tehnike povećava potencijalni rizik disfunkcije jetre zbog ishemičko-perfuzijskih povreda, posebno kod pacijenata koji imaju izraženu hroničnu bolest jetre (1,2). Širom svijeta ulažu se veliki naponi kako bi se poboljšao ishod liječenja kod pacijenata podvrgnutih resekciji jetre, a u radu želimo prikazati naša zapažanja kod primjene CC-LR metode. **Cilj:** da prikazemo naša zapažanja kod pacijenata operisanih klasičnom metodom resekcije jetre (CC-LR), uz poseban osvrt na klinički značaj intraoperativnog gubitka krvi na tok i ishod liječenja kod ovih pacijenata. **Materijal i metode:** ova klinička studija provedena je na pacijentima koji su podvrgnuti klasičnom resekcijom zahvatu jetre (CC-LR). Ispitivanjem je obuhvaćeno trideset pacijenata koje je operisala ista ekipa hirurga sa praktično istim iskustvom. **Rezultati:** Pearsonovim korelacionim testom između ispitivanih varijabli u uzorku utvrdili smo da postoji pozitivna signifikantna korelacija između gubitka krvi i dužine hospitalizacije ($r = ,392$ $p = 0,032$). Također utvrđeno je da postoji i negativna signifikantna korelacija između gubitka krvi i postoperativnih vrijednosti hemoglobina. **Zaključak:** klasična tehnika CC-LR ostaje pozudana metoda resekcije jetre osobito kod promjena većih dimenzija, a efektivnost ove tehnike najviše zavisi od iskustva hirurga. Smatramo da se tehnike resekcije jetre trebaju kombinovati kako bi se što više iskoristile njihove mogućnosti.

Ključne riječi: jetra, hirurgija, krvarenje, komplikacije, hospitalizacija, prognoza

hemostasis, falling ligature-clips, or inadequate ligation of the blood vessel (2).

The surgeon is often in a dilemma when performing complex operations on the liver; whether to use the classic method, "Crash-clamping" (CC-LR) with clamping of the hepatic pedicle (selective or total occlusion) or to use new technical aids such as RF resector (1, 2). Hepatic pedicle clamping increases the potential risk of hepatic dysfunction caused by ischemic-perfusion injuries, especially in patients with severe chronic liver disease. Several techniques have been developed that could potentially reduce blood loss during hepatic parenchyma transection with or without vascular occlusion (2-5).

Classical liver resection (CC-LR) is used in various medical centers. It is done under general anesthesia, and collaboration with the anesthesiologist is of great importance. During the surgery, the anesthesiologist must maintain CVP values in the interval of 2 to 5. Upon opening the abdomen, the liver is mobilized and inflow and

outflow vascular control are prepared. First, a change in the liver is determined by ultrasound, and then a hepatic pedicle is clamped or a selective occlusion of the blood vessels is made. Hepatic veins are also clamped selectively, thereby outflow vascular control. Resection of the hepatic parenchyma begins after preconditioning lasting 15 min. The liver is resected gradually over a period of 15-20 min with 5 min breaks and the procedure is repeated until complete resection. In cirrhotic liver, ischemia periods are shorter and last up to 10 min with 5 min pauses. In this way, the length of liver resection in a healthy person can be increased up to a total of 120 min, and in the cirrhotic liver up to a total of 60 min, without the risk of ischemic-perfusion injury of the liver parenchyma (1,2,5). Resection of the hepatic parenchyma is done gradually by the "Crash-clamping" technique (CC-LR) with fine peanuts, by crushing the liver tissue with the instrument, and then all the biliovascular structures are ligated or clamped (1,3). Great efforts are being made worldwide to improve the outcome of treatment in patients undergoing liver resection, and we want to present our observations in the application of the CC-LR method (5).

AIM

The aim of the study was to present our findings in patients treated with classical methods of liver resection (CC-LR), with special emphasis on the clinical significance of intraoperative blood loss on the course and outcome of treatment in these patients.

MATERIALS AND METHODS

This clinical retrospective study was conducted at Clinic of General and Abdominal Surgery of the Clinical Center University of Sarajevo on patients undergoing classical resection of the liver (CC-LR), regardless of cause. The trial included thirty patients operated by the same team of surgeons with practically the same experience. Patients were monitored for postoperative complications, analyzed deviations of postoperative versus preoperative laboratory parameters taken the day before and after surgery, recorded intrahospital blood loss, and demographic data. In the analysis, we used data from case histories, anesthesia records, and surgery findings. The data were processed using the descriptive statistics method, and we used the Pearson test to prove the correlation between the variables. The most significant results are presented in the form of tables and charts.

RESULTS

The average age of the patients in the sample was 54.03 ± 16.48 years. We had 16 (53%) male patients and 14 (47%) female patients. The age structure of the patients is shown in Table 1.

Table 1 The age structure of the patients.

AGE GROUP	NUMBER	PERCENT
<20	0	0,00%
20-30	6	20,0%
31-40	0	0,0%
41-50	2	6,66%
51-60	12	40,0%
>60	10	33,34%
TOTAL	30	100%

Analysis of the causes of the disease in our study resulted in the highest number of colorectal adenocarcinoma metastases, 17 (28.33%). Slightly fewer related to primary liver tumor (HCC), 5 (8.33%) cases, and gallbladder cancer, 2 (3.33%) cases.

As for benign diseases, we had 2 (3.33%) cases of hemangiomas and Echinococcal cyst in 3 (5%) cases. Only 1 (1.66%) patient had metastases of other gastrointestinal tumors.

Hemoglobin

The preoperative value of Hb was $135 \pm 20, 98$. The postoperative value of Hb was $117, 23 \pm 19, 75$. Statistical analysis of preoperative and postoperative values of Hb showed that there was a statistically significant difference within the group T-test = 4,450 ($p < 0,0005$).

Hematocrit

The preoperative value of Hct was $39, 70 \pm 4, 84$, and the postoperative value was $34, 30 \pm 5, 08$. Statistical analysis of preoperative and postoperative Hct values revealed that there was a statistically significant difference within the group T-test = 4,97 ($p < 0,001$).

AST

The preoperative AST value was $26,23 \pm 19,71$. The postoperative AST value was $74, 20 \pm 149, 48$. Statistical analysis of preoperative and postoperative AST values showed that there was no statistically significant difference within the group. T-test = 0,748 ($p = 0,46$).

ALT

The preoperative value of ALT was $30, 57 \pm 20,135$. The postoperative ALT value was $108, 83 \pm 178, 64$. Statistical analysis of the preoperative and postoperative ALT values showed that there was a statistically significant difference within the group. T-test = 2,351 ($p = 0,026$).

Bilirubin

The preoperative value of total bilirubin was $13,96 \pm 14,04$. The postoperative bilirubin value was $23, 41 \pm 23, 22$. Statistical analysis of preoperative and postoperative bilirubin values showed that there was a statistically significant difference within the group. T-test = 2,26 ($p = 0,03$).

Blood loss

Blood loss ranges from 50-1200 ml with a mean value $M = 390$ ml \pm SD 284,48, as shown in Table 2.

Table 2 Description of blood loss in the study group.

Type of surgery	Number	Range	Min.	Max.	Sum	Mean	Std. Deviation
CC-LR	30	1150	50	1200	11700	390,00	284,484

The length of hospitalization ranges from 5-45 days with an average of $M = 16,8 \pm SD = 8,97$ days, as shown in Table 3.

Table 3 Lengths of hospitalization in the study group.

Type of surgery	N	Minimum	Maximum	Sum	Mean	Std. Deviation
CC-LR	30	5	45	504	16,80	8,969

Statistical analysis of postoperative complications showed that in the study group there were 7 (23, 3%) patients with complications, while 23 (76,7%) patients had no complications. The analysis data are presented in Figure 1.

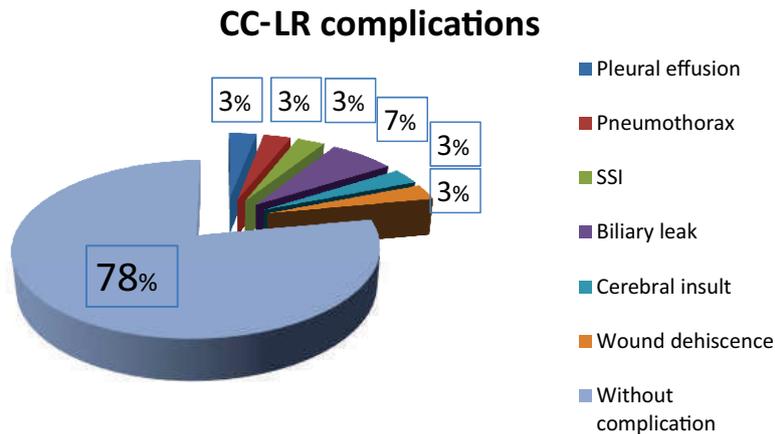


Figure 1 Complications reported in operated patients.

Relationship between variables

By Pearson's test of the correlation between the examined variables in the sample, we found that there was a positive correlation

between blood loss and length of hospitalization ($r = .392$, $p = 0.032$)*. A negative significant correlation between blood loss and postoperative hemoglobin values was also found. The correlation between the variables monitored is shown in Table 4.

Table 4 Correlation between the monitored variables.

Correlations		Post. Hb	Post. Hct	Post. AST	Post. ALT	Post. Bilirubin	Blood loss	Hospitalization	Complications	Ages
Post. Hb	Corelation Pearson	1	,705**	-,059	,024	-,025	-,376*	-,121	,549	-,253
	p		,000	,758	,898	,053	,041	,523	,202	,178
Post. Hct	Corelation Pearson	,705**	1	-,040	,022	,000	-,300	-,192	,684	-,228
	p	,000		,834	,909	,998	,107	,309	,090	,225
Post. AST	Corelation Pearson	-,059	-,040	1	,977**	,456*	,097	-,078	-,296	-,291
	p	,758	,834		,000	,011	,610	,681	,519	,118
Post. ALT	Corelation Pearson	,024	,022	,977**	1	,376*	,098	-,053	-,179	-,362*
	p	,898	,909	,000		,041	,607	,781	,700	,049
Post. Bilirubin	Corelation Pearson	-,025	,000	,456*	,376*	1	-,210	,092	-,150	-,228
	p	,897	,998	,011	,041		,266	,630	,748	,226
Blood loss	Corelation Pearson	-,376*	-,300	,097	,098	-,210	1	,392*	-,446	,212
	p	,041	,107	,610	,607	,266		,032	,315	,260
Hospitalization	Corelation Pearson	-,121	-,192	-,078	-,053	,092	,392*	1	,099	,127
	p	,523	,309	,681	,781	,630	,032		,833	,505
Complications	Corelation Pearson	,549	,684	-,296	-,179	-,150	-,446	,099	1	-,680
	p	,202	,090	,519	,700	,748	,315	,833		,093
Ages	Corelation Pearson	-,253	-,228	-,291	-,362*	-,228	,212	,127	-,680	1
	p	,178	,225	,118	,049	,226	,260	,505	,093	

**Correlation is significant at the 0,01 level * Correlation is significant at the 0,05 level

DISCUSSION

Liver resection is a crucial part of treating primary liver cancer, secondary tumor changes, and sometimes injuries, hemangiomas, and minor Echinococcal cysts (1). Liver resection is the treatment of choice for liver tumors. Despite standardized techniques and technological advances in liver resection, intraoperative bleeding ranges from 700 to 1200 mL, with a postoperative morbidity rate of 23% to 46% and a surgical death rate of 4% to 5% (6-11). The "blood loss" parameter plays a central role in the outcome of liver surgery, and various strategies that reduce it are key for improving resection results. The average blood loss after liver resection in our study (50-1200mL) is similar compared to the data available in the literature, where it ranges from 140-750ml.

