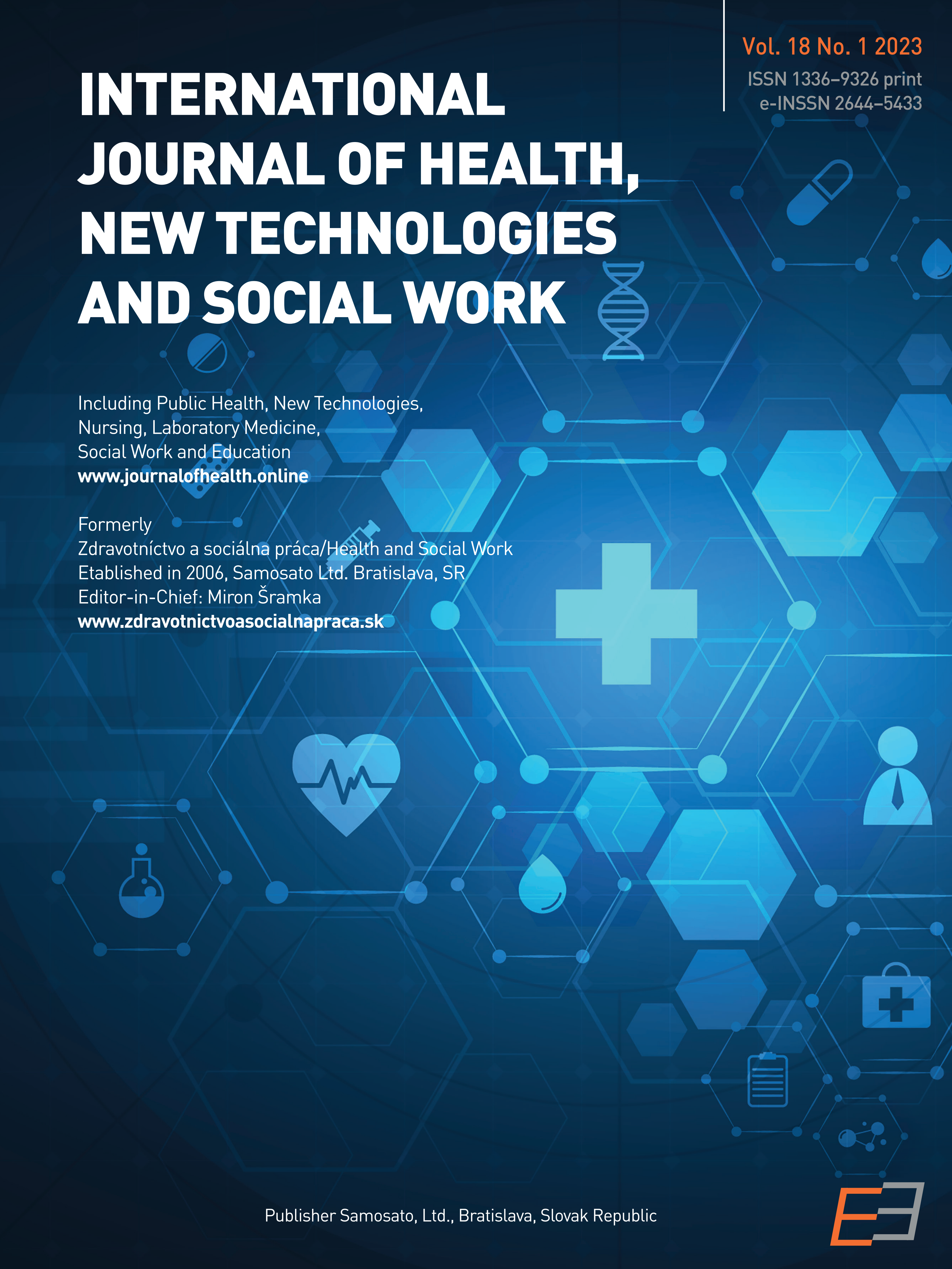

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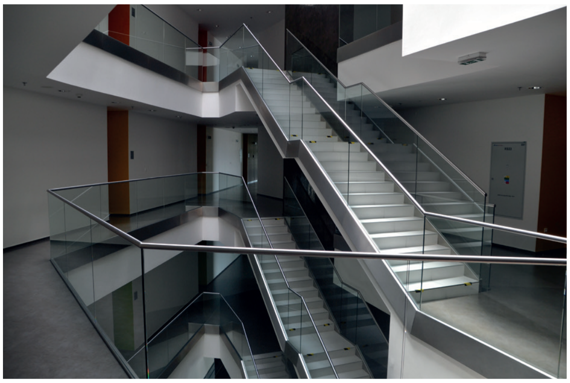

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contents

editorial

Dear Readers,

The journal "Zdravotníctvo a sociálna práca" (Health and Social Work) was renamed in 2021 to International Journal of Health, New Technologies and Social Work.

Our long-term effort is to gradually acquire for the journal European significance and be included in international databases. Starting with issue No. 4 in 2016, the journal accepted the Harvard style of referencing, and changed guidelines for the authors. The aim of the changes was to move closer to the standard in international journals published in English in the area of health and helping professions. The editors are aspiring for registration in other relevant international databases. Since last 2020 the journal has published all articles in English only.

The journal "Zdravotníctvo a sociálna práca" (Health and Social Work) was established in 2006 at Faculty of Health and Social Work blessed to P. P. Gojdič in Prešov and St. Elizabeth University College of Health and Social Work in Bratislava. In 2021, the journal celebrated its 17th year of publication.

Previously professional journal, within 5 years developed into an international, peer-reviewed scholarly journal, published quarterly (4 issues per year). The journal were published by the St. Elizabeth University of Health and Social Work in Bratislava. The journal became international in 2009. The journal was published and distributed in the Slovak Republic and also in the Czech republic.

Since 2011, the journal is published both in print and as electronic issues, available from: www.zdravotnictvoasocialnapraca.sk. Starting by issue No. 3 in 2014, the scope of the journal has broaden and the journal is covering health sciences, such as Public Health, Nursing, Laboratory Medicine, but also helping professions such as Social Work or Pedagogy. Collaboration with Faculty of Health and Social Work of Trnava University in Trnava was initiated.

The journal is indexed in the following databases: Central and Eastern European Online Library — CEEOL (since 2018), Bibliographia Medica Slovaca (BMS), and Slovak reference database CiBaMed.

The part of journal is Supplementum, to publish abstracts from international conferences organized by the St. Elizabeth University of Health and Social Work in Bratislava.

prof. Miron Šrámka, MD, DSc.
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Post-covid-19 syndrome and impact of physical activity on mental well-being

Postcovid-19 syndróm a vplyv fyzickej aktivity na mentálne zdravie

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ABSTRACT

Introduction: Following the COVID-19 pandemic, there was a need to understand the post-Covid syndrome and its impact on the mental and physical well-being of vulnerable populations.

Objective: The occurrence of post-covid syndrome has been confirmed already 6 — 12 weeks after overcoming the covid-19 disease, which is accompanied by long-lasting post-covid symptoms, discomfort and reduces the quality of life of men and women, especially people over 45 years of age.

Methods: The aim of the research is to find out the relationship between physical activity, mental health and post-covid-19 syndrome, 106 women aged 30 — 50 with post-covid symptoms were involved in the research, they were involved in the post-covid rehabilitation process and subjectively evaluate the reduction mental well-being, which is closely related to psychological resistance to the stress.

Results: Risk of mental wellbeing decrease was confirmed at people who face post-covid symptoms more than 8 weeks ($p = 0023$); level of mental wellbeing is directly associated with the readiness to copy with life difficulties ($p = 0028$).and the ability to adapt life changes ($p = 0032$). There is relation between mental wellbeing decrease and frequency of the post-covid symptoms ($p = 0019$).

Conclusion: In connection with the occurrence of post-covid syndrome, in addition to physical health, it is necessary to pay attention to measures aimed at supporting mental well-being, it turned out that emotions affect copy strategies and the abilities of human being to adapt to new life situation and accept changed health status.

Keywords: Post-covid syndrome. Physical activity. Wellbeing.

ABSTRAKT

Úvod: Po pandémii COVID-19 vyvstala potreba pochopiť post-Covidový syndróm a jeho dopad na duševnú a fyzickú pohodu zraniteľných skupín populácie.

Cieľ: Už 6 — 12 týždňov po prekonaní ochorenia Covid-19 je potvrdený výskyt post-covid syndrómu, ktorý je sprevádzaný dlhotrvajúcimi post-covidovými príznakmi, diskomfortom a znižuje kvalitu života mužov a žien, najmä u osôb starších ako 45 rokov.

Metódy: Cieľom výskumu je zistiť vzťah medzi fyzickou aktivitou, duševným zdravím a post-covid-19 syndrómom, do výskumu boli zapojené 116 žien vo veku 30 — 50 rokov s post-covidovými symptómami, V rámci liečby boli zaradené do post-covid rehabilitačného procesu a subjektívne hodnotili zníženú psychickú pohodu, ktorá úzko súvisí s psychickou odolnosťou voči záťažovým situáciám.

Výsledky: Riziko zníženia duševnej pohody bolo potvrdené u ľudí, ktorí čelia post-covidovým symptómom viac ako 8 týždňov (p = 0023); úroveň duševnej pohody je priamo spojená s pripravenosťou vyrovnať sa so životnými ťažkosťami (p = 0028) a schopnosťou prispôsobiť sa životným zmenám (p = 0032). Existuje vzťah medzi poklesom duševnej pohody a frekvenciou post-covidových symptómov (p = 0019).

Záver: V súvislosti s výskytom post-covid syndrómu je potrebné okrem fyzického zdravia venovať pozornosť aj opatreniam zameraným na podporu psychickej pohody, ukázalo sa, že emócie ovplyvňujú copingové stratégie a schopnosti človeka prispôsobiť sa novej životnej situácii či akceptovať zmenený zdravotný stav.

Kľúčové slová: Post-covid syndróm. Fyzická aktivita. Pohoda.

INTRODUCTION

In the first year of the COVID-19 pandemic, global prevalence of anxiety and depression increased by a massive 25 %, according to a scientific brief released by the World Health Organization today (WHO 2022).

Post-COVID-19 syndrome is one of those challenges, having become increasingly common as the pandemic evolves. The latest estimates suggest that 10 to 20 % of the SARS-CoV-2 patients who undergo an acute symptomatic phase are experiencing effects of the disease beyond 12 weeks after diagnosis (Jimeno-Almazán, Pallarés, Buendía-Romero, et al. 2021). The physical activity help to respond to the negative symptoms of the covid-19 (Faghy et al, 2021), these symptoms are long-them and affected the body dysfunctions (Davis et al. 2020), tailored and supervised exercise training may be an effective multisystemic therapy for post-COVID-19 syndrome that suits diversity of the cases and symptoms (Faghy et al. 2021; Martinez-Cava 2021).