Other authors have similar results, and among them, we single out the names of authors with a special contribution to hepatobiliary surgery: Karamarković (12) Kin (13), Yamamoto (14) Suzuki (15) Petrowski (16) and Tanaka (17). In our study, we obtained a significant positive correlation between length of hospitalization and intraoperative blood loss ($r = 0.713$ $p = 0.000$). Bleeding must be considered a major concern for a hepatic surgeon for a number of reasons. First, bleeding is certainly the major intraoperative surgical complication and cause of death and is historically one of the most important postoperative complications along with bile leakage and liver failure (10,11,18-20). High intraoperative blood loss is associated with a higher rate of postoperative complications, shorter long-term survival and longer hospitalization (21-23).

Furthermore, it is associated with a wide variety of liver blood vessel occlusion techniques, which is directly related to the increased risk of postoperative liver failure. A higher value of intraoperative blood loss is associated with a higher rate of perioperative transfusions, and host immunosuppression associated with transfusions is correlated with a higher rate of complications (especially infectious) and recurrence of malignancies in cancer patients (22-31). The mentioned reasons explain the positive and statistically significant correlation between intraoperative hemorrhage and length of hospitalization in patients in our study.

Torzilli showed that the rate of hemoglobin and hematocrit after liver resection showed a steady and significant decline until the third postoperative day, followed by an increase, so a negative correlation between intraoperative blood loss and postoperative hemoglobin values in our results could be considered as physiological (32). A retrospective review study on a smaller sample of patients operated by one surgeon addressed the factors that affect the length of hospitalization in patients undergoing liver resection. ASA score was the strongest predictors of length of hospitalization, while other parameters, including intraoperative blood loss, had no statistically significant effect on length of hospitalization. The length of hospitalization probably does not reflect the quality of the surgeon or institution, as this variable is multifactorially dependent and is more related to different populations as well as to the selection of high-risk patients in accordance with surgical experience (33).

The length of hospitalization in our study was 16.8 ± 8.96 . Similar results have been published by other authors so that according to their reports, the average hospitalization time ranges from 10.5 to 53.3 days. Thus, in a study of 16 patients, Petrowski (16) reported a hospitalization period of 10.5 days. Similar results were obtained by Adams (34). CC-LR is a fast, inexpensive technique, associated with a low morbidity rate, but it requires extensive experience to be able to effectively use it in liver resection, and especially in cirrhotic liver (33).

CONCLUSION

Intraoperative blood loss was and remains a variable that undeniably influences treatment outcome. In our study, we obtained a positive correlation between hemorrhage and length of hospitalization, which is consistent with the data in the available medical literature. Classical resection remains a reliable technique for liver resection, especially for large pathological changes, and the effectiveness of this technique depends most on the experience of the surgeon. We believe that in accordance with new technical advances, liver resection techniques should be combined to maximize their potential and ultimately provide the best outcome for the patient.

REFERENCES

- Šabanović J, Muhović S, Rovčanin A, Mušanović S, Bajramagić S, Kulović E. Radiofrequency Assisted Hepatic Parenchyma Resection Using Radiofrequency Generator (RF) Generator. *Acta Inform Med.* 2018;26(4):265.
- Sugo H, Mikami Y, Matsumoto F, Tsumura H, Watanabe Y, Kojima K, et al. Hepatic resection using the harmonic scalpel. *Surgery Today.* 2000;30(10):959-962.
- Bachelier P, Ayav A, Pai M, Weber J, Rosso E, Jaeck D, et al. Laparoscopic liver resection assisted with radiofrequency. *Am J Surg.* 2007;193(4):427-430.
- Elias D, Lasser P, Debaene B, Doity L, Billard V, Spencer A, et al. Intermittent vascular exclusion of the liver (without vena cava clamping) during major hepatectomy. *BJS.* 1995;82(11):1535-1539.
- Hutchins R, Bertucci M. Experience with TissueLink™ – Radiofrequency-Assisted Parenchymal Division. *Digestive Surgery.* 2007;24(4):318-321.
- Kirzin S, Portier G. Hémi-colectomie droite réglée pour cancer par laparotomie. *Journal de Chirurgie.* 2009;146(3):275-280.
- Foster J. Primary benign solid tumors of the liver. *Am J Surg.* 1977;133(4):536-541.
- Poon R, Fan S, Lo C, Liu C, Lam C, Yuen W, et al. Improving Perioperative Outcome Expands the Role of Hepatectomy in Management of Benign and Malignant Hepatobiliary Diseases. *Transactions of the Meeting of the American Surgical Association.* 2004;CXII(&NA):296-308.
- Fortner J, Maclean B, Kim D, Howland W, Turnbull A, Goldiner P, et al. The seventies evolution in liver surgery for cancer. *Cancer.* 1981;47(9):2162-2166.
- Fan S, Poon R, Yeung C, Lam C, Lo C, Yuen W, et al. Outcome after partial hepatectomy for hepatocellular cancer within the Milan criteria. *BJS.* 2011;98(9):1292-1300.
- Imamura H. One Thousand Fifty-Six Hepatectomies Without Mortality in 8 Years. *Archives of Surgery.* 2003;138(11):1198.
- Aleksandar RK, Kristina SD. Resekcije jetre u liječenju kolorektalnih metastaza. *Sanamed.* 2010;5:9-16.
- Kin T, Nakajima Y, Kanehiro H, Hisanaga M, Ohyama T, Nishio K, et al. Repeat Hepatectomy for Recurrent Colorectal Metastases. *World J Surg.* 1998;22(10):1087-1091.
- Yamamoto J, Kosuge T, Shimada K, Yamasaki S, Moriya Y, Sugihara K. Repeat liver resection for recurrent colorectal liver metastases. *Am J Surg.* 1999;178(4):275-281.
- Suzuki S, Sakaguchi T, Yokoi Y, Kurachi K, Okamoto K, Okumura T, et al. Impact of repeat hepatectomy on recurrent colorectal liver metastases. *Surgery.* 2001;129(4):421-428.
- Petrowsky H, Gonen M, Jarnagin W, Lorenz M, DeMatteo R, Heinrich S, et al. Second Liver Resections Are Safe and Effective Treatment for Recurrent Hepatic Metastases from Colorectal Cancer. *Annals of Surgery.* 2002;235(6):863-871.
- Tanaka K, Adam R, Shimada H, Azoulay D, Lévi F, Bismuth H. Role of neoadjuvant chemotherapy in the treatment of multiple colorectal metastases to the liver. *BJS.* 2003;90(8):963-969.
- Araujo R, Gonen M, Allen P, Blumgart L, DeMatteo R, Fong Y, et al. Comparison Between Perioperative and Postoperative Chemotherapy After Potentially Curative Hepatic Resection for Metastatic Colorectal Cancer. *Ann Surg Oncol.* 2013;20(13):4312-4321.
- Cescon M. Outcome of Right Hepatectomies in Patients Older than 70 Years. *Archives of Surgery.* 2003;138(5):547.
- Heriot A, Reynolds J, Marks C, Karanja N. Hepatic resection for colorectal metastases - a national perspective. *Ann Roy Coll Surg Eng.* 2004;86(6):420-424.
- Correa-Gallego C, Gonen M, Fischer M, Grant F, Kemeny N, Arslan-Carlon V, et al. Perioperative complications influence recurrence and survival after resection of hepatic colorectal metastases. *Ann Surg Oncol.* 2013;20(8):2477-2484.

22. Opelz G, Terasaki P. Prolongation effect of blood transfusions on kidney graft survival. *Transplantation*. 1976;22(4):380-383.
23. Gascón P. Immunologic Abnormalities in Patients Receiving Multiple Blood Transfusions. *Ann Intern Med*. 1984;100(2):173.
24. Keown P, De Scamps B. Improved renal allograft survival after blood transfusion: a nonspecific, erythrocyte-mediated immunoregulatory process? *The Lancet*. 1979;313(8106):20-22.
25. Kwon A, Matsui Y, Kamiyama Y. Perioperative blood transfusion in hepatocellular carcinomas. *Cancer*. 2001;91(4):771-778.
26. Blumberg N, Heal J. Perioperative blood transfusion and colorectal cancer recurrence. *Transfusion*. 1994;34(5):450-452.
27. Peterman T. Transfusion-Associated Acquired Immunodeficiency Syndrome in the United States. *JAMA*. 1985;254(20):2913.
28. Arsura E. Transfusion-Associated-Graft-vs-Host Disease in a Presumed Immunocompetent Patient. *Arch Intern Med*. 1988;148(9):1941.
29. Shinozuka N, Koyama I, Arai T, Numajiri Y, Watanabe T, Nagashima N, et al. Autologous blood transfusion in patients with hepatocellular carcinoma undergoing hepatectomy. *Am J Surg*. 2000;179(1):42-45.
30. Triulzi D, Vanek K, Ryan D, Blumberg N. A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. *Transfusion*. 1992;32(6):517-524.
31. Wei A, Tung-Ping Poon R, Fan S, Wong J. Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. *BJO*. 2003;90(1):33-41.
32. Torzilli G, Makuuchi M, Midorikawa Y, Sano K, Inoue K, Takayama T, Kubota K. Liver Resection Without Total Vascular Exclusion: Hazardous or Beneficial? *Ann Surg*. 2001;233(2):167-175.
33. Lorenzo CSF, Limm WM, Lurie F, Wong LL. Factors affecting outcome in liver resection. *HPB*. 2005;7(3):226-230
34. Adam R, Bismuth H, Castaing D, Waechter F, Navarro F, Abascal A, et al. Repeat Hepatectomy for Colorectal Liver Metastases. *Ann Surg*. 1997;225(1):51-62.