Study highlights the benefits of exercise in post-COVID-19 syndrome, emphasize the need for symptom-titrated physical activity and tailored exercise in rehabilitation (NIHR, 2021), lack of physical activity, especially among older people, weakens their quality of life, reduces mobility and increases dependence on social services. (Ludvigh Cintulová et al. 2022). Physical activity induces pleasant feelings and neurotransmitters that increase mental well-being, if it is performed regularly, a person acquires the right life habits that help him increase resistance to post-covid related issues (Cintulová, Budayová, Bredová 2022).

Treatment for lung diseases helps to improve peak pulmonary oxygen uptake, systematic oxidative stress, muscle strength, muscle size, functional capacity, and quality of life (Alcazar 2019); structured rehabilitation programs after cardiac disease led to improvements in mortality, hospital readmission, cardiopulmonary fitness and functional status (Spruit 2019).

Diabetes, hypertension, and cardiovascular diseases were reported as the most frequent comorbidities among patients with COVID-19 requiring hospitalization (Chen, Zhou et al. 2020). Physical activity (PA) has proven to be beneficial in improving the clinical conditions that are most frequently associated with severe COVID-19. Physical activity contributes to the reduction of overall cardiovascular risks, bring positive effects on metabolic syndrome and insulin sensitivity (Swer et al. 2020).

The benefits of these physical and educational programs in patients with chronic cardiopulmonary disorders have also been shown from the psychosocial point of view, improving quality of life and mood. The family environment plays a significant role in supporting a person's motivation for physical activity, if a passive lifestyle prevails, such behavior is transmitted to all members of the family system (Ludvigh Cintulová, Rác, Bundzelová 2020). Tomanek (2019) adds that life habits built in the family at a younger age have an impact on the preference of values in adulthood, the attitude towards physical activity is thus also determined by the value system and internal motivation of the individual himself. At present, new relational and family patterns together with a new lifestyle are sought (Hamarova 2019) and concept of spirituality might have the impact of the lifestyle of the human being associated with the society changes (Lichner, Hamarova 2021).

There were significant differences in well-being outcomes in the inactive population between those who were more active, the same or less active ($p < 0.001$) but this was not seen in the active population. Inactive participants who spent more time engaged in outdoor physical activity had lower anxiety than those who spent less time in outdoor physical activity (Lesser et al. 2020).

METHODS

The main goal of the research was to analyse the impact of rehabilitation on mitigating the effects of post-covid symptoms in patients under 45 years of age who have overcome covid-19 as well as factors that determine their mental well-being. The sample consisted of 106 clients in the rehabilitation programme who overcame the covid-19 disease in the last 6 months and had post-covid symptoms for more than 8 weeks. As a research tool, we used a questionnaire that measured the degree of influence in two dimensions: 1. Physical activity and mental well-being. The sample was consisted of 88 women, they have been involved in the exercise training and did physical activity.

Respondents completed the wellbeing questionnaire, consisting of 19 questions, 4level-scales were determined — psychical mental health (6 items), physical (6 items); social-environment mental health (7 items) and 8 questions included well-being dimension, the values were transformed to a 1 — 4 scale representing 1 very low — 6 to very high impact. The scale rating scale in the questionnaire allows for a more objective assessment of the level of impact of one variable on another (Radková et al. 2018) and to determine their mutual relationship based on a significance level of $p \leq 0.005$. Correlation means variables are statistically associated. Medium level of mental wellbeing means that a change in one variable psyhical activity at the 6-scale statements. The term correlation refers to the statistical dependency among pairs of factors. This is different from interaction, which refers to the presence of nonadditive operations between two or more factors within a model's structural equations. Correlations can be statistically derived from samples collected in a factors or independent of a numerical model (Pan et al. 2011).

RESULTS

The sample is consisted of 106 women involved in the rehabilitation programme to reduce symptoms of post-covid syndrome and they were regularly practicing the physical exercises 2-times per week during last 2 — 6 months. The sample is divided according to age to two groups: 48 % up to 40 years old and 52 % at aged 41 — 50.

H1: there is significant correlation between the effect of physical activity and mental wellbeing ($p = 0.004$; $r = 0.78$) and different level of mental health ($p \leq 0.05$).

The level of significance confirmed the effect of physical activity on overall mental well-being at a moderate level in both age groups of women with post-covid syndrome ($p = 0.020$). Physical health improved moderately among women under 40 and moderately among women under 50 (42.3 %, $p = 0.012$).

Post-covid syndrome etermines mental well-being at a moderate level in both age groups ($p = 0.031$) (Table 1).

The positive impact of the social-environmental dimension affects the well-being of women aged 41 — 50 at a higher level compared to women under 40 ($p = 0.036$). The impact on the psychological dimension of health was not significant ($p = 0.069$).

Table 1. Correlation betwwen physical activity and mental well-being dimensions

30 — 40 years old					41 — 50 years old				
Variable: Physical activity	low	medium	high	SD	Low	Medium	High	SD	p
Mental wellbeing	31.8 %	53.9 %	14.3 %	1.2	46.7 %	39.6 %	13.7 %	1.2	0.020
Physical dimension	43.8 %	40.8 %	15.4 %	0.8	22.4 %	42.3 %	35.3 %	0.9	0.012
Psychological	48.1 %	34.7 %	17.2 %	1.8	24.7 %	36.6 %	38.7 %	1.9	0.069
Social/environmental	26.4 %	63.2 %	10.4 %	2.4	22.1 %	59.5 %	18.5 %	2.2	0.036
Post-covid syndrome	23.0 %	29.8 %	23.2 %	0.6	38.2 %	35.5 %	26.3 %	1.9	0.031

Table 2. Impact factors related to physical activity on the mental wellbeing

Sample 30 — 40 years old SD				41 — 50 years old SD			Impact on mental wellbeing
Variable Mental wellbeing	Very low-to low	Low-Medium	medium-High	Very low-to low	Low-Medium	medium-High	P
Physical activity	1.5	2.6	1.8	1.6	2.7	2.1	0.007
Training and exercises	2.1	3.4	1.3	2.2	2.0	1.3	0.014
Regular rehabilitation	0.8	2.2	1.7	1.8	2.2	2.1	0.006
Motivation to physical activity	1.5	2.1	3.6	1.4	2.4	3.1	0.008
Environment	2.1	3.1	1.6	1.1	2.9	3.5	0.025
Free-time activities	1.3	2.4	0.8	2.8	0.9	1.1	0.067
Social interaction	2.7	1.2	1.5	2.1	0.8	3.3	0.034

In the dimension of physical activity, the highest correlation between mental well-being on performing regular physical activity (p = 0.007), participation in a specialized training rehabilitation program for post-covid patients (p = 0.006) and internal motivation for physical activity (p =0.08) was shown (Table 2). For the age group of women under 50, social interaction (sd 3.3) and social environment (sd 3.5) associated with mental health are important factors. This may be related to the narrowed network of social contacts of this age group, which is mostly limited to work and family contacts, also previous coronavirus outbreaks increased stress due to social distancing that might have impact on free time activities that were reported to younger group of women (sd 2.4) compared to women up to 50 (sd 0.9) at medium level.

The results has shown the significant impact of physical activity in patients with post-covid symptoms on individual body systems (Table 3). 46.7 % of people under the age of 40 and 51.3 % under the age of 50 confirmed the positive effects of mental health at a medium level (p = 0.024) compared to neurological aspects, on which physical activity had rather a low impact (p = 0.032). Physical activity had a significant impact on the musculoskeletal system (p = 0.040) and the cardiovascular system (p = 0.028), where respondents reported high scores. In the respiratory system there was no significant impact of the physical activity (p = 0.091).

Table 3. The impact of rehabilitation on mitigating the effects of post-covid symptoms

30 — 40 years old SD				41-50 years old SD			
Variable: Physical activity	Very low-to low	Low-Medium	medium-High	Very low-to low	Low-Medium	medium-High	p
Psychological	22.4 %	46.7 %	30.9 %	19.8 %	51.3 %	28.9 %	0.024
Neurological	38.9 %	30.2 %	30.9 %	42.3 %	35.4 %	22.3 %	0.032
Cardiovascular	19.6 %	31.3 %	49.1 %	17.6 %	28.9 %	53.5 %	0.028
Respiratory	35.7 %	34.9 %	29.4 %	37.2 %	37.2 %	25.6 %	0.091
Musculoskeletal	19.9 %	37.4 %	42.7 %	12.7 %	38.7 %	48.6 %	0.040
Others	31.2 %	35.2 %	66.4 %	32.7 %	36.3 %	31.0 %	0.105

DISCUSSION

Study Jimeno-Almazán *et al.* (2021) suggest that multiple and/or synergistic causal mechanisms may underlie post-COVID-19 syndrome. Genetic host factors, pre-existing lesions of COVID-19 targeting organs due to comorbidities and acute COVID-19 organ failure itself, may be involved. Cross-sectional studies (i.e., online survey) report a list of more than 200 different symptoms in the evolution of post-COVID-19 syndrome (David *et al.* 2020). Exercises and rehabilitation programs and physical activity level can reduce clinical manifestations and improve prognosis in many chronic diseases.

Thus, motivating patients to start with an exercise programme is a key challenge. However, whereas entering an exercise program is physically and mentally challenging in people with chronic pain, once the practice starts, making exercise a pleasant, fun and well-tolerated experience contributes in setting the routine and eventually achieving health improvements (Bilberg *et al.* 2020). Motivation and energy among people with post-COVID-19 syndrome plays key role, environment of rehabilitation programs help to empower women to go on and avoid overtraining by working out within individuals limits and allowing enough recovery time due to post-covid symptoms. Individual and targeted exercise is highly recommended as a non-pharmacologic strategy for treating rheumatic and musculoskeletal diseases, characterized by chronic pain, muscle weakness, physical limitations, fatigue and low tolerance to exercise (Jimeno-Almazán *et al.* 2021). Tomanek (2020) in his study highlights the aspect of accessibility, rehabilitation problems are often inaccessible to older people due to geographical distance, long waiting times and financial costs.

Physical training and excercises confer unique, multi-systemic benefits to the musculoskeletal system, improving both morphological (increasing number of sarcomeres in parallel, increasing the synthesis of contractile assemblies of actin and myosin and altering muscle fibres' composition) and neural (improving neurological system and intermuscular coordination) factors and regulating the whole body metabolism (Maestroni *et al.* 2020).

Results have shown positive impact physical activity on the mental well-being of women involved in the rehabilitation programs due to post-covid symptoms and this environment reduce their frustration, negative emotions and anxiety that they could easily and faster overcome compared to time during home-exercises.
No do nothave information about the post-covid syndrome at childen. Social-legal protection of children is an important matter in modern society, which implements principles assuring the best interests of children into its legal regulations (Lešková, Haburajová Ilavská 2021).

CONCLUSION

The physically active female patients with post-covid syndrome have better recovery period compared to unactive people, physical activity makes an postive impact on their mental wellbeing, reduce frustration and stress, enviroment of practicing exercises brings positive emotions empowering them o better adapt to changes health status due to Covid-19. Women over 40 prefer social interactions, only physical exerices at home do not affect them in the way compared with the interaction with trainers. Rehabilitation and exercises environment outside the household makes more postive impact on changing their exercise routine and creatives possive effects on the mental wellbeing.

Author contributions
The author hereby declares to be actively involved in the research and has approved its publication.

Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this article.

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The impact of the COVID-19 Pandemic on selected health indicators of clients in homes for the elderly

Vplyv pandémie COVID-19 na vybrané ukazovatele zdravia klientov v domovoch seniorov

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ABSTRACT

Introduction: In connection with the global outbreak of COVID-19, there is an urgent need to identify and understand its impact on the living conditions, mental and physical well-being of vulnerable population groups.

Aim of the study: To evaluate the impact of the COVID-19 pandemic on selected indicators of physical and mental health in vulnerable groups (seniors in senior houses and to propose appropriate interventions.

Material and methods: We assess the physical and mental health in the pilot sample of 74 clients using the Medical Outcomes Short Form-12 (SF-12v2™ Health Survey; MCS- Mental Component Scale, PCS — Physical Component Scale) together with a general Questionnaire for seniors.

Results: The average score of physical and mental health of seniors was below the average of the general population. Almost 60 % of seniors felt limited in their social activities, more than 50 % suffered from sleep disorders and felt sad, and more than 40 % had tearful periods. Nevertheless, more than 70 % are looking forward to the future. The MCS score was significantly positively affected if the respondents still feel needed and useful and do not restrict their social activities.

Conclusion: The living conditions of the elderly living in senior houses, anxiety and social isolation should be raised and appropriate interventions should be proposed. In the future we plan to enlarge the sample and to design appropriate intervention procedures.

Key words: Senior houses. COVID-19 pandemic. Questionnaire. Mental and physical health. Living conditions.

ABSTRAKT

Úvod: Po pandémii COVID-19 vyvstáva potreba pochopiť jej dopad na životné podmienky, duševnú a fyzickú pohodu zraniteľných skupín populácie.

Cieľ: Vyhodnotiť vplyv pandémie COVID-19 na vybrané ukazovatele zdravia u seniorov v domoch seniorov, upozorniť na ich životné podmienky, úzkosť a sociálnu izoláciu a navrhnúť vhodné intervenčné postupy na podporu ich fyzického a duševného zdravia.

Materiál a metódy: Hodnotíme fyzické a duševné zdravie klientov na pilotnom súbore 74 klientov pomocou dotazníka Medical Outcomes Short Form-12 (SF-12v2™ Health Survey; MCS- Mental Component Scale, PCS — Physical Component Scale) spolu so všeobecným Dotazníkom pre seniorov.

Výsledky: Priemerné skóre fyzického a mentálneho zdravia seniorov bolo pod priemerom všeobecnej populácie. Takmer 60 % seniorov pociťovalo obmedzenie svojich spoločenských aktivít, viac ako 50 % trpelo poruchami spánku a malo pocity smútku, viac ako 40 % mávalo plačlivé obdobia. Napriek tomu viac ako 70 % sa teší na budúcnosť. Skóre mentálneho zdravia významne pozitívne ovplyvňuje, ak sa cítia stále potrební a užitoční a neobmedzujú svoje spoločenské aktivity.

Záver: Na životné podmienky seniorov žijúcich v domovoch seniorov, na úzkosť a sociálnu izoláciu treba upozorniť a navrhnúť vhodné intervenčné postupy na podporu ich fyzického a duševného zdravia.

Kľúčové slová: Domy seniorov. Pandémia. COVID-19. Dotazník. Duševné a fyzické zdravie. Životné podmienky.

INTRODUCTION

The COVID-19 pandemic, caused by the coronavirus SARS-CoV-2, has claimed more than 6 million lives worldwide, infecting more than 600 million people. As of November 14, 2022, 1,854,371 confirmed cases of COVID-19 had been reported, and 20,676 people had died of COVID-19 in Slovakia (Worldometer, 2022).

The occurrence of COVID-19 was laboratory confirmed by the National Reference Laboratory for Influenza at the Public Health Authority of the Slovak Republic on March 6, 2020 and there was a long-term risk of spreading this communicable disease in the Slovak Republic.

In the first phase, it was necessary to prevent the introduction of this respiratory disease, which spread mainly by air, to patients hospitalized in hospital wards of health facilities, staff of health facilities, as well as to persons placed in social services, including staff of social services, because complicating the disease by this infection can seriously endanger the clinical condition of hospitalized patients or clients or endanger their lives. In connection with the global outbreak of this disease, there is an urgent need to identify and understand how this pandemic affects public health, living conditions, and the mental and physical well-being of vulnerable subgroups of the population in Slovakia. These groups include seniors, especially clients in senior houses. The vulnerability of seniors in residential facilities has also been potentiated due to the risk of the rapid spread of infections in social care homes, the severe course, and the high mortality rate of COVID-19 in polymorbid seniors (Danis, Fonteneau, Georges, et al. 2020). Quarantine measures, long-term isolation, and limited social contact with relatives have adversely affected clients‘ mental health (Yahya, Khawaja, 2020). These measures, which were supposed to protect them from infection, on the other hand, exposed them to extraordinary risk of depression and loneliness.

AIM

The aim of the study is to evaluate the impact of the COVID-19 pandemic on selected health indicators in vulnerable groups (seniors in nursing homes) living in the outbreak, to draw attention to their living conditions, anxiety, and social isolation and to propose appropriate interventions to support their physical and mental health.

MATERIAL AND METHODS

Sample

In the period from 15 May to 15 July 2021, a pilot study was carried out on a group of 75 seniors from the Senior House in Bratislava. There are 21.6 % males in the sample, 52.7 % widows/widowers, almost 80 % are seniors living alone, 44.6 % have secondary education and 14.9 have university education. Almost 90 % of seniors have children. The average age of seniors is 84.5 years, the youngest respondent was 65 years old and the oldest 99 years old. Almost half of the seniors were relatively mobile and lived in separate apartments, 27 percent moderately mobile, requiring partial nursing care, and almost 26 % with significantly reduced mobility requiring continuous nursing care (Tab.1). According to the statements of the responsible personnel, it was the group of moderately mobile seniors who were most exposed to the disease of COVID-19.

Questionnaire

Using the Slovak version of the international validated questionnaire Medical Outcomes Short Form-12 (SF-12v2™ Health Survey; MCS — Mental Component Scale, PCS — Physical Component Scale) in our pilot study we evaluated the physical and mental health of clients living in homes for the elderly in model Bratislava region.

The SF-12 is a well-validated and widely used 12-item survey that measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, and role limitations due to emotional problems, and mental health. The survey yields scaled scores for each of these eight health domains, and two summary measures of physical and mental health: the physical component summary (PCS) and mental component summary (MCS). Scores range from 0 to 100, with higher scores corresponding to better health. Although mean scores vary by age and gender, both PCS-12 and MCS-12 scales are transformed to have a mean of 50 and a standard deviation of 10 in the general population (Ware, Kosinski, Keller 1996; Kudielka, Hanebuth, Kanel et al. 2005).

The questionnaire is strictly anonymous and is used only for scientific purposes, or for the implementation of later qualitative research and possible corrective measures. The provision of data is voluntary, the data are statistically processed and evaluated in order to identify the problems and difficulties that clients in senior houses most often encounter and to design appropriate health promotion procedures. All provided data are protected in accordance with Act No. 18/2018 Coll. and EU Regulation 2016/679 (GDPR) of the European Parliament and of the Council on personal data protection. Clients participating in the survey signed an informed consent to participate in the study.

We distributed the questionnaire in cooperation with the management and employees of the selected Senior House in Bratislava. Respondents first filled out a general Questionnaire for seniors, with the help of which we briefly evaluated basic demographic, environmental, behavioral, and psychosocial factors in the given group.

Tab. 1. Characteristics of the pilot sample of respondents (n = 74)

Variable*	N	%
Gender		
Males	16	21.6
Females	53	78.4
Age (years) (average ± SD)	84.6 ± 7.5	
Marital status		
Single	4	5.4
Married/Partnership	13	17.6
Divorced	16	21.6
Widowed	41	55.4
Education		
Elementary	10	13.5
High school without certificate	20	27.0
High school with certificate	33	44.6
University and graduate	11	14.9
Offsprings		
No	8	11.0
Yes	65	89.0
Mobility		
Below average	19	25.7
Average	20	27.0
Above average (independent housing)	35	47.3

* Some data are missing in each variable category

Statistical analysis

The methods of desciptive and analytical statistics were used to identify mutual associations between the impact of the COVID-19 pandemic on selected indicators of senior health. We descriptively evaluated the obtained data in percentages and analyzed the interrelationships between the variables using bivariate analysis (t-test, chi-square test, analysis of variance for one factor — one-way ANOVA). The statistical significance level was set at $\alpha = 0.05$. Statistical packages EPI-INFO 7.2.2.16 and SPSS version 25 (International Business Machines Corp., New Orchard Road, Armonk, NY, USA) were used for statistical data processing.

RESULTS

According to the interim results of our pilot study on a group of 74 seniors from the Senior House in Bratislava, which took place in the summer of the year 2021, the average score of physical and mental health of seniors was below the average of the general population (PCS = 38.3 ± 10.7; MCS = 48.3 ± 12.9). Almost 60 % of seniors felt limited in their social activities, more than 50 % suffered from sleep disorders and felt sad, and more than 40 % had tearful periods.

More than 30 % of seniors considered their physical condition to be not very good to bad, and more than 60 % of clients considered their health condition to be fair to bad. More than 16 % of respondents considered their quality of life to be bad to very bad. More than 50 % of seniors had feelings of sadness and disappointment, and more than 50 % felt tired. Nevertheless, more than 60 % of them are engaged in hobbies and personal interests, more than 50 % have a feeling of necessity and usefulness, and more than 70 % are looking forward to the future (Tab. 2, 3).

The differences between males and females in the scores of physical and mental health were not significant, but there were significantly more women in the pilot group (78.4 %). Males have slightly higher physical health scores (PCS = 39.3 vs. 37.9) and lower mental health scores (MCS = 46.5 vs. 48.8) than females.