Reprint requests and correspondence:

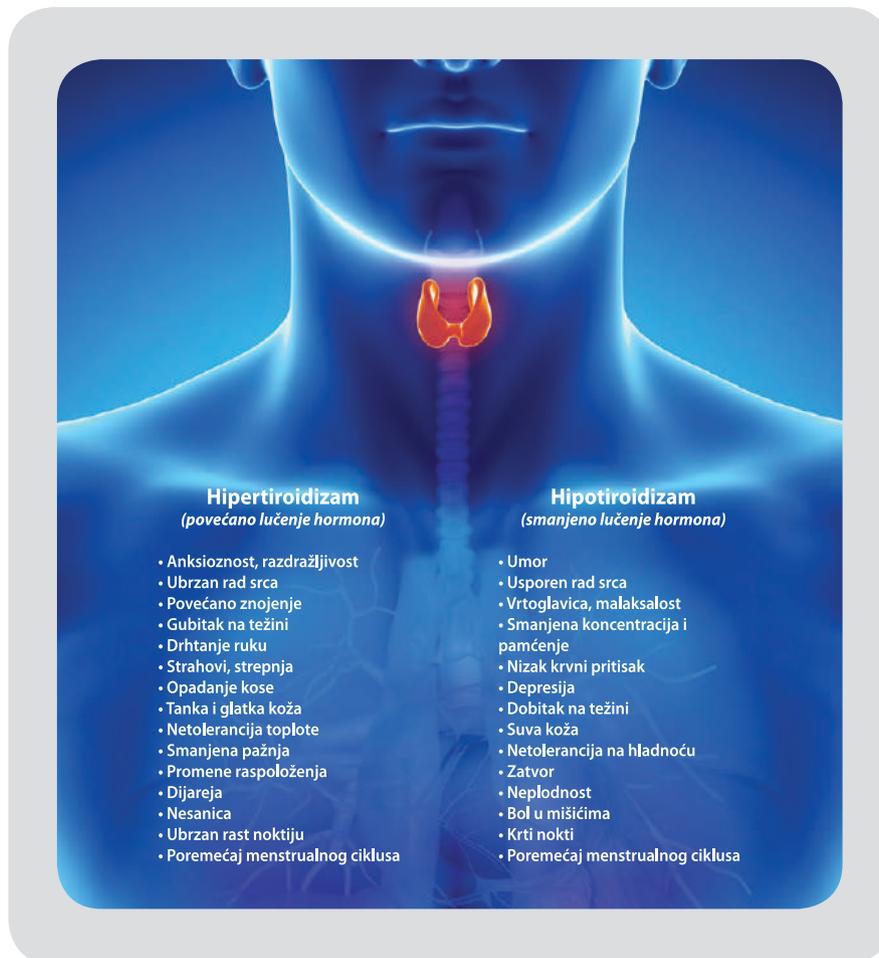
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Comparison of clinical outcome of modified Lichtenstein hernioplasty versus classical Lichtenstein hernioplasty

Komparacija ishoda liječenja ingvinalne hernije modificiranom u odnosu na klasičnu Lichtenstein tehniku

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ABSTRACT

Introduction: an inguinal hernia repair is one of the most common operations in surgery. At our institution, surgical treatment of inguinal hernia employs both classic and the modified Lichtenstein technique, which includes placement of additional retrofunicular sutures. Aim: to evaluate the differences between standard and modified Lichtenstein technique in inguinal hernia operation in relation to the occurrence and intensity of intraoperative, early and late postoperative complications and hernia recurrence. Materials and methods: we analyzed collected data of 120 patients older than 18 years of age, diagnosed with primary inguinal hernia, divided into two groups of 60 depending on the repair technique. Statistical analysis was made in the IBM SPSS Statistics v. 21.0 for Windows. Results: there were no intraoperative complications in either group during the study period. The evaluation of early and late postoperative complications and clinical outcomes of our patients treated with the modified Lichtenstein technique showed approximately the same results compared to the classical Lichtenstein technique. The incidence of hernia recurrence during the period covered by our study was lower than in other studies. Although the classic Lichtenstein technique has revolutionized the treatment of inguinal hernias, many clinical trials have been done to eventually improve treatment outcome. By reviewing the literature, we found similar results as in the same or almost the same studies: the use of a modified Lichtenstein technique with retrofunctional sutures has no significant advantage over the classical method. Despite the justified attitude that the use of additional retrofunctional sutures does not provide a significant benefit, still use them most often for reasons of their own safety and habit. Conclusion: there are no significant advantages or disadvantages in the application of this technique compared to the classical Lichtenstein technique.

Key words: general surgery, inguinal hernia, methods, attitude

INTRODUCTION

The prevalence of anterior abdominal wall hernia is 1.7% in all age groups and 4% for those aged over 45 years. 75% of abdominal wall hernias are inguinal hernias, with a risk of 27% in men and 3% in

SAŽETAK

Uvod: plastika ingvinalnog kanala je jedna od najčešćih operacija u hirurgiji. U našoj ustanovi za hirurško liječenje ingvinalne kile koriste se klasičnai modificirana Lichtensteina tehnika koja uključuje postavljanje retrofunkcionalnih šavova. Cilj: procijeniti razlike između standardne i modificirane Lichtenstein tehnike u operaciji ingvinalne kile u odnosu na pojavu i intenzitet intraoperativnih, ranih i kasnih postoperativnih komplikacija i recidiva kile. Materijali i metode: analizirali smo podatke 120 pacijenata starijih od 18 godina, kojima je dijagnosticirana primarna ingvinalna kila a koji su podjeljeni u dvije grupe od po 60 pacijenata u zavisnosti od primjenjene tehnike. Statistička analiza urađena je u programu IBM SPSS Statistics v. 21.0 za Windows. Rezultati: tokom razdoblja ispitivanja nije bilo intraoperativnih komplikacija niti u jednoj skupini. Procjena ranih i kasnih postoperativnih komplikacija i kliničkih ishoda naših pacijenata liječenih modificiranom Lichtensteinovom tehnikom pokazala je približno jednakerezultate u odnosu na klasičnu Lichtensteinovu tehniku. Učestalost recidiva kile tijekom razdoblja obuhvaćenog našom studijom bila je nešto niža nego u ostalim studijama. Iako je klasična Lichtenstein tehnika odnijelarevoluciju u liječenju ingvinalnih kila, rađena su mnoga klinička ispitivanja kako bi se poboljšao ishod liječenja. Pregledom literature pronašli smo rezultate slične našim u istim ili gotovo istim studijama. Nema značajne koristi u korištenju modificirane tehnike Lichtensteina s retrofunkcionalnim šavovima, u poređenju sa klasičnom metodom. Većina naših hirurga, uprkos važećem stavu da nema značajne koristi u apliciranju dodatnih retrofunkcionalnih šavova i dalje stavlja iste najčešće radi vlastite sigurnosti i navike. Zaključak: nema značajnih prednosti ili nedostataka u primjeni ove tehnike u odnosu na klasičnu Lichtensteinovu tehniku.

Ključne riječi: opšta hirurgija, ingvinalna kila, metode, stav

women (1). Inguinal hernia reconstruction is one of the most common operations in general surgery, with rates ranging from 10 per 100,000 population in the United Kingdom to 28 per 100,000 in the United States (2). Surgical repair is the treatment of choice, whether open or laparoscopic.

Open surgical treatment of inguinal hernias in adults consists of three elements:

- dissection of the hernia sac from the structures of the funiculus,
- reduction of the content of the hernia sac and reduction / resection of the hernia sac,
- reconstruction and / or strengthening of a fascial defect on the posterior wall of the inguinal canal.

Surgical techniques for the treatment of hernia are divided into tension and non-tension techniques in relation to the placement of the mesh during the repair of hernial defect. A meta-analysis of the *EU Hernia Trialists Collaborat* compared mesh technique with suture techniques from 58 trials involving a total of 11,174 patients. Relapse was less common in patients operated on by the mesh technique compared to the control group (3). A population-based study on the risk of hernia recurrence five years and more after the Lichtenstein operation included a total of 13 674 operated patients. The recurrence after mesh repair was four times lower compared to the non mesh technique (4). The classic Lichtenstein technique involves placement of the mesh while preserving the integrity of the transversal fascia, thereby achieving the necessary strengthening of the posterior wall of the inguinal canal. In our clinic, in addition to the classical technique, we also use a modified Lichtenstein's technique, which, besides the placement of the mesh, implies an earlier tense herniography of the defect of the posterior wall of the inguinal canal with several individual sutures. By reviewing the literature, we found that similar modified techniques can be used in inguinal hernia plastic because they have a low recurrence rate (<0.01%) and other postoperative complications such as urinary retention, painful scarring, hematoma and testicular atrophy (5). The incidence of intraoperative, early and late postoperative complications of the modified technique compared to the classical Lichtenstein should be examined.

AIM

The aim of this study was to evaluate and compare the outcome, intraoperative, early and late postoperative complications and relapses in standard and modified Lichtenstein technique, and then compare the results with those in the available medical literature.

MATERIALS AND METHODS

In this retrospective-prospective study performed at Clinic of General and Abdominal Surgery of the Clinical Center University of Sarajevo (CCUS), we evaluated patients surgically treated for primary inguinal hernia in the 2015 and 2016 period. The study was designed as a comparative examination of intra- and postoperative complications after surgical treatment of primary inguinal hernias by two techniques: classical and modified Lichtenstein technique. The study included 120 patients of both sexes, over the age of 18 years, who were diagnosed with primary inguinal hernia and who underwent hernioplasty. According to the type of performed operative technique, patients are divided into two groups:

- The first group of subjects (Lichtenstein group, n = 60) consists of patients operated by a classical Lichtenstein technique.
- The second group of subjects (Modified Lichtenstein, n = 60) consists of patients operated by a modified Lichtenstein technique (modification by retrofunctional suture sutures).

In all patients undergoing hernioplasty, intraoperative and early postoperative complications (postoperative pain, wound infection, seroma, wound hematoma, and scrotum swelling) were monitored and recorded within the first seven postoperative days, after the first month, and late postoperative complications (persistent postoperative

pain, recurrence) after the first 6 months after surgery. Patients included in the study were admitted to the Clinic in elective admission, with no data of previous lower abdominal surgery. Patients with incarcerated hernia, patients with proven malignancy, patients on immunosuppressive therapy, or those with proven systemic collagen disease were not included in the study. Statistical analysis was done in IBM SPSS Statistics v. 21.0 for Windows. The results are presented in the form of tables and graphs, using classical methods of descriptive statistic (measures of central tendency and dispersion), depending on the nature of the data and the scale of measurement. The test of the normality of the distribution of continuous numerical variables was performed by histogram inspection and formal testing using the Kolmogorov-Smirnov test. Student T test and Hi-square test / Fisher exact test were used for statistical analysis. The statistical significance threshold was set at the conventional level ($p < 0.05$).

RESULTS

In the Lichtenstein group, 21 patients (35%) were older than 60 years, and only one patient was younger than 20 years (1.7%). In the Modified Lichtenstein group, the majority of patients, 16 (26.7%), were also over 60 years old, while 6 (10%) were in the interval of 21-30 years. The age structure of the patients included in the study is shown in Figure 1.