When comparing individual groups according to the degree of mobility and affected by the COVID-19, seniors with above-average mobility, living independently, have a significantly higher physical condition ($p < 0.01$), think they live healthier (p< 0001), better cope with routine duties ($p < 0.05$), have more hobbies and interests ($p < 0.001$). Both physical and mental health scores (PCS and MCS) were higher in independently living and moderately mobile respondents compared to respondents with low mobility. In the respondents from the group most affected by the COVID-19, we recorded higher PCS and MCS scores compared to the least mobile group, but lower MCS score compared to the group with the highest mobility. For mental health scores, these results were significant. Seniors with higher education, as well as those who have no problem coping with routine responsibilities, have significantly higher PCS physical health scores. The MCS mental health score is significantly positively affected if the respondents still feel needed and useful and do not restrict their social activities. These social activities, however, were significantly limited during the so-called COVID period.

Tab. 2. Selected physical health indicators in the pilot sample of respondents (n = 74)

Variable*	N	%
Physical condition		
Very good	4	5.4
Good	15	20.3
Average	25	33.8
Bad	20	27.0
Very bad	10	13.5
Body weight — subjective		
Adequate	39	53.4
Lower than should be	10	13.7
Higher than should be	27	32.9
Sleep quality		
Very good	16	21.9
Rather good	30	41.1
Rather bad	19	26.0
Very bad	8	11.0
Physical pain		
None	15	20.8
Very weak/weak	14	19.5
Medium	27	37.5
Strong/very strong	16	22.2
Coping with routine duties		
Yes	33	44.6
No	41	55.4
Poor performance		
Yes	47	64.4
No	26	35.6
Overall assessment of health status		
Excellent	0	0.0
Very good	2	2.7
Good	27	36.5
Persistent	35	47.3
Bad	10	13.5
Average score of physical health — PCS (Average ± SD)	38.3 ± 10.7	

* Some data are missing in each variable category

Tab. 3. Selected mental health indicators in the pilot sample of respondents (n = 74)

Variable*	N	%
Subjective quality of life		
Very good	6	8.2
Good	30	41.1
Average	25	34.2
Bad	9	12.3
Very bad	3	4.1
Feelings of sadness, helplessness, disappointment		
No	36	48.6
Yes	38	51.4
Presence of tearful periods		
No	42	56.8
Yes	32	43.2
Limitation of social activities		
Never	15	20.5
Seldom	13	17.8
Sometimes	16	21.9
Nearly always	14	19.2
Always	15	20.5
Hobbies		
Yes	45	66.2
No	12	17.6
I have lost interest	11	16.2
A feeling of tiredness		
No	32	44.4
Yes	40	55.6
A feeling of usefullness		
Yes	41	55.4
No	33	44.6
Looking forward to the future		
Yes	54	74.0
No	19	26.0
Average score of mental health — MCS (Average ± SD)	48.3 ± 12.9	

* Some data are missing in each variable category

DISCUSSION

There are not many publications on the impact of the COVID-19 pandemic on mental health. According to some authors, the mental health of the population deteriorated during the COVID-19 pandemic (Carr, Steeg, Webb, et al. 2021). Social isolation, depression, and anxiety have increased, especially in the elderly and disabled (Robb, de Jager, Ahmadi-Abhari, et al. 2020). The likely mechanism is that COVID-19-related limitations have led to disruption of daily routine, loss of social contact, and increased isolation and loneliness, which are important factors in mental illness (Santini, Koyanagi, 2021). A review published in The Lancet highlights the detrimental effect of quarantine on mental health but offers only limited advice on how to mitigate this effect (Brooks, Webster, Smith, et al. 2020). The living conditions of the elderly living in senior houses, anxiety and social isolation should be raised and appropriate interventions to support their physical and mental health should be proposed.

Online technologies and they use by seniors have proven to be a possible solution to their social isolation duasring the pandemic. The use of online technologies in senior houses has the potential to support mental health of the elderly in the future and can be used not only to maointain contact with relatioves and friends but also for cognitive behavioral online therapies and interventions (Armitage, Nellums, 2020). The results of a qualitative study examining the effects of the COVID-19 pandemic on the mental health, behavior, and social activities of the elderly pointed to mental health problems, such as fear, anxiety, social isolation, and inability to visit family, friends, physicians and sleep deprivation. Seniors stated keeping in touch with online technologies, engaging in hobbies, and watching television as useful strategies to deal witthe the negative impact of pandemics (Chakrawarty, Ranjan, Klanidhi, et al. 2021).

The study also benefits from its intervention character. As part of the qualitative research, we plan to conduct semi-structured personal interviews with clients, focusing on the areas of physical and mental health, which will be identified based on the results of the SF-12 questionnaire as the most affected. The aim of the qualitative research is to evaluate how clients in nursing homes have survived the COVID-19 pandemic period in detail, to assess its impact on their physical and mental health, and to promote and improve the physical and mental health of seniors living in senior houses during and after the COVID-19 pandemic.

In the future, we plan to expand our sample of respondents using a stratified random selection from the list of facilities for seniors maintained by the Bratislava Self-Governing Region. With an expected response rate of 70 %, we would like to get at least 350 respondents from the basic group of 500 seniors. The limitation of our study is precisely the lack of cooperation on the part of seniors and the difficulty of obtaining data using a questionnaire.

CONCLUSION

In this pilot study, we have evaluated selected indicators of physical and mental health in seniors living in houses for seniors during the outbreak of the COVID-19 infection. We drew attention to their living conditions, anxiety and social isolation. Based on the analysis of the results of quantitative and qualitative research and on the basis of published research results from other countries, we plan to propose appropriate intervention procedures to support their physical and mental health.

Conflicts of Interest:
The authors declare no conflict of interest in the connection with the published article.

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Comparative analysis of sample preparation methods for laser scanning cytometry

Porovnávacia analýza metód na prípravu vzoriek pre laserovú skenovaciu cytometriu

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ABSTRACT

Objective: Laser scanning cytometry (LSC) is a technology that combines some features of flow cytometry (FCM), digital microscopy and image analysis. The goal of the work is to verify methodological procedures for processing formalin-fixed and paraffin-embedded tissue, which would be suitable for the analysis of archival material

Methods: We processed tissues embedded in paraffin. 10 paraffin blocks with ovarian normal and carcinoma tissue. We prepared the monocellular suspension by enzymatic disintegration with 1 % pepsin. We used the method with heating and without heating.

Results and Conclusions: By comparing the results of two methodical procedures without heating and with heating of the tissue section, we found that the methodical procedure without heating is a more suitable method for the preparation of monocellular suspension.

Keywords: laser scanning cytometry, cancer, DNA analysis, cell cycle.

ABSTRAKT

Cieľ: Laserová skenovacia cytometria (LSC) je technológia, ktorá spája v sebe niektoré vlastnosti prietokovej cytometrie (FCM), digitálnej mikroskopie a obrazovej analýzy. Cieľom práce je overiť metodické postupy na spracovanie formalínom fixovaného a do parafínu zaliateho tkaniva, ktorý by bol vhodný na analýzu archívneho materiálu.

Metóda: Spracovali sme tkaniva zaliate do parafínu. 10 parafínových bločkov s tkanivom normálneho ovária a karcinomu ovária. Monocelulárnu suspenziu sme pripravili enzýmovou dezintegráciou s 1 % pepsínom. Použili sme metódu so zahrievaním a bez zahrievania.

Výsledky a záver: Porovnaním výsledkov dvoch metodických postupov bez zahrievania a so zahrievaním tkanivového rezu sme zistili, že vhodnejšou metódou na prípravu monocelulárnej suspenzie je metodický postup bez zahrievania.

Kľúčové slová: Laserová skenovacia cytometria. Nádorová choroba. DNA analýza. Bunkový cyklus.

INTRODUCTION

In the last twenty years, great progress has been made in the knowledge of the biology of human tumors, the range of diagnostic methods for tumor detection has expanded. One of the modern methods of investigating cell populations is cytometric analysis. It enables rapid characterization of cell populations and their fractions based on a number of parameters in various fields and applications, such as leukocyte immunophenotyping, protein expression, apoptosis studies, cell cycle analysis, proliferative activity determination, and tumor cell DNA content analysis. Cytometric analysis of cell populations can be performed in principle in two ways: flow cytometry (FCM) and laser scanning cytometry (LSC). The principle of both devices is based on the qualitative and quantitative evaluation of the light scattering of the laser beam and the laser-excited fluorescence emitted from cells stained with fluorochromes. FCM requires cells in suspension for analysis, while LSC analyzes cells fixed on a microscopic glass slide. Laser scanning cytometry (LSC) is a new technology developed by Kamentsky LA and Kamentsky LD (1991). By quantifying key features of selected cells in a sample, flow cytometry can contribute useful prognostic information. Since little cell loss occurs for sample preparation, LSC is particularly suitable for hypocellular samples. LSC can also be used to analyze histological sections. Samples can be destained and restained to measure additional attributes of the same cells. In addition, the LSC repositioning function allows each cell to be precisely identified according to its location on the slide

MATERIAL AND METHODS

It is possible to use samples of fresh, frozen and formalin-fixed tissue embedded in paraffin for cytometric analysis, as well as cytological material. It is necessary to prepare a cell suspension from the tissue. The cell suspension can be prepared by mechanical disintegration or by using proteases. The cells on the glass slide are stained with suitable fluorochromes. Fluorescent dyes that stoichiometrically bind to DNA (propidium iodide — PI, 7-amino-actinomycin D — 7-AAD) and fluorochrome-labeled monoclonal antibodies (e.g. fluorescein isothiocyanate — FITC, phycoerythrin — PE, tetramethylrhodamine isothiocyanate — TRITC, allophycocyanin) are most often used. When staining DNA, nuclear and cytoplasmic antigens, it is first necessary to permeabilize the cell membrane so that the reagents can penetrate inside the cell. Alcohols or aldehydes or detergents (saponin) can be used for permeabilization.

We obtained tissue samples embedded in paraffin from the archive of the Institute of Laboratory Investigation Methods of the VŠZaSP St. Elizabeth, in Bratislava. For analysis, we selected 8 blocks with different histological types of ovarian tumors (Figure 7) and 2 blocks of negative tissue from the ovary (Figure 1). Tissue samples were fixed in 4 % formalin and routinely processed and embedded in paraffin. We processed the tissue using a modified procedure according to Leers MPG et al (Leers MPG et al, 1999). From each block, we made two 50 µm thick sections on a sled microtome and placed them in two glass tubes. We deparaffinized the sections in two xylene baths for 30 minutes at room temperature. They were then rehydrated in 96 % alcohol, 70 % alcohol, and distilled water for 5 min each and rinsed in PBS solution (pH 7.2).

In the next step, we incubated the tissue in the first test tube for 60 minutes in a 1 % pepsin solution (Applichem GmbH, Darmstadt, Federal Republic of Germany) in 0.1 N HCl at 37 °C.