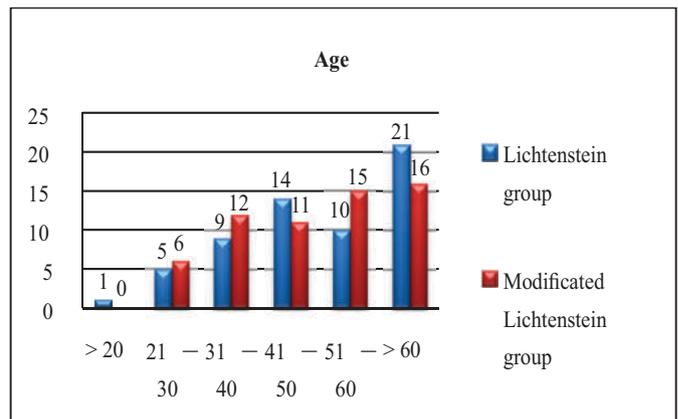


Figure 1 Age of patients.

There was no statistically significant difference between the number of patients who reported pain within the first seven postoperative days ($p = 0.767$), as shown in Table 1.

Table 1 Presence of pain in the first 7 postoperative days.

Postoperative day	Presence of pain in the area of the operative wound			
	Lichtenstein group		Modified Lichtenstein group	
	Number of patients	%	Number of patients	%
1.	60	100	60	100
2.	60	100	60	100
3.	51	85	53	88,3
4.	33	55	40	66,6
5.	15	25	16	26,6
7.	3	5	5	8,3

In the first to six months, the incidence of postoperative pain as a late complication is shown in Table 2. In the Lichtenstein group, after

one month, there were 21 patients (35%) with postoperative pain. There were 16 (27%) such patients in the Modified Lichtenstein group. The analysis showed that there was no statistically significant difference between the study groups regarding the incidence of postoperative pain after one month of surgery ($p = 0.482$). After six months, postoperative pain was present in 12 patients (20%) in the Lichtenstein group, and 10 (16.7%) in the Modified Lichtenstein group. The analysis showed that there was no statistically significant difference between the onset of postoperative pain even after six months of surgery ($p = 0.967$), as shown in Table 2.

Table 2 Ratio of postoperative pain at follow-up period (neuralgia).

Time (months)	Lichtenstein group (n=60)		Modified Lichtenstein group (n=60)	
	Postoperative pain			
	YES	NO	YES	NO
	Number of patients	Number of patients	Number of patients	Number of patients
1. month	21	39	16	44
6. month	12	48	10	50

In the Lichtenstein group, wound infection occurred in 3 patients (5%) and in the Modified Lichtenstein group in 4 patients (6.7%). Statistical analysis of the incidence of wound infections in the early postoperative period shown that there was no statistically significant difference in the incidence of postoperative wound infections between the two observed groups ($p = 0.810$), as shown in Table 3.

Table 3 Occurrence of wound infections in the early postoperative period.

	Lichtenstein group (n=60)		Modified Lichtenstein group (n=60)	
	Without wound infection	With wound infection	Without wound infection	With wound infection
	Number of patients.	Number of patients	Number of patients	Number of patients.
First 7 days	57	95	3	5
			56	93,3
			4	6,7

In the Lichtenstein group, 3 patients (5%) showed postoperative seroma. The Modified Lichtenstein group had 5 patients (8.3%) who experienced this complication. Statistical analysis showed that there was no statistically significant difference in the incidence of this postoperative complication in these two groups of patients ($p = 0.767$), as shown in Table 4.

Table 4 Occurrence of seroma in the early postoperative period.

Patients:	Lichtenstein group (n=60)		Modified Lichtenstein group (n=60)	
	Number of patients	%	Number of patients	%
With seroma	3	5	5	8.3
Without seroma	57	95	55	91.7
$p=0.767$				

In the Lichtenstein group, hematoma occurred in 4 patients (6.7%). In the Modified Lichtenstein hematoma group, it occurred in 7 patients (11.7%). Statistical analysis showed that there was no statistically significant difference in the incidence of this postoperative complication in patients from the two study groups ($p = 0.601$), as shown in Table 5.

Table 5 Frequency of hematoma occurrence.

Patients	Lichtenstein group (n=60)		Modified Lichtenstein group (n=60)	
	Number of patients	%	Number of patients	%
With hematoma	4	6,7	7	11,7
Without hematoma	56	93,3	53	88,3
$p=0.601$				

In the Lichtenstein group, scrotum swelling occurred in 4 patients (6.7%). In the Modified Lichtenstein group, scrotum swelling occurred in 6 patients (10%). The analysis revealed that there was no statistically significant difference in the occurrence of this postoperative complication between the observed patient groups ($p = 0.351$), as shown in Table 6.

Table 6 Report of scrotum swelling.

Patients	Lichtenstein group (n=60)		Modified Lichtenstein group (n=60)	
	Number of patients	%	Number of patients	%
With swelling	4	6,7	6	10
Without swelling	56	93,3	54	90
$p=0.351$				

Hernia recurrence was not verified in any operated patient in both groups after a follow-up period of six months.

DISCUSSION

The discovery of the Lichtenstein technique in 1984 as a non-tension hernioplasty with polypropylene mesh represents one of the most significant milestones in the treatment of inguinal hernia since the discovery of Bassini's hernioplasty. This surgical procedure was set by the American Association of Surgeons at the National Congress in Chicago in 2000 as the standard for surgical repair of inguinal hernia (5).

Hernia recurrence, which was a major problem after inguinal canal plasticity, decreased with the advent of the Lichtenstein method to 1-2% (6-10). In our study, we did not have any recurrence during the stated follow-up period in any of the study groups, which is correlated with studies that addressed this issue (10).

As for the early postoperative pain in our study, we found that there was no statistically significant difference in pain reported in patients from both study groups. Comparing ours with the results of similar studies, we found similar data (11-15). This can be explained by the fact that in all patients, the mesh favored the onset of extruded

pain. With respect to the presence of pain one month after surgery, the analysis showed that there was no statistically significant difference between the study groups ($p=0.482$). In the study of Naveen and Srinath (12), no statistically significant differences were found between the same groups tested, but it is still worth mentioning that in this study the value ($p = 0.096$) gives a slight advantage to the classical Lichtenstein technique. Further analysis showed that there was no statistically significant difference between the onset of postoperative pain after six months of surgery ($p=0.967$), which was consistent with the results from the available medical literature (16). More recent studies indicate that the overall prevalence of chronic pain after hernia mesh repair varies from 0.5% to 11% regardless of technique (17, 18).

Infection is one of the most common complications after hernioplasty. The ratio of wound infection after inguinal hernioplasty ranges from 0.9 to 9%, depending on the clinical variables of the population, as well as whether mesh and antibiotic prophylaxis are used. Several studies in the UK have reported a relatively high incidence of surgical wound infection after inguinal hernioplasty. Holmes and Readman reported the occurrence of wound infection in 4% of operated patients after the first postoperative month (19). Bailey et al. reported wound infections after inguinal hernioplasty in 9% of cases (20). The use of wound drains showed no benefit, and may have contributed to the increase in the number of infections. By statistical analysis of the incidence of wound infections in the early postoperative period, we concluded that there was no statistically significant difference ($p = 0.810$) in the occurrence of this complication between the studied groups. Our results correlate with a similar study by Naveen and Srinath ($p = 0.493$), who have similar results of wound infection in the early postoperative period (5.7%) (12).

Seroma occurred postoperatively in 3 patients (5%) in the Lichtenstein group, while in the Modified Lichtenstein group it occurred in 5 patients (8.3%). The analysis showed that there was no statistically significant difference in the occurrence of this complication in the studied groups ($p = 0.767$). In the case of Anand- et al. in a sample of 429 patients operated by the Lichtenstein technique, seroma occurs in 2.8% of patients, which is a slightly better result compared to ours (21).

Statistical analysis showed that there was no statistically significant difference in the occurrence of postoperative hematoma between the studied groups ($p = 0.601$). We expected that the insertion of additional retrofunicular sutures in a modified technique would be conducive to hematoma formation, which was not the case. We believe that the appearance of hematomas can be reduced by careful surgical technique and the use of more modern suture and prosthetic materials.

Scrotum swelling occurred in 4 patients (6.7%) in the Lichtenstein group, while it occurred in 6 patients (10%) in the modified technique group, without statistical significance between the two groups ($p = 0.351$). Our results slightly better correlated with other major studies of Harjai and Nagpal, which incidence of postoperative scrotum swelling was 14.29% in the classical Lichtenstein technique, but this study also included patients operated in an emergency program, which was not the case with our study (22).

Opinions of surgeons at our clinic are diverse regarding the use of a modified Lichtenstein technique. Despite the validity of the opinion that there is no significant benefit in the use of additional retrofunicular sutures, nevertheless 19 (82.6%) of our surgeons place it mostly for additional safety and habit. Given that there are no proven contraindications to this modification, we believe that this practice is justified.

CONCLUSION

On the basis of the evaluation and comparison of the obtained results, we can conclude that the modified Lichtenstein technique with retrofunctional sutures has its place in daily surgical practice. With regard to interoperative, early and late postoperative complications compared to the classical Lichtenstein technique, we conclude that the application of this technique has no significant advantages or disadvantages compared to classical Lichtenstein technique.