The tissue in the second tube was immersed in a cold solution of citric acid (2 mg/1 ml of distilled water, pH 6) and the tube was heated at 80 °C for 2 hours in a thermoblock (Stuart Scientific Bibby, Heverlee, Belgium). After heating, the sample was cooled at room temperature for 15 min, then rinsed in PBS solution and incubated for 15 min in a 1 % pepsin solution (Applichem GmbH, Darmstadt, Germany) in 0.1 N HCl at 37 °C.

After the incubation of the tissue in the pepsin solution, we carefully transferred the monocellular suspension from the test tube with a micropipette into a 10 ml centrifuge tube and centrifuged it for 5 min at 470 × g in an ALC® 4218 table centrifuge (ALC International SrI, Italy) at room temperature. The supernatant was aspirated and the cells were resuspended in 100 µl of PBS solution. We adjusted the cell concentration to 15 × 103 — 15 × 104 cells/ml. From this diluted suspension, 1 ml was transferred to a cytocentrifuge chamber (CytoFuge 2, model M801-22, StatSpin, Norwood, MA, U. S. A.) and the cells were centrifuged on a standard microscope slide (76 × 26 mm) for 8 minutes at 265 × g at laboratory temperature. The result of centrifugation was a uniform concentration of cells in the center of the slide on an area of 15 — 10 mm. The cells on the glass slide were then immersed for 5 minutes in concentrated methanol at 4 °C. We then dried the slides in air at room temperature and stained the cells with fluorochromes. We used the propidium iodide (PI) intercalation dye (Sigma-Aldrich, U. S. A.) to stain the nuclei. To determine the presence of cytoplasmic remnants around isolated nuclei from tumor cells, we stained eight samples with a monoclonal antibody against cytokeratins 8, 18 and 19 conjugated with fluorescein isothiocyanate (pan-anticytokeratin FITC) (MACS Miltenyi Biotec, Bergisch Gladbach, Federal Republic of Germany). Stained cell samples were mounted in pure glycerin and covered with a 24 × 32 mm coverslip. Cell samples were analyzed using a CompuCyte laser scanning cytometer (CompuCyte Corporation, Cambridge, MA, USA) coupled to a BX51 microscope (Olympus, Japan). The measured parameters were displayed in graphic form as scattergrams (PI max pixel/PI integral, PI max pixel/Area, PI integral/Area, Green max pixel/PI integral, Green max pixel/Green integral) and histogram (PI integral/number of cells). From the measured data, we evaluated the DNA index (DI) and the S phase fraction of the cell cycle (SPF). We determined the DNA index as diploid DI = 1.0, near-diploid 0.95; DI; 1.1, aneuploid 1.1; DI; 1.9, DNA tetraploid 1.9; DI; 2.05, hypertetraploid DI; 2.05. We evaluated cell cycle phase from DNA histograms after subtracting fragments from broken cells. We defined the S phase as low at SPF < 10 % and high at SPF ≥ 10 %. We compared the results of cell analysis obtained by two different procedures for processing material from paraffin blocks according to the amount of isolated cells, the stainability of nuclei with propidium iodide and the quality of histograms.

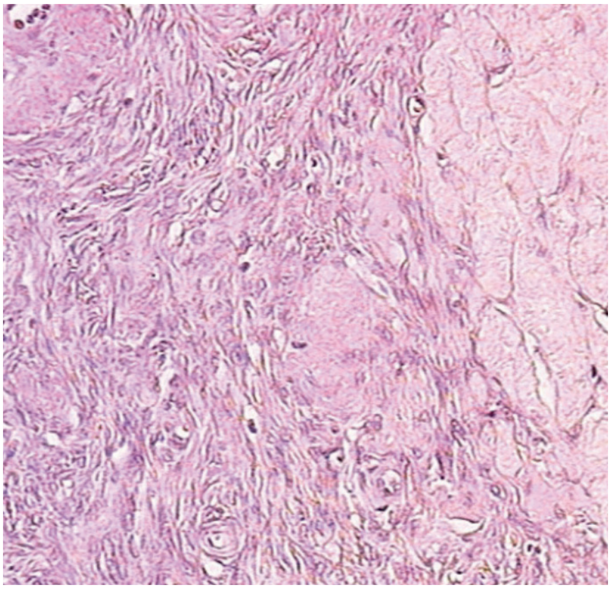

Figure 1. Ovary without neoplastic changes (block no. 1) (hematoxylin, eosin, × 100)

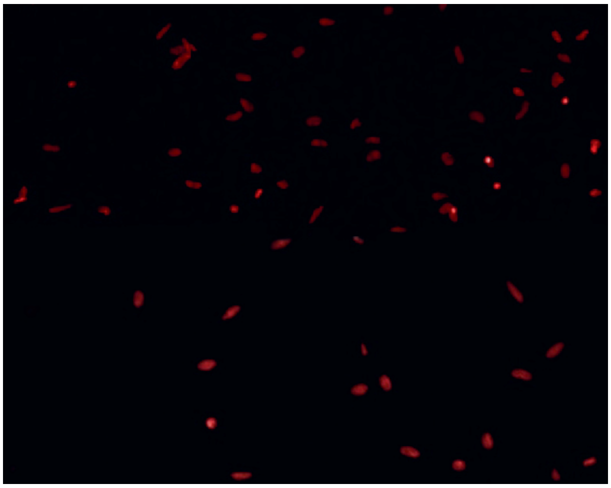

Figure 2. Suspension of cells from block no. 1
(1 % pepsin, PI, × 400) (1 % pepsin, PI, × 400) heating

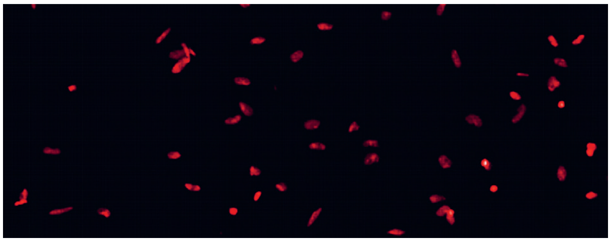

Figure 3. Suspension of cells from block no. 1

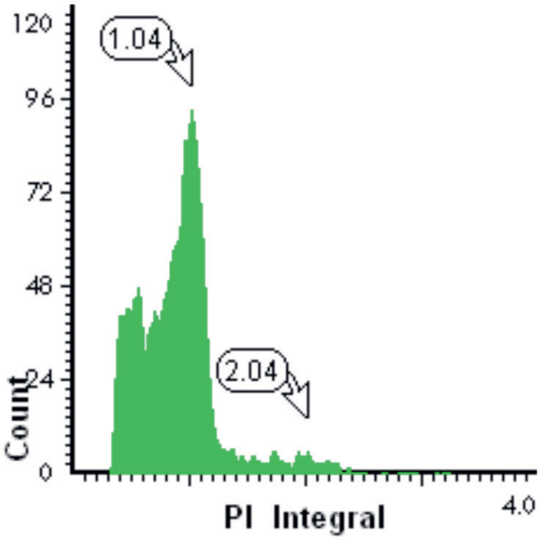

Figure 4. DNA histogram of cell suspension no. 1 pepsin

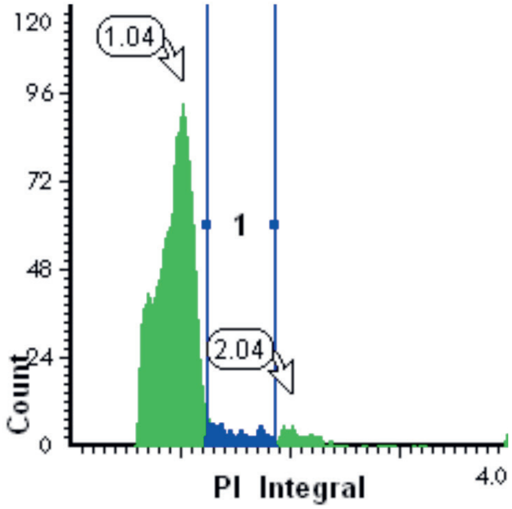

Figure 5. S phase (blue area) of cell n from block suspension block no. 1 pepsin

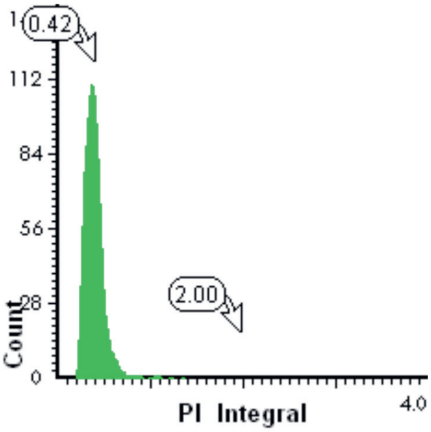

Figure 6. DNA histogram of cell suspension from block no. 1 (heating + 1 % pepsin)

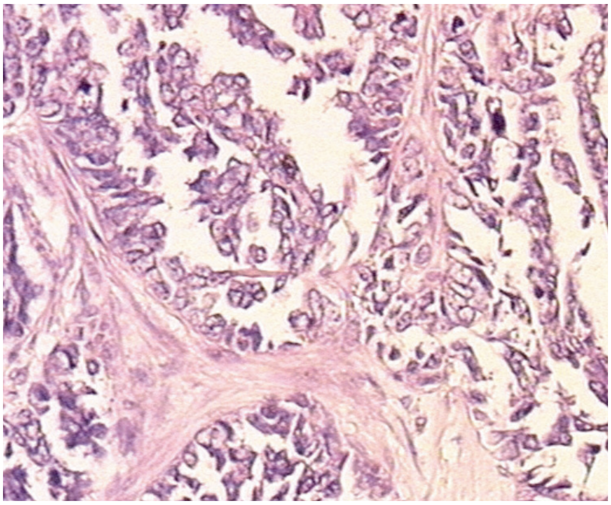

Figure 7. Serous papillary adenocarcinoma (block no. 3) (hematoxylin, eosin, × 100)

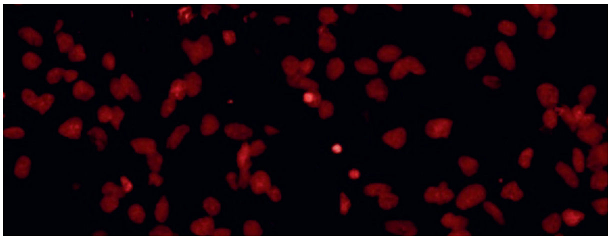

Figure 8. Suspension of cells from block no. 3 (1 % pepsin, PI, × 400)

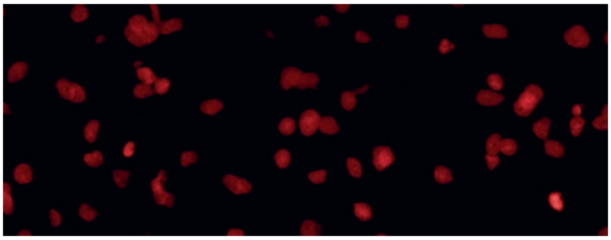

Figure 9. Suspension of cells from block no. 3 (+ 1 % pepsin, PI, × 400)

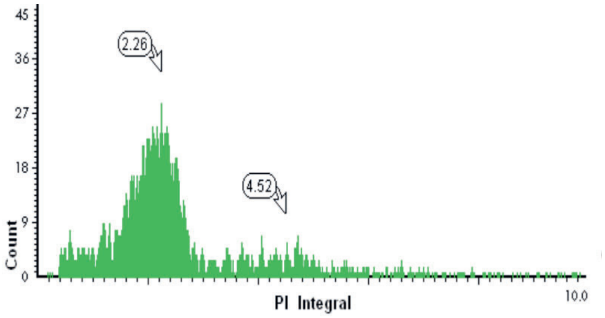

Figure 10. DNA histogram of cell suspension from block no. 3 (1 % pepsin)

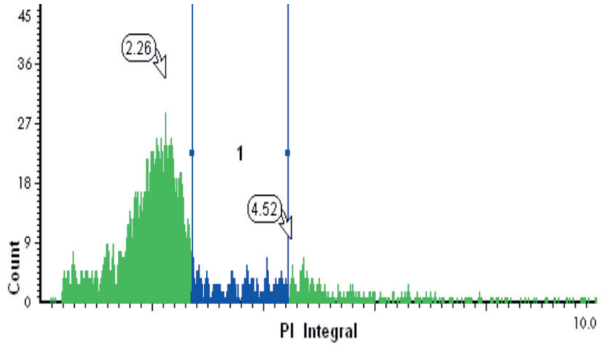

Figure 11. S phase (blue area) of cell suspension block no. 3 (1 % pepsin)

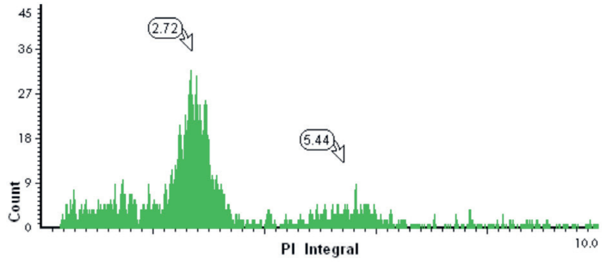

Figure 12. DNA histogram of cell suspension from block no. 3 (heating + 1 % pepsin)

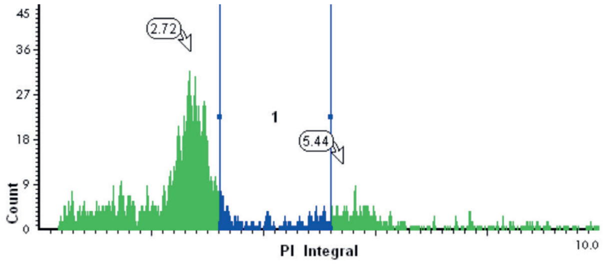

Figure 13. S phase (blue area) of cell suspension from block no. 3 (heating + 1 % pepsin)

RESULTS

The amount of isolated cells when processed by the method with digestion of the section with 1 % pepsin fluctuated in the range from 40.38 × 103/ml to 15.31 × 104/ml. When processed by the method with heating and subsequent digestion of the section with 1 % pepsin, the amount of isolated cells fluctuated in the range from 18.39 × 103/ml to 11.10 × 104/ml. The average number of isolated cells was higher in the first method (= 87.66 × 103 ± 33.12 × 103/ml) than in the second method (= 57.02 × 103 ± 31.77 × 103/ml). Thus, the method without heating the section had a higher cell yield.

The presence of destroyed and broken cells was higher in the method without heating than in the method with heating. The amount of aggregated cells and cell clusters was also higher in the non-heating method. Cell clumps and debris affected the analysis only to a lesser extent because they were filtered out during the analysis using the LSC software setting.

The morphological structure of the nuclei was better preserved in the methodical procedure without heating. Nuclei retained fine chromatin structure and nucleoli remained visible. Also, propidium iodide stainability of nuclei was better preserved with the method without heating (Figures 2,8) During the methodical procedure with heating, the chromatin of the nuclei condensed and the fine chromatin structure was lost, and the nuclei were also less visible (Figures 3, 9). The staining of the nuclei with propidium iodide was lower with this method, which was also reflected in the lower intensity of fluorescence and fluctuated considerably in individual sections compared to the method without heating.

DNA histograms were better analyzed using the non-heating method. In the method with heating, the position of the peaks fluctuated more during individual sections and repeated measurements, which was also related to the worse colorability of the nuclei (Figure 6, 10). The quality of the histograms with respect to the coefficient of variation (CV) of the peaks corresponding to the G0/G1 phase was higher in the method without heating. The average value of CV in the methodology without heating was 10.8 % ± 3.3 % and in the methodology with heating 12.2 % ± 3.6 %.

The DNA indices obtained by analyzing the monocellular suspension prepared by the method without heating were more conclusive and accurate (Figures 4, 10). The DNA index fluctuated more during the methodical procedure with heating. In the analyzed material from paraffin blocks of eight ovarian tumors, we determined 2 tumors as DNA diploid, 4 tumors as DNA aneuploid and 2 carcinomas as DNA hypertetraploid. In the method without heating, all DNA index values were representative. In the material processed by the method with heating, we considered 5 values of the DNA index to be unrepresentative, because they were located in the hypodiploid region and were lower compared to the values of the DNA index obtained by the method without heating. Determination of DNA content based on DNA index values obtained by both methods more or less coincided, if we do not take into account non-representative values.. We considered the DNA index value obtained by the method without heating to be authoritative, since all other DNA indices obtained by this method were representative.

When determining the percentage of S phase, we used the DNA histogram after deducting destroyed cells and fragments. Based on the percentage of S phase in negative ovarian tissue samples, we set the threshold value for low S phase to be 10 % and for high value above 10 %. In the analyzed material from ten paraffin blocks, we determined a low S phase value in five cases and a high S phase value in four cases. The result also correlates with the histological findings. Determination of the percentage of S phase obtained by both methods more or less coincided, but we consider the percentage of S phase determined from the cell suspension prepared by the methodological procedure without heating to be more conclusive, considering that the DNA histograms in the methodology with heating were shifted to the hypodiploid region (Figures 5, 11, 13).

To determine the presence of cytoplasmic remnants around isolated nuclei from tumor cells, eight samples were stained with FITC-conjugated monoclonal antibody against cytokeratins 8, 18 and 19. In neither case did we find cytokeratin positive cell subpopulations.

We used the relocalization ability of LSC in the analysis of the monocellular suspension from block no.3. The DNA histogram shows the presence of two populations of cells with different DNA index To confirm the assumption that the population of cells. The DNA histogram shows the presence of two populations of cells with different DNA index. To confirm the assumption that the cell population with DI = 0.98 is composed of stromal cells and leukocytes and the cell population with DI = 1.46 is tumor cells, we stained the sample with hematoxylin and eosin. Using relocalization, we searched for the same cells and according to morphological criteria, we confirmed that the population of cells with a lower DNA index consists of leukocytes and stromal cells, and the population with a higher DNA index consists of tumor cells (Figure 14).

DISCUSSION

Analysis of cell cycle and DNA content by area of interest and intensive study of tumor cells. Current knowledge suggests that in most solid tumors, abnormal DNA content (aneuploidy) and a high percentage of S phase may have a significant prognostic value and is associated with a more aggressive tumor behavior.

The analysis of DNA content and proliferative activity using LSC allows to examine a large number of cells, is objective and independent of subjective estimation (Pozarowski P et al 2013). Polychromatic LSC analysis of cells using multiple fluorescent dyes is particularly important for samples with low cell. The detection and quantification of several different fluorochromes using LSC is not developed to the same extent as with flow cytometry, which with the current technical equipment of FCM allows parallel immunophenotyping with up to seventeen fluorochrome-labeled antibodies. LSC on the other hand, allows repeated analysis of the same cells using relocalization ability and morphological assessment. Based on morphological criteria, distinctly different cells can be re-stained with other fluorochromes and re-searched by precise localization of individual cells on the glass slide and re-analyzed. The results from several analyzes can be merged into one data set and thus significantly increase the amount of information obtained from one cell. After conventional staining of the sample with hematoxylin and eosin, individual cells can be identified based on morphological criteria (Mittag, et al 2006). A problem with LSC analysis is the fading of fluorochromes. Scanning of the sample takes place more slowly compared to fast excitation in FCM. Due to the different range of photostability of fluorochromes, it is more appropriate to use fluorochromes with higher stability in LSC, or the different photostability can be used to increase the number of parameters analyzed in one sample (Tárnok et Gerstner 2002). A monocellular suspension of cells can be prepared by mechanical disintegration or by using proteases. Kamada et al. (Kamada et al 1997) used a grater for mechanical disintegration. Kamiya et al. (1999) used 0.25 % trypsin or 0.5 % pepsin for enzymatic tissue disintegration. In our work, we used the method according to Leers et al (1999) for enzymatic tissue disintegration. We adjusted the concentration of pepsin to 1 %, considering that we achieved a much lower cell yield at lower concentrations. Leers et al. (1999) obtained a higher yield of cells in the methodological procedure with heating of the tissue section and subsequent digestion with 0.1 % pepsin. In our case, the method with heating turned out to be less suitable, because we achieved a lower yield of cells than in the methodological procedure without heating. The values of the coefficients of variation of both methodological procedures are slightly higher than the published values (CV — 8 %) The coefficient of variation was low enough to distinguish diploid and near-diploid populations with the methodology without heating.