REFERENCES

1. Silen W. Inguinal and incisional hernias. *The Lancet*. 2004;363(9402):83-84. [Internet]. Ccity.com. 2020 [cited 27 April 2020]. Available from: http://www.ccity.com/ace/2009/ip0948/ip0948_print.pdf.
2. Grant A. Open mesh versus non-mesh repair of groin hernia meta-analysis of randomized trials leased on individual patient data. *Hernia*. 2002;6(3):130-136.
3. Bisgaard T, Bay-Nielsen M, Kehlet H. Authors' reply: Risk of recurrence 5 years or more after primary Lichtenstein mesh and sutured inguinal hernia repair (*Br J Surg* 2007; 94: 1038-1040). *British Journal of Surgery*. 2007;94(11):1438-1439.
4. Neumayer L, Fitzgibbons R, Itani K, Jonasson O. Laparoscopic Inguinal Hernia Repair. *Journal of the American College of Surgeons*. 2005;201(3):486-487.
5. Heikkinen T, Bringman S, Ohtonen P, Kunelius P, Haukipuro K, Hulkko A. Five-year outcome of laparoscopic and Lichtenstein hernioplasties. *Surgical Endoscopy*. 2004;18(3):518-522.
6. Sajid M, Craciunas L, Singh K, Sains P, Baig M. Open transinguinal preperitoneal mesh repair of inguinal hernia: a targeted systematic review and meta-analysis of published randomized controlled trials. *Gastroenterol Rep*. 2013;1:127-137.
7. Olmi S, Erba L, Magnone S, Bertolini A, Croce E. Prospective clinical study of laparoscopic treatment of incisional and ventral hernia using a composite mesh: indications, complications and results. *Hernia*. 2006;10(3):243-247.
8. MacFadyen B, Mathis C. Inguinal Herniorrhaphy: Complications and Recurrences. *Surgical Innovation*. 1994;1(2):128-140.
9. McCormack K, Scott N, Go P, Ross S, Grant A. Laparoscopic techniques versus open techniques for inguinal hernia repair. *Cochrane Database Syst Rev*. 2003;(1):CD001785.
10. PMC E. Europe PMC [Internet]. Europepmc.org. 2020 [cited 27 April 2020]. Available from: <https://europepmc.org/abstract/MED/20698388>
11. NN, RS. A Comparative Study Between Modified Bassini's Repair and Lichtenstein Mesh Repair of Inguinal Hernias in Rural Population. *J Clin Diagn Res*. 2014 Feb;8(2):88-91.
12. Pukar M. Combination of Lichtenstein Repair with Herniorrhaphy in Open Inguinal Hernia Repair- A Prospective Observational Single Center Study. *J Clin Diagn Res*. 2014;8(10):NC03-NC080.
13. Kurzer M, Kark A, Hussain S. Day-case inguinal hernia repair in the elderly: a surgical priority. *Hernia*. 2008;13(2):131-136.
14. Amid P, Shulman A, Lichtenstein I. The Lichtenstein open ?tension-free? mesh repair of inguinal Hernias. *Surgery Today*. 1995;25(7):619-625.
15. Pielaciński K, Szczepanik A, Wróblewski T. Effect of mesh type, surgeon and selected patients' characteristics on the treatment of inguinal hernia with the Lichtenstein technique. Randomized trial. *Videosurgery and Other Miniinvasive Techniques*. 2013;2:99-106.
16. Alfieri S, Amid P, Campanelli G, Izard G, Kehlet H, Wijsmuller A et al. International guidelines for prevention and management of post-operative chronic pain following inguinal hernia surgery. *Hernia*. 2011;15(3):239-249.
17. Nienhuijs S, Rosman C, Strobbe L, Wolff A, Bleichrodt R. An overview of the features influencing pain after inguinal hernia repair. *Inter Journ Surg*. 2008;6(4):351-356.
18. Holmes J, Readman R. A study of wound infections following inguinal hernia repair. *Journal of Hospital Infection*. 1994;28(2):153-156.
19. Bailey I, Karran S, Toyn K, Brough P, Ranaboldo C, Karran S. Community surveillance of complications after hernia surgery. *BMJ*. 1992;304(6825):469-471.
20. Anand A, Sinha P, Kittappa K, Mulchandani M, Debrah S, Brookstein R. Review of Inguinal Hernia Repairs by Various Surgical Techniques in a District General Hospital in the UK. *Indian Journal of Surgery*. 2011;73(1):13-18.
21. Harjai M, Nagpal B, Singh P, Singh Y. A Prospective Randomized Controlled Study of Lichtenstein's Tension Free versus Modified Bassini Repair in the Management of Groin Hernias. *Medical Journal Armed Forces India*. 2007;63(1):40-43.

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**Our contribution to the reduction of cardiovascular diseases in Bosnia and Herzegovina!
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Meningiomas of the skull base - a case series of microsurgically treated patients and our experience with recent European guidelines

Meningeomi baze lobanje - serija mikrohirurški tretiranih slučajeva i naša iskustva sa aktuelnim Evropskim vodičima

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ABSTRACT

Skull base meningiomas (SBM) represent 30% of all meningiomas, where majority of them are benign tumors. The World Health Organization (WHO) classified meningiomas in 3 grades: I-benign, II-atypical, III-malignant meningioma. Surgery of SBM is one of the biggest neurosurgical challenges due to deep location on the basis of skull and proximity of many intracranial anatomical structures. However, the total surgical resection is still the therapy of choice for SBM. In cases where the risk of total resection is beyond benefit, a partial resection is also an option. The remains after the partial meningioma resection or even recurrence can be treated with radiotherapy or radiosurgery. Such approach has been common practice for many years although new recommendations have introduced a little bit different approach. The meningiomas should be followed for a long term period given that they have a remarkable recurrence rate. This article presents a few illustrative cases of SBM at different locations, treated at our department in the recent years. Contemporary protocols for the treatment and follow up are also presented.

Key words: meningioma, skull base, Simpson Grade System, EANO guidelines

SAŽETAK

Meningeomi baze lobanje predstavljaju 30% svih meningeoma, a većina su benigni tumori. Svjetska zdravstvena organizacija je klasificirala meningeome u tri gradusa: I-benigni, II-atipični, III-maligni meningeom. Operacije meningeoma baze lobanje predstavljaju jedan od najvećih neurohirurških izazova, jer se nalaze duboko na bazi lobanje u blizini važnih intrakranijalnih anatomskih struktura. I pored kompleksnosti operativnog pristupa, totalna hirurška resekcija tumora predstavlja prvi terapijski izbor za meningeome. U slučajevima gdje je ukupni benefit od totalne resekcije menigeoma manji od operativnog rizika, tumor se parcijalno odstranjuje. Kod parcijalne resekcije meningeoma preostali dio može se tretirati radioterapijom ili radiohirurgijom. Ovakav pristup je uobičajena praksa, iako nove preporuke donose nešto drugačiju strategiju. Praćenje meningioma mora biti dugo, jer ovi tumori pokazuju veliku sklonost ka recidivanju. U ovom članku selektirali smo nekoliko ilustrativnih slučajeva mikrohirurški tretiranih meningeoma baze lobanje na različitim lokacijama, koji su operirani na našoj klinici unazad nekoliko godina. Također su prikazani savremeni protokoli za tretman i praćenje pacijenata sa meningeomima.

Ključne riječi: meningeomi, baza lobanje, Simpson gradusni sistem, EANO preporuke

INTRODUCTION

Neurosurgical treatment of skull base meningioma (SBM) is one of the most complex surgical interventions in neurosurgery. The incidence rate of meningioma in the United States is 1.8 for men and 4.2 for women per 100.000 population. From all brain tumors meningioma is the most common primary intracranial brain tumor and it represent 20% to 30 % of all brain tumors, with 30% of them located on the skull base (1-3). In a study of 276 patients treated for skull meningiomas the localization was as follows: sphenoid ridge (16%), convexity (14%), cerebellopontine angle (13%), parasellar (12%), parasagittal (11%), posterior fossa (8%), olfactory groove (8%), falx (7%), foramen magnum (3%), orbit (3%) and other (6%) (3,4).

Clinical features of meningioma include three big clinical signs: raised intracranial pressure, focal neurosurgical signs and epilepsy. In 2016 the World Health Organization (WHO) published a new classification of central nervous system tumors where meningeoma were classified in three grades: benign (grade I), atypical (grade II) and malignant meningioma (grade III) (5). For the majority of tumors gross total resection (GTR), known as Simpson grade I resection is the therapy of choice (6-9). Simpson grade I resection is a macroscopically complete removal of tumor, with excision of its dural attachment, and of any abnormal bone and includes resection of venous sinus if involved. Simpson Grading System is shown in Table 1 (10).

Table 1 Simpson Grading System for removal of meningiomas.

Grade	Description
I	Macroscopically complete removal of tumor, with excision of its dural attachment, and of any abnormal bone. Includes resection of venous sinus if involved.
II	Macroscopically complete removal of tumor and its visible extensions with coagulation of its dural attachment.
III	Macroscopically complete removal of the intradural tumor, without resection or coagulation of its dural attachment or its extradural extensions.
IV	Partial removal, leaving intradural tumor in situ.
V	Simple decompression, with or without biopsy.

However the resection of SBM can be very difficult and challenging. The deep location and proximity of the skull base delicate structures specially blood vessels and cranial nerves involvement are factors which making these tumors a challenge to a neurosurgeon (11). Such features of SBM imply that in some cases the neurosurgeon cannot remove the complete meningioma, which leads to a higher resection grade (11-16). In such cases or in cases of recurrent tumor patients undergo radiotherapy or radiosurgery, depending of the grades of meningioma based on WHO classification, and on its location (17). Long term recurrence of the meningioma, especially of those partially resected, is a big concern and need monitoring for up to 20 years (18).

This article presents a few typical SBM surgery cases, based on the corresponding author's personal series (7), and gives a brief review of European Association of Neuro-Oncology (EANO) guidelines protocol for treatment of meningiomas.

CASE 1

A 57-years-old female patient with a headache history, gait disturbance, left eye amblyopia and pituitary dysfunction was admitted to our department. She did not have any other neurological signs. A MRI showed a tumor mass located on sphenoid wing and optic sheath (Figure 1). The radiological features of the tumor indicated meningioma. A surgical resection of the tumor was performed (Simpson grade III), and meningioma was confirmed pathologically. After the surgery the patient's symptoms improved. As shown on the 3 year follow up contrast MRI, there is a small part of residual tumor very close to the important neurovascular structures on the anterior cranial fossa and pituitary (Figure 2). No additional therapy except initial surgery has been needed so far. The patient is pretty good and tumor is followed up.

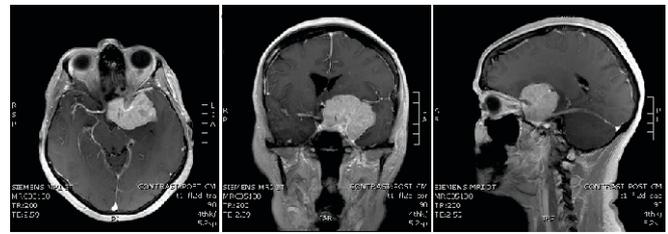


Figure 1 Preoperative T1 MRI scan with contrast revealed meningioma on the optic sheath and sphenoid wing. *Left:* Axial T1-weighted scan. *Middle:* Coronal T1-weighted scan. *Right:* Sagittal T1-weighted scan. It is obvious that the both internal carotid artery and middle cerebral artery with its branches are involved in the tumor which makes it very difficult and even dangerous for complete resection.

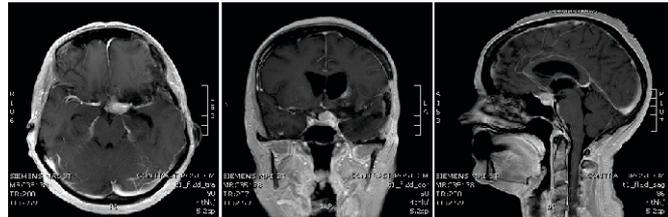


Figure 2 Postoperative contrast MRI scan after 3-year follow up show a small rest of the tumor but there is no evidence of grow up compared to the previous follow up scans. Also this rest does not produce any obvious symptoms, so the "wait and see" strategy was chosen. *Left:* Axial T1-weighted scan. *Middle:* Coronal T1-weighted scan. *Right:* Sagittal T1-weighted scan.

CASE 2

A 36-years-old female patient with partial paresis of the III, IV and VI cranial nerve (after the first surgery) and right eye mydriasis was admitted to our department. She had a meningioma surgery 6 years ago at other institution, with a gross total resection. A part of the tumor was left in the right cavernous sinus (CC), and followed up. After 6 years her condition deteriorated in hearing and gait disturbance. MRI showed a recurred tumor mass located in the right pontocerebellar angle (PCA) (Figure 3). The radiological features of the tumor indicated that it was meningioma, which was macroscopically and pathologically confirmed. A micro surgical total resection of the tumor in the PCA was performed (Simpson grade II resection). At the 6-month postoperative outpatient clinical follow-up, the patient's symptoms improved. MRI was performed 2-year postoperatively, showing no recurrence of the meningioma in PCA (Figure 4), but with minimal growth of the CC part. Patient underwent a Gamma Knife surgery of the cavernous sinus meningioma.