CONCLUSION

LSC enables the objective characterization and quantification of cell subpopulations and can help reveal the biological properties of tumor cells and thereby help refine the diagnosis and prognosis of cancer. It is a particularly suitable method for the analysis of clinical material with a small cell content, such as cytological material obtained in a minimally invasive

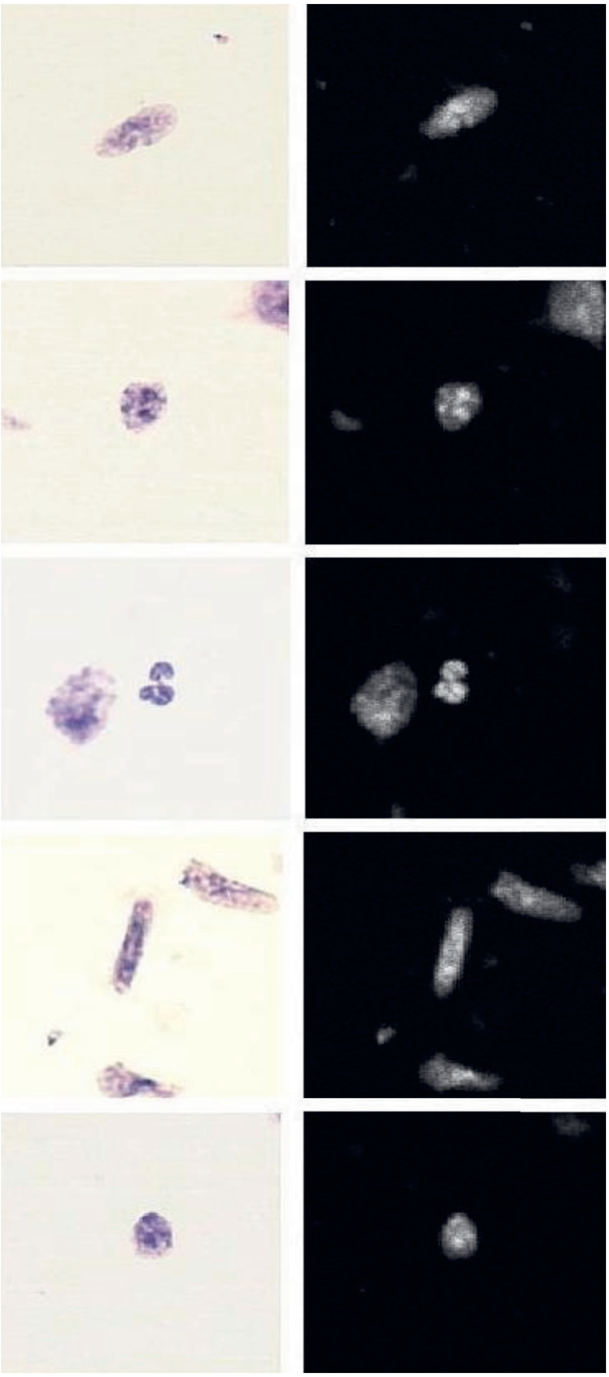

Figure 14. Relocalization of peak cells with DI = 0.98 from block no.3 hematoxylin, eosin, × 400; PI, × 400)

way. Through its relocalization ability and repeated staining with different fluorochromes, it enables the analysis of the same cells without significant loss of material. Determination of DNA content and immunophenotyping using LSC in cytological material helps in the differential diagnosis of atypical lesions. Current knowledge suggests that in most solid tumors, abnormal DNA content (aneuploidy) and a high percentage of S phase may have significant prognostic value and are associated with a more aggressive tumor behavior. We verified the appropriate method for processing formalin-fixed and paraffin-embedded tissue on a set of 8 paraffin blocks with different histological types of ovarian tumors and 2 paraffin blocks of negative tissue from the ovary. We prepared the monocellular suspension by enzymatic disintegration with 1 % pepsin. By comparing the results of two methodical procedures without heating and with heating of the tissue section, we found that the more suitable method for preparing monocellular suspension from formalin-fixed and paraffin-embedded material is the methodical procedure without heating

Autorship
All autors have read and approved the final version of the manuscript and all authors listed as co-workers met the criteria for author ship.

Conflict of Interest
The authors declared no conflict of interest in relation to the article.

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Radial nerve formation in the axillar region

Formovanie sa vretenného nervu v pazuchovej oblasti

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ABSTRACT

Introduction: The radial nerve is the terminal and largest branch of the posterior cord of the brachial plexus. It supplies the majority of the posterior and extensor components of the arm and forearm. There is little information about its possible variable formation in the axilla in the available literature.

Research objectives: The aim of our work was to elucidate the variability of radial nerve formation in the axillar region.

Material and methods: Our work was realised on 50 human bodies, whereas the brachial plexus was revealed on both sides (we analysed totally 100 of brachial plexuses).

Results: We have observed the communication of the radial nerve with the ulnar nerve in 2 cases (2 %) — 1 case on the right side, 1 case on the left side. We did not follow the further distal courses of the brachial plexus terminal branches. We confront our findings with similar works from the literature and give a possible embryological basis for the explanation of the variation presence.

Conclusion: Reports of the peripheral nerve's anatomical variations are important to medical personnel: especially to orthopaedists, traumatologists, neurophysicians, physiotherapists, radiologists, anaesthesiologists, anatomists or also to other medical specialists.

Keywords: Brachial plexus. Radial nerve. Formation. Variation.

ABSTRAKT

Úvod: Vretenný nerv je koncovou a najväčšou vetvou zadného zväzku ramennej splete. Inervuje väčšinu vystieračov a kože zadnej časti ramena a predlaktia. V dostupnej literatúre nie je veľa informácii o variáciách jeho vzniku v oblasti pazuchy.

Cieľ: Cieľom našej práce bolo ozrejmiť variabilitu vzniku vretenného nervu v pazuchovej oblasti.

Material a metódy: Naša práca bola realizovaná na 50 ľudských kadáveroch, pričom sme ramennú spleť ozrejmili na oboch stranách kadáveru (celkovo sme preskúmali 100 ramenných spletí).

Výsledky: Z celkového počtu 100 ramenných spletí sme našli 2 odchýlky vzniku vretenného nervu (2 %)-spojka s lakťovým nervom (1 vpravo a 1 vľavo). Distálny priebeh vretenného nervu sme nesledovali. Naše pozorovanie sme konfrontovali s výsledkami podobných prác a predkladáme aj možnú embryologickú príčinu variácií.

Záver: Údaje o anatomických variabilitách periférnych nervov (hlavne v pazuchovej oblasti) by mohli zaujímať lekárskych odborníkov viacerých špecializácií: obzvlášť ortopédov, traumatológov, neurológov, neurochirurgov, fyzioterapeutov, rádiológov, anesteziológov, anatómov a príp. i iných odborníkov.

Kľúčové slová: Ramenná spleť. Vretenný nerv. Vznik. Variácia.

INTRODUCTION

The radial nerve (C 5- 8, T1) is the largest branch of the plexus usually the continuation of the posterior cord of the brachial plexus. Supplies the majority of the posterior and extensor components of the arm and forearm. It innervates the triceps, anconeus, brachialis, brachioradialis, and extensor carpi radialis longus muscles and gives the posterior cutaneous nerve of the arm, lower lateral cutaneous nerve of the arm, posterior cutaneous nerve of the forearm (Marathe 2010, Standring 2008). Variations in the cutaneous innervation of the radial nerve are quite well documented in the literature, especially for the forearm and hand regions. But also axillar branching pattern of the brachial plexus terminal branches is important for various surgical traumatology, orthopaedics and anaesthesiologic blocks approaches.

RESEARCH OBJECTIVES

Our work aimed to identify the variability in the formation of the radial nerve from the posterior cord of the brachial plexus in the axillar region.

MATERIAL AND METHODS

The study was performed on 50 bodies not fixed previously in the Department of Forensic Medicine University Hospital Bratislava), and the approval of the University Hospital´s Ethic Committee was obtained before the beginning of our study. The brachial plexus was dissected and studied bilaterally on each body- we have analyzed 100 brachial plexuses. We have accessed the brachial plexus from the laid position of the body with the slightly abducted upper limb. A skin section was done from the lateral upper third of the sternocleidomastoid muscle to the medial third of the clavicle and then the cut was followed to the lateral side of the clavicle and via the deltopectoral line to the inner area of the shoulder until its lower third. The skin and subcutaneous tissue were removed and the supraclavicular part of the plexus was analyzed first. The preparation of the spinal nerves at the intraforaminal level up to the beginning of the dura mater by resectioning the tips of the transverse processes. In this case we need to isolate the lower plexus part such as the C 7 spinal root or the middle and inferior trunks truncus medius, et inferior, we removed the anterior scalene muscle attachment to the anterior tubercle or cut a part of the muscle. After the preparation of trunks and their branches, we separated the pectoralis major muscle approximately 2 3 cm from the clavicle and the clavicle itself from its medial to the lateral side. By this procedure, we revealed the clavipectoral axillar aponeurosis subclavius muscle and pectoralis minor muscle the inferior trunk truncus inferior and the medial cord fasciculus medialis. In the area covered by the pectoralis minor muscle the roots of the trunk were found one close to another surrounding the axillar artery. The incision of the pectoralis minor and major muscles enabled the reveal of the infraclavicular part of the brachial plexus all its pectoral nerves and also all terminal branches in a view. The formation of the fascicles was usually not higher than the lower margin of the clavicle. If variation was found we proceeded in our work by using the magnifier. We did not follow the distal courses of tach terminal branch.

RESULTS

In the supraclavicular and infraclavicular areas, we have found complicated nerve connections. Variations either supraclavicular or infraclavicular occurred more frequently on the left side. The simultaneous participation of the C 4 and T 2 roots in the formation of the brachial plexus was not found. Plexus was not the same on both sides, no perfect symmetry exists. In the older cadavers, the nerve elasticity and strength were markedly reduced during the preparation, and the nerves were more vulnerable like ”weak” (Figure 1A, Figure 1B). For the radial nerve in 2 (2 %) cases were observed an anastomotic branch to the ulnar nerve in 1 case (1 %) on the right side, and also in 1 case (1 %) on the left side (Figure 2A, Figure 2B).

DISCUSSION

The majority of the literature sources deal with variabilities in the forearm and hand cutaneous innervation distribution of the radial nerve (Tubbs 2016, Davidovich 2014, Cherchel 2013, Yogesh 2011). There are only a few papers dealing with the variabilities in the formation of the nerve in the axillar region which is also important for the

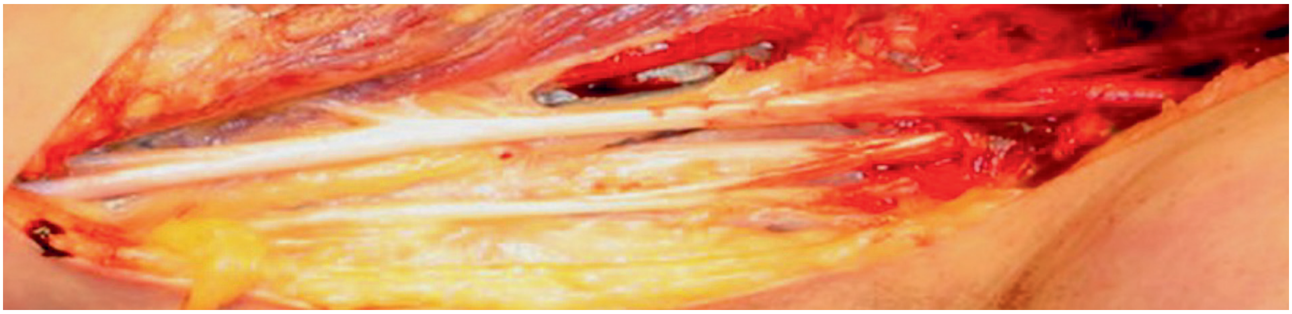

Figure 1A: Brachial plexus in the right axillar region: communicating branch of the radial nerve to the ulnar nerve.