Figure 3 Preoperative contrast MRI scan revealed meningioma in the posterior cranial fossa - PCA. *Left:* Axial T1-weighted scan

with contrast. *Middle*: Coronal T1-weighted scan. *Right*: Sagittal T1-weighted scan.



Figure 4 Postoperative 6-months follow up contrast enhanced MRI scans. *Left*: Axial T2 FLAIR- scan. *Middle*: Coronal T1-weighted scan. *Right*: Sagittal T1-weighted scan. No signs of recurrence in the middle fossa and CPA, but with small rest in CC.

CASE 3

A 62-years-old female patient with history of anosmia, gait disturbance, cognitive changes, visual deterioration, especially of the left eye, and pituitary dysfunction was admitted to our department. A MRI showed a tumor mass located suprasellar (Figure 5). Complete (Simpson grade I) resection was performed, and the pathology confirmed meningioma. After the surgery the patient's symptoms improved. After 15 months follow up MRI showed no recurrence of the meningioma. The patient is completely asymptomatic with no neurological deficit.

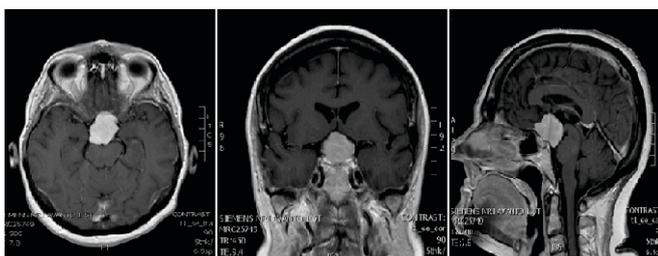


Figure 5 Preoperative contrast MRI scan revealed suprasellar (diaphragma sellae) meningioma. *Left*: Axial T1-weighted scan. *Middle*: Coronal T1-weighted scan. *Right*: Sagittal T1-weighted scan.

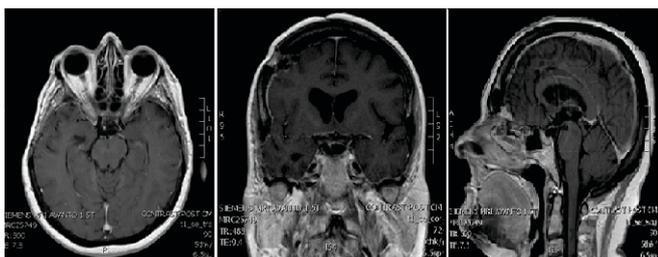


Figure 6 Postoperative 5-year follow up contrast enhanced MRI scan show no recurrence. *Left*: Axial T1-weighted scan. *Middle*: Coronal T1-weighted scan. *Right*: Sagittal T1-weighted scan.

CASE 4

A 60-years-old male patient with a history of dysphasia, gait, cognitive changes and left sided hemiparesis was admitted to our

department. A MRI showed a tumor mass located on the sphenoid wing, with radiological features of meningioma (Figure 7). A total surgical resection (Simpson grade I) was performed, which was pathologically confirmed as meningioma. After the surgery the patient's symptoms improved. After 2 years of follow up MRI was performed (Figure 8). As shown on the MRI there was no recurrence of the meningioma. The patient has neurologically improved.

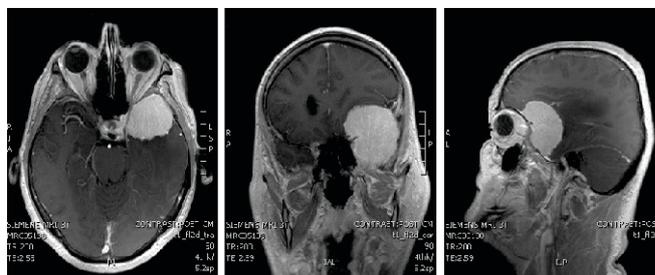


Figure 7 Preoperative contrast MRI scan revealed large meningioma on the sphenoid wing on the left side. *Left*: Axial T1-weighted scan. *Middle*: Coronal T1-weighted scan. *Right*: Sagittal T1-weighted scan with contrast.

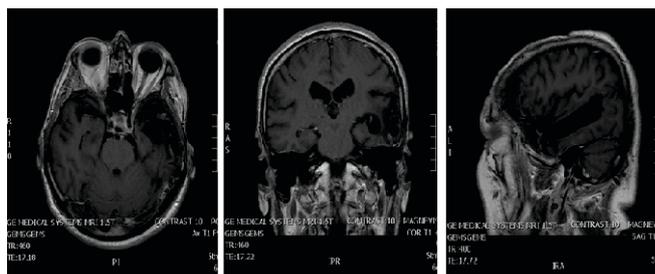


Figure 8 Postoperative contrast MRI scan after 2 years of follow up. There is no recurrence of the tumor. *Left*: Axial T1-weighted scan. *Middle*: Coronal T1-weighted scan. *Right*: Sagittal T1-weighted scan.

CASE 5

A 59-years-old female patient with a history of hearing problems, gait disturbance, facial nerve symptoms, and mild right hemiparesis was scheduled for surgery after the contrast enhanced brain MRI revealed large petroclival meningioma of the left side (Figure 9). Complete surgical resection (Simpson grade I) was achieved after extended left retrosigmoid approach was performed. Postoperative MRI showed that the tumor was completely removed (Figure 10).

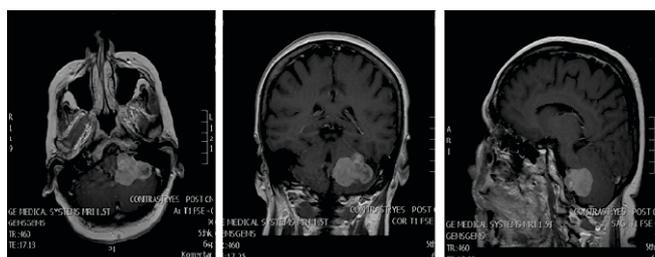


Figure 9 Preoperative contrast MRI scan revealed left petroclival meningioma. *Left*: Axial T1-weighted scan. *Middle*: Coronal T1-weighted scan. *Right*: Sagittal T1-weighted scan.

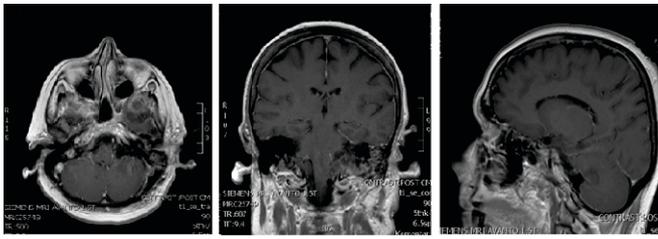


Figure 10 Postoperative contrast MRI scan. Extended left retrosigmoid approach was used. There is no evidence of tumor residual. *Left:* Axial T1-weighted scan. *Middle:* Coronal T1-weighted scan. *Right:* Sagittal T1-weighted scan.

CASE 6

A 48-years-old female patient with a history of gait disturbance and headache was scheduled for surgery after the contrast enhanced brain MRI revealed foramen magnum meningioma (Figure 11). The MRI showed that the tumor involved vertebral arteries and was compressing the brainstem. Complete surgical resection (Simpson grade I resection) was achieved. Postoperative MRI showed that the tumor was completely removed with a subacute epidural hematoma on the side where it was resected (Figure 12). Postoperatively, conservative treatment by Colistin was performed due to meningitis (Acinetobacter).

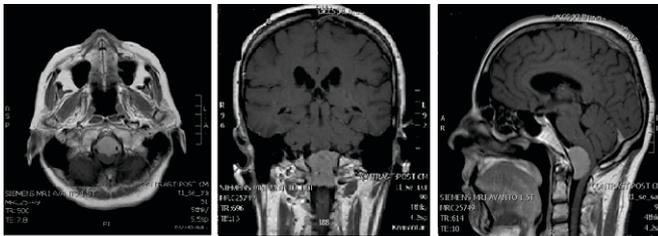


Figure 11 Preoperative contrast MRI scan revealed foramen magnum meningioma. *Left:* Axial T1-weighted scan. *Middle:* Coronal T1-weighted scan. *Right:* Sagittal T1-weighted scan

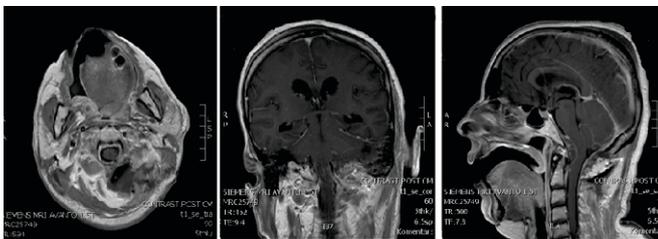


Figure 12 Postoperative contrast MRI scan. There is no evidence of rest tumor. Subacute epidural hematoma is seen on the ventral side of brain stem, where the tumor was resected. *Left:* Axial T1-weighted scan. *Middle:* Coronal T1-weighted scan. *Right:* Sagittal T1-weighted scan.

DISCUSSION

Most meningiomas are benign tumors WHO grade I, which can and should be successfully treated with surgery alone. Minorities of meningiomas are WHO grade II or III, which besides surgery also

require radiotherapy, radiosurgery, chemotherapy or some other pharmacotherapy (10-13,19). In 2016 the European Association of Neuro-Oncology published guidelines for diagnosing and treatment of meningiomas (6). Prior to the guidelines the treatment of meningioma mostly depended on neurosurgeon's decision. These guidelines are standardizing management of meningioma across the world, with clear protocol showed in Figure 13 (6).

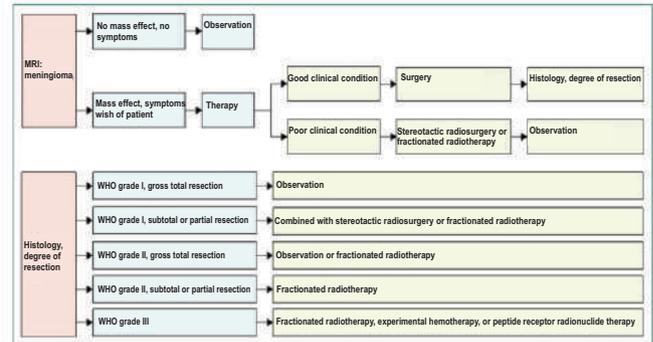


Figure 13 Recommendations for the therapeutic management of meningiomas of WHO grades I-III concerning EANO guidelines.

Five presented cases involved the first surgery of the meningioma, and one case is related to the second surgery for recurrent meningioma. We have shown different locations of SBM and different grades of SBM resection. Five patients were treated before EANO guidelines, and only the sixth patient was treated following the EANO guidelines publication. In Case 1 Simpson Grade III resection was performed due to neurovascular structures involved in the meningioma mass, internal carotid and middle cerebral artery. The rest tumor was monitored and it did not show any symptoms nor did it increase in size. Due to the rest tumor features we decided to monitor it on annual basis, with no additional therapy. This strategy was not in accordance with the EANO guidelines for WHO grade I meningioma where the rest tumor should be treated with radiosurgery or fractionated radiotherapy (6). If the rest tumor started to show any symptoms or increases in size we would treat it with radiotherapy or radio-surgery. In our Institution we used Linac SRS. In Case 2 we presented a patient with recurrent meningioma 6 years after the surgery. The recurrence of meningioma is one of the biggest concerns in the postoperative follow up, as shown in this particular case. After Simpson Grade II resection the patient underwent Gamma knife surgery for the little tumor rest in the CC. The risk of injuring neurovascular structures of cavernous sinus was much higher than the benefit of a total surgical resection. This was in line with the EANO protocol for subtotal resection of meningioma (6). In all other cases we presented GTR and Simpson I resection of differently located SBM.

Meningiomas have a slow growth pattern and are minimal or almost never involve brain parenchyma (18). The total surgical resection of the tumor for majority meningioma is the best therapy choice, especially for those with WHO grade I (4,16). But in the case of SBM the surgical approach and the resection of the meningioma can be very difficult due to deep location and anatomic structures nearby. In these cases a combined surgical and radiotherapy approach can give better results than the surgery alone (15,16). With this approach the risk of total surgical resection can be minimized. After complete excision of benign meningiomas, the 5-year control rate is 72 to 100%. The 5-year control rate after subtotal surgical resection is 31 to 70%. With the addition of postoperative radiotherapy/radiosurgery, the control rate at 5 years has been reported to be 80 to 98% (20-23). Radiological diagnosis of

meningioma should be made by MRI. When MRI shows a clear radiological image of meningioma the pathological confirmation is even not mandatory (20). Preoperative embolization of the meningioma is not recommended, only in selected cases such as petroclival meningioma (7,15,20). In comparison to non-skull meningioma, skull meningioma requires surgical intervention at younger ages, and they have a lower MIB-1 index and majority of them are WHO grade I. Recurrence of skull meningioma has more than 100 months non-recurrence time than non-skull meningioma. These findings can have implications on surgical decision, long term follow up, and can predict the possibility of the need for the second intervention (18). Regarding the EANO recommendations of the WHO grade I meningioma should be followed up annually, and then every 2 and 5 years respectively, for WHO grade II the follow up is required every 6 months, and then annually after 5 years, and for WHO grade III the follow up is required every 3-6 months (7,13,20).

Nowadays good results in the SBM surgery can be linked not only with the well skilled and meticulously trained neurosurgeons but maybe even more to a few other points (24-29). They are primarily:

- well collected, published and wide accessible knowledge about SBM
- routine availability of highly sophisticated preoperative imaging
- clear understanding of skull base neuroanatomy
- routine but critically use of complex skull base approaches and avoidance of complications connected with those approaches
- better understanding of natural history and biology of those tumors especially with remnant application of intraoperative neuromonitoring
- availability of adjuvant and alternative modalities of treatment (30-33).

CONCLUSION

Total surgical resection is recommended and for the majority of meningioma the first option therapy. Each patient with meningioma needs a long term follows up. Radio therapy and radio surgery should be taken into consideration in patients with partially resected and small recurrent meningioma. Through a group of patients with postoperative results we have shown that at our institution, Clinical Center University of Sarajevo, the most complex pathology is successfully treated according to cotemporary guidelines and up to date knowledge, but also according to the *state of the art* surgical technique and world standards comparable postoperative results.

REFERENCES

1. Burkhardt JK, Zinn PO, Graenicher M, Santillan A, Bozinov O, Kasper EM, et al. Predicting postoperative hydrocephalus in 227 patients with skull base meningioma. *Neurosurg Focus*. 2011;30(5):E9.
2. Patibandla MR, Lee CC, Sheehan J. Stereotactic Radiosurgery of Central Skull Base Meningiomas - Volumetric Evaluation and Long-term Outcomes. *World Neurosurg*. 2017;108:176-184.
3. Mendenhall WM, Friedman WA, Amdur RJ, Foote KD. Management of benign skull base meningiomas: a review. *Skull Base*. 2004;14(1):53-60.
4. Condra KS, Buatti JM, Mendenhall WM, Friedman WA, Marcus RB Jr, Rhoton AL. Benign meningiomas: primary treatment selection affects survival. *Int J Radiat Oncol Biol Physiol*. 1997;39:427-36.
5. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 2016;131(6):803-20.

6. Goldbrunner R, Minniti G, Preusser M, Jenkinson MD, Sallabanda K, Houdart E, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol*. 2016;17(9):e383-91.
7. Donald Simpson. The recurrence of intracranial meningiomas after surgical treatment. *J Neurol Neurosurg Psychiatry*. 1957;20:22-39.
8. Schulz C, Mathieu R, Kunz U, Mauer UM. Treatment of unresectable skull base meningiomas with somatostatin analogs. *Neurosurg Focus*. 2011;30(5):E11.
9. Morita A, Coffey RJ, Foote RL, Schiff D, Gorman D. Risk of injury to cranial nerves after gamma knife radiosurgery for skull base meningiomas: experience in 88 patients. *J Neurosurg*. 1999;90(1):42-9.
10. Mansouri A, Klironomos G, Taslimi S, Kilian A, Gentili F, Khan HO, et al. Surgically resected skull base meningiomas demonstrate a divergent postoperative recurrence pattern compared with non-skull base meningiomas. *J Neurosurg*. 2016;125(2):431-40.
11. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvent A, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007;114:97-109.
12. Iwai Y, Yamanaka K, Ikeda H. Gamma Knife radiosurgery for skull base meningioma: long-term results of low-dose treatment. *J Neurosurg*. 2008;109(5):804-10.
13. Nutting C, Brada M, Brazil L, Sibtain A, Saran F, Westbury C, et al. Radiotherapy in the treatment of benign meningioma of the skull base. *J Neurosurg*. 1999;90(5):823-827.
14. Azar M, Kazemi F, Jahanbakhshi A, Chanideh I, Jallesi M, Amini E, et al. Gamma Knife radiosurgery for cavernous sinus meningiomas: Analysis of Outcome in 166 Patients. *Stereotact Funct Neurosurg*. 2017;95(4):259-267.
15. da Silva CE, de Freitas PEP. Classification of meningiomas based on their surgical removal, World Health Organization grade, and cytogenetic profile: a treatment algorithm. *World Neurosurg*. 2017;105:289-293.
16. Almefty R, Dunn IF, Pravdenkova S, Abolfotoh M, Al-Mefty O. True petroclival meningiomas: results of surgical management. *J Neurosurg*. 2014;120(1):40-51.
17. Couldwell WT, Cole CD, Al-Mefty O. Patterns of skull base meningioma progression after failed radiosurgery. *J Neurosurg*. 2007;106(1):30-5.
18. Samii M, Gerganov VM. Giant meningiomas of the posterior fossa. *J Neurosurg*. 2010;112(5):905-6; discussion 906.
19. Samii M, Gerganov VM. Surgery of extra-axial tumors of the cerebral base. *Neurosurgery*. 2008;62(6 Suppl 3):1153-66; discussion 1166-8.
20. Adachi K, Kawase T, Yoshida K, Yazaki T, Onozuka S. ABC Surgical Risk Scale for skull base meningioma: a new scoring system for predicting the extent of tumor removal and neurological outcome. *Clinical article*. *J Neurosurg*. 2009;111(5):1053-61.

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Pulmonary endarterectomy for treatment of thromboembolic pulmonary hypertension - real benefit through clinical practice

Plućna endarterektomija u tretmanu hronične tromboembolijske plućne hipertenzije - stvarni benefit u kliničkoj praksi

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ABSTRACT

Introduction: in 4% of cases, the complication of pulmonary embolism is chronic thromboembolic pulmonary hypertension (CTEPH). Aim: to show the treatment of the patient with diagnosis of severe CTEPH with pulmonary endarterectomy (PEA) with a review of therapy success. Results: echocardiography verified size of right ventricle 5.1 cm, of right atrium 4.9x6.1 cm, with tricuspid valve regurgitation grade 2, in the sinus rhythm with right ventricular systolic pressure (RVSP) of 100 mmHg + central venous pressure (CVP). Six months after PEA treatment echocardiography showed right ventricle 3cm, right atrium 4x5cm, tricuspid valve regurgitation grade 1-2 with RVSP about 40 mmHg. Conclusion: the success of PEA is very good, and clinical recovery is obvious. The development of the CTEPH registry in the ground of Bosnia and Herzegovina is an imperative.

Key words: pulmonary hypertension, chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy.

SAŽETAK

Uvod: u 4% slučajeva komplikacija plućne embolije je hronična tromboembolijska plućna hipertenzija (CTEPH). Cilj: prikaz terapijskog modaliteta pacijenta s dijagnozom teške CTEPH, s plućnom endarterektomijom (PEA), uz osvrt na uspjeh terapije. Rezultati: ehokardiografski se verificira dijametar desnog ventrikula 5.1 cm, dimenzije desnog atrija 4.9x6.1 cm, s umjerenom trikuspidalnom regurgitacijom. Pacijent je bio u sinusnom ritmu, s sistoličkim pritiskom desnog ventrikula (RVSP) od 100 mmHg + središnji venski pritisak (CVP). Šest mjeseci nakon PEA, ehokardiografijom se verificira dijametar desne komore 3cm, dimenzije atrija 4x5cm, uz blagu trikuspidalnu regurgitaciju s RVSP oko 40 mmHg. Zaključak: uspjeh PEA je vrlo dobar, a klinički oporavak je očit. Razvoj registra CTEPH na tlu Bosne i Hercegovine je imperativ.

Ključne riječi: plućna hipertenzija, hronična tromboembolijska plućna hipertenzija, plućna endarterektomija.

INTRODUCTION

Pulmonary hypertension (PH) is an increase of blood pressure in pulmonary vasculature, elevation of blood flow resistance through the pulmonary blood vessels (arteries or veins). It can be arterial, venous, caused by left heart disease, hypoxic, thromboembolic, and also can be caused by diseases that directly affect the pulmonary vessels. In addition PH can be of unclear or multifactorial etiology (1,2). In 4% of cases, the complication of pulmonary embolism is chronic thromboembolic pulmonary hypertension (CTEPH) (3,4). The diagnosis is often unrecognized but is one of the most common precapillary pulmonary hypertension (5). CTEPH is characterized with vascular remodeling initiated by a combination of abnormal

angiogenesis, impaired fibrinolysis and endothelial dysfunction. (5,6) In case of right ventricular systolic pressure (RVSP) on echocardiography >50 mm Hg, without clinical or echocardiographic signs of right ventricular failure, chronically "conditioned" right ventricle is more likely to be the case (6).