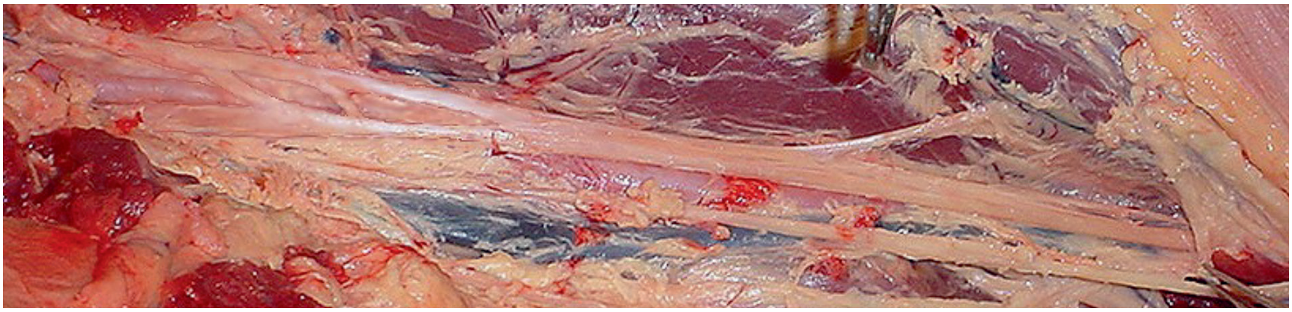

Figure 2A: Brachial plexus in the left axillar region: communicating branch of the left radial nerve to the left ulnar nerve.

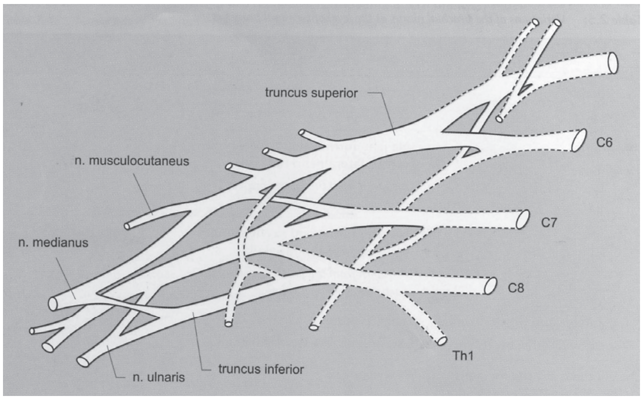

Figure 1B. Schematic illustration of Figure 1A.

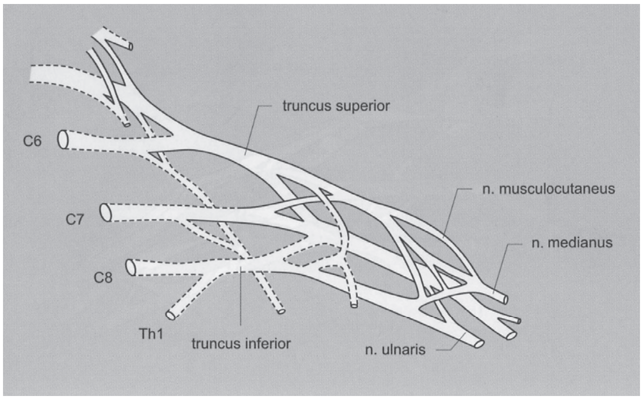

Figure 2B: Schematic illustration of Figure 2B.

traumatologist and orthopaedist performing surgeries for humeral fractures (Namking 2013, Yogesh 2011). Even Bergmann's Illustrated Encyclopaedia of the Human Anatomic variation deals more with the variations in the distal cutaneous distribution of the radial nerve, although in the text is mentioned the possible connections with the ulnar nerve but without the statistical expression and description (Tubbs 2016). As we have examined 100 brachial plexuses (on 50 cadavers) the statistical expression of the found variation was quite simple. Marathe et al. (Marathe 2010) reported an unusual communication between the radial nerve and the medial cutaneous nerve of the forearm in the axillar region. Namking et al. (Namking 2013) observed one case of the split and reunited radial nerve in the axilla forming a loop around the ectopic muscle probably a part of the latissimus dorsi muscle. Marathe (2010) and Yogesh (2011) also offer a possible embryological explanation of the presence of peripheral nerve variations: forelimb muscles develop from the mesenchyme of paraxial mesoderm in the 5th week of intrauterine life. The radial extensor muscles of the forearm have a different origin from other extensor muscles of the forearm. Regional expression of five Hox D (Hox D1 to Hox D5) genes is responsible for upper limb development. The motor axons arrive at the base of the limb bud they mix to form brachial plexus in the upper limb. The growth cones of axons continue in the limb bud. The guidance of the developing axons is regulated by the expression of chemoattractants and chemorepulsant in highly coordinated sight-specific fission. The tropic substances attract the correct growth cones or support the viability of the growth cones that happen to take the right path. Tropic substances include brain-derived neurotropic growth factor *c kit ligand*, *neutrin 1*, *neutrin 2* etc. Significant variations in nerve patterns may be the result of altered signalling between mesenchymal cells and neuronal growth cones or circulatory factors at the time of fission of brachial plexus cords.

CONCLUSION

Clinical significance knowledge of possible variations of the brachial plexus branching patterns in the axillar region may be helpful, especially in the management of traumatological and orthopaedic surgeries of the shoulder joint and arm avoiding possible iatrogenic damage during reconstructive and repair operations in the axillar region. Such comprehension is useful also in nerve grafting and neurophysiological evaluation for diagnosing peripheral neuropathies (Marathe 2010).

Conflict of Interest: none

Financial support: none

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Expectations of participants in biobanking research – review study

Očakávania participantov v biobankingovom výskume – prehľadová štúdia

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ABSTRACT

Introduction: Several experts in Slovakia point to the need for participation in international biobanking structure. Sociology of biobanking focuses on various issues of biobanking research.

Objectives: The aim of this study is to identify key findings on expectations of biobanking participants (donors, public) based on a review study of the findings published in PubMed database.

Findings: Several specific areas of expectations of biobanking participants were identified, as a) expectations of participants of information, overview and transparency of biobanking research, b) expectations of individual and family benefits of biobanking, c) expectations in the area of the common good, d) expectations type of consent, controllability and clarity of data. Key moderating variables of biobanking expectations were identified, as sociodemographic variables of age, education, nationality, religiosity, and perception of the legitimacy of participation in biobanks, trust in scientists and institutions as well as a specific tissue type.

Conclusion: Expectations of participants in the biobanking were followed as one of the factors biobanking participation in addition to institutional support, awareness, information sources and perception of risks in biobanking. Specific areas of expectations and mediating variables of biobanking participants were identified. The study includes recommendations for future research in the field of expectations in biobanking.

Key words: Biobanking. Expectations of participants in biobanking. Genomic data sharing. Donors. Tissues.

ABSTRAKT

Úvod: Viacerí odborníci na Slovensku poukazujú na potrebu participovať v medzinárodných biobankových štruktúrach. Sociológia biobankingu sa zameriava na viaceré otázky spojené s participáciou v biobankingovom výskume.

Ciele práce: Cieľom tejto štúdie je identifikovať kľúčové zistenia v oblasti očakávaní darcov, verejnosti (participantov v biobankingu) na základe prehľadovej štúdie zistení publikovaných vo databáze PubMed.

Zistenia: Na základe prehľadovej štúdie zistení publikované v database PubMed boli identifikované očakávania participantov v biobankingu v nasledujúcich oblastiach: a) očakávania participantov v oblasti informovanosti, prehľadu a transparentnosti výskumu, b) očakávania v oblasti individuálnych a rodinných benefitov biobankingu, c) očakávania v oblasti spoločného dobra, d) očakávania v oblasti typu súhlasu a kontrolovateľnosti dát. Identifikované boli kľúčové sprostredkujúce premenné očakávaní participantov v biobankingu, ako sociodemografické premenné veku, vzdelania, národnosti, religiozity, vnímania legitimity participácie v biobankingu, dôvera vedcom a inštitúciám a typ tkaniva

Záver: Očakávania darcov a verejnosti v biobankingovom procese boli sledované ako faktor participácie v biobankingovom výskume popri inštitucionálnej podpore, informovanosti, informačných zdrojov a vnímaní rizík spojených s biobankingom. V práci boli identifikované špecifické oblasti očakávaní participantov v biobankingu a ich sprostredkujúce premenné. Štúdia obsahuje odporúčania pre ďalší výskum v oblasti očakávaní darcov a sociológie biobankingu.

Kľúčové slová: Biobanking. Očakávania participantov v biobankingu. Zdieľanie genomických dát. Darcovia. Tkanivá.

INTRODUCTION

In contemporary society, changes in the qualitative and quantitative environment are emphasized also in the medical field. The available and high-quality information can expand the possibilities of personalized medicine and the development of new treatment and diagnostic procedures (Kajo K *et al.* 2016). The main purpose of creating databases based on the connection between genotypes and phenotypes, accessible for various research projects — a biobank — is aimed at improving diagnostics, prevention and treatment (Henderson *et al.* 2013). Biobank can be defined as „collection of human biological samples and stored and regulated for use in scientific studies by linking the sample to the donor's phenotypic and demographic data" (Henderson *et al.* 2013, p. 2). Various types of biobanks include population-based biobanks that focus on a long-term storage of biological samples (e.g. blood or DNA) of healthy individuals of a certain population (located e.g. in Iceland, UK, Sweden, Denmark, Latvia, Estonia, Canada, South Korea, Japan, Singapore, USA (DeSouza, Greenspan 2013), or disease-oriented biobanks, that focus on biological material of patients with certain diseases, e.g. of tumor tissues and cells. The estimated number of European tissue biobanks is over 200, including at least 70 internationally recognized initiatives. For blood and DNA, the numbers are even higher (Yuille 2008). A significant increase in biobanks occurs after 1990 as well as research interest in biobanking. There is „only one registered tumor tissue biobank also in Slovakia, which has been operating since 2012 and several unregistered tumor repositories that operate especially at academic institutions" (Kajo K *et al.* 2016, p. 372).

Biobanking research has become a relevant subject of interdisciplinary scientific interest in many countries (D'Abramo, Schildmann, Vollmann 2015), focused on psychological, sociological and economic aspects of the activity of biobanks in various social environments. Several studies applied sociological foundations to analyse donation process, as e.g. different sociological approaches were used in research on the donor population (people with a serious illness vs. healthy donors vs. ethnic group), the type of donated tissue (e.g. tumour vs. blood vs. DNA), as well as in connection with donation (recruitment of patients