Treatment for CTEPH can be pharmacological (calcium channel blockers, endothelin receptor antagonists, prostacyclin analogues, soluble guanylyl cyclase (sGC) stimulators, phosphodiesterase type 5 inhibitors (off label use) and surgical (pulmonary thrombectomy and bilateral endarterectomy) (3,6), while bilateral lung transplant is a salvage therapy (4).

AIM

Treatment of severe CTEPH with pulmonary endarterectomy (PEA) and the therapy success review.

CASE REPORT

In March 2017, a 37 year old male was admitted to the Clinical Centre University of Sarajevo due to massive bilateral thromboembolism, subsequently verified by CT (with dilatation of the right part of the heart) (Figure 1). In his medical history the following was found: operative treatment of Achilles tendon rupture at the age of five, re-operation at the age of seven, appendectomy at the age of ten, and at the age of 16 surgical treatments on left kidney due to hydronephrosis. Anticoagulant factors antithrombin III, protein C and protein S were in reference range. Color Doppler did not verify deep vein thrombosis. Electrocardiogram verified peaked P wave (P pulmonale) with negative T wave in diaphragmatic leads, right bundle branch block, with the signs of hypertrophy of the right ventricle (Figure 2). Echocardiographic finding showed dilatation of the right heart cavities (right ventricle (4.8 cm) and right atrium 4.7x5.4 cm), left heart cavities were in regular dimensions. Tricuspid valve regurgitation grade 3 was verified with right ventricular systolic pressure (RVSP) of 105 mmHg. All of these findings confirmed diagnosis of severe chronic thromboembolic pulmonary hypertension (CTEPH). Therapy was administered with clinical and subjective recovery. The control CT was performed one and five months later showing signs of bilateral pulmonary thromboembolism assessed as regression compared to the previous finding. In November 2017, echocardiography verified size of right ventricle 5.1 cm, right atrium 4.9x6.1cm, right atrium area 28.7cm², tricuspid annular plane systolic excursion (TAPSE) 1.4cm, tricuspid annular peak systolic velocity (TAPSV) 10.4 cm, pulmonary artery diameter 3.0cm with tricuspid valve regurgitation grade 2, in the sinus rhythm with RVSP of 100 mmHg + central venous pressure (CVP) and RVSP 64 mmHg + CVP during extrasystoles. The width of the inferior vena cava was 19/16 mm. After 15 minute break in the right ventricle, RVSP was 87 mmHg + CVP. He was classified as NYHA Stage III of heart failure, and therapy with riociguat was started, while pulmonary endarterectomy (PEA) was indicated (Figure 3). PEA was performed at AKH Wien (Austria) (Figure 4). Preoperative right heart catheterization revealed pulmonary hypertension at rest (pulmonary arterial pressure (PAP) (s/d/m) 88/33/50 (mmHg), pulmonary vascular resistance (PVR) Thermo 11.1 pr Fick 10.2 (WU) and cardiac index (CI) Thermo 1.56 (L/min/m²). First postoperative day patient was extubated and transferred to continuous positive airway pressure (CPAP) because of atelectasis prevention. Swan Ganz catheter showed on second postoperative day PAP (s/d/m) 44/20/29 (mmHg), PVR 2.25 (WU). Patient was discharged with following therapy: enoxaparin, furosemide and potassium supplement. In September 2018, echocardiography verified right ventricle 3.2 cm, right atrium 4x5cm, tricuspid valve regurgitation grade 1-2 with RVSP about 40 mmHg and systolic function of 62%. After that patient received acenocumarol with diuretics. Control echocardiography showed right ventricle 3cm, right atrium 4x5cm, tricuspid valve regurgitation grade 1-2, with RVSP around 40 mmHg, and systolic function of left ventricle about 62%.

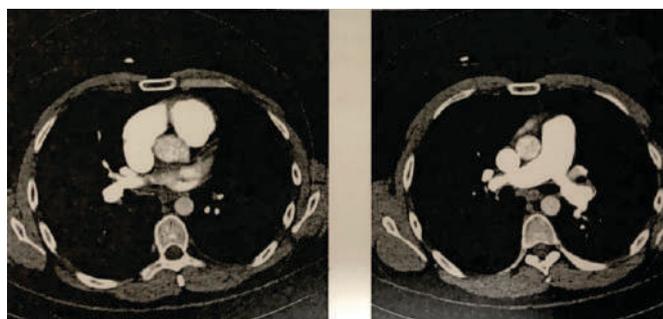


Figure 1 Defects in contrast filling of both pulmonary arteries from the origin, with propagation into their segmental branches.

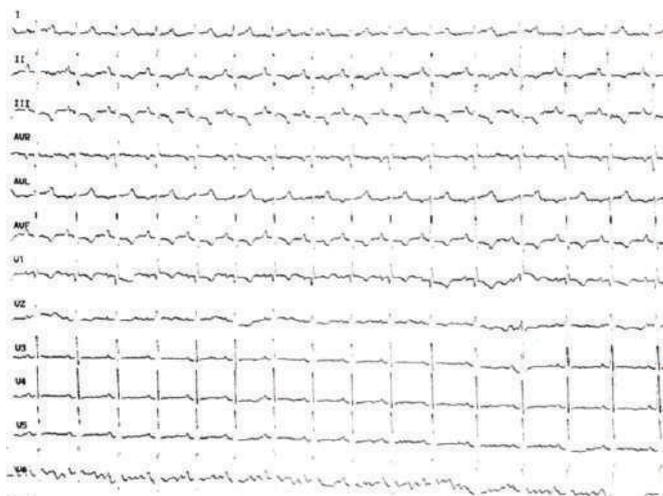


Figure 2 Electrocardiogram verified peaked P wave (P pulmonale) with negative T wave in diaphragmatic leads, right bundle branch block, with the signs of hypertrophy of the right ventricle.



Figure 3 Preoperative pulmonary angiography.

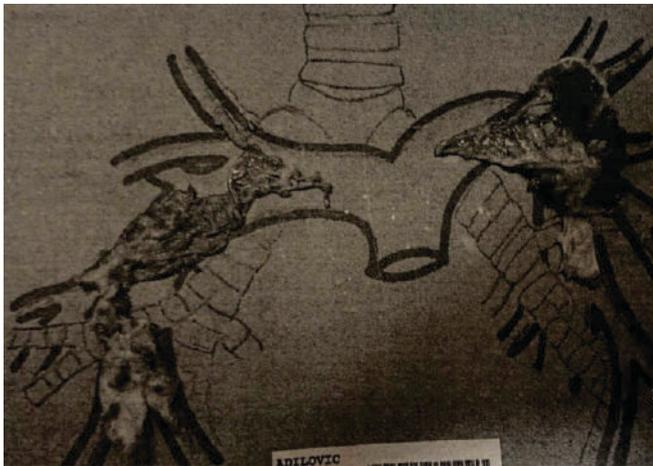


Figure 4 Surgical sample.

DISCUSSION

The CTEPH incidence depends on the authors, and its clear value is often dubious. In France, an incidence of 3.4% is estimated on 30,000 newly diagnosed acute pulmonary embolism (7), while Guerin et al. mentioned incidence of 4.8% (8), and Coquoz et al. have reported CTEPH incidence of 0.79% (after right heart catheterization) in the two-month investigation (9).

Lung ventilation/ perfusion scintigraphy represents standard in the diagnosis of chronic thromboembolic pulmonary hypertension (a superior method in comparison to computed tomography pulmonary angiography). Digital subtraction angiography is used to characterize morphology of blood vessels. The outcome of CTEPH correlates to the level of pulmonary vascular resistance (PVR) and the degree of right ventricular dysfunction (associated with mean pulmonary arterial pressure) (6). If not treated, pulmonary hypertension will progress with right ventricular dysfunction which leads to lethal outcome (10). Definitive treatment for CTEPH is PEA (stripping of the diseased intimal layer from the media) (6, 12). Data reported 3-year survival of 90% in operated patients and 70% in those who were not operated (11). For patients that cannot be operated (distal obstructive changes or co-morbidities) balloon angioplasty can be considered (6,12). Lung (or heart-lung) transplantation is option for the patients where PEA is not indicated or when significant pulmonary hypertension persists following PEA. Surgical treatment results are generally good with significant improvements in haemodynamics and functional capacity (7,12). No matter these results, number of performed PEA in the United States per year is 0.9 to 1 endarterectomies per million of the population while in Europe it is about 1.7 per million of the population (12). Pharmacological treatment is began with calcium channel blockers (when other drugs are not available), while bosentan, prostacyclin analogues and iloprost are used until the PEA, or after PEA when results are not satisfactory (7,12). Inoperable CTEPH are treated with bosentan. After PEA all patients have to be on anticoagulant treatment with warfarin, while antiplatelet agents can be considered in case of thrombocytopenia (12).

CONCLUSION

It is important to clearly identify CTEPH, with the fact that PEA is a therapeutic choice for CTEPH patients. Pharmacological treatment, and balloon pulmonary angioplasty are the secondary

treatment lines. The success of PEA is very good, and clinical recovery is obvious. The development of the CTEPH registry in the ground of Bosnia and Herzegovina is an imperative.

REFERENCES

1. Hoepfer MM, Ghofrani HA, Grünig E, Klose H, Olschewski H, Rosenkranz S. Pulmonary Hypertension. *Dtsch Arztebl Int.* 2017;114(5):73-84.
2. Pesto S, Begić Z, Prevljak S, Pecar E, Kukavica N, Begić E. Pulmonary Hypertension - New Trends of Diagnostic and Therapy. *Med Arch.* 2016;70(4):303-7.
3. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med.* 2004; 350(22):2257-64.
4. Kooperkamp H, Mehta I, Fary D, Bates M. Pulmonary Thromboendarterectomy for Pulmonary Hypertension before Considering Transplant. *Ochsner J.* 2017;17(1):66-70.
5. Mayer E, Jenkins DP, Lindner J, D'Armini A, Kloek J, Meyns B, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an International Prospective Registry. *J Thorac Cardiovasc Surg.* 2011;141(3):702-10.
6. Yandrapalli S, Tariq S, Kumar J, Aronow WS, Malekan R, Frishman WH, et al. Chronic Thromboembolic Pulmonary Hypertension: Epidemiology, Diagnosis, and Management. *Cardiol Rev.* 2018;26(2):62-72.
7. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. *Thromb Haemost.* 2000;83(5):657-60.
8. Guérin L, Couturaud F, Parent F, Revel M-P, Gillaizeau F, Planquette B, et al. Prevalence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *Thromb Haemost.* 2014;112(3):598-605.
9. Coquoz N, Weilenmann D, Stolz D, Popov V, Azzola A, Fellrath J-M, et al. Multicentre observational screening survey for the detection of CTEPH following pulmonary embolism. *Eur Respir J.* 2018;51(4):1702505.
10. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest.* 1982;81(2):151-8.
11. Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, et al. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. *Circulation.* 2016;133(9):859-71.
12. McNeil K, Dunning J. Chronic thromboembolic pulmonary hypertension (CTEPH). *Heart.* 2007;93(9):1152-1158.

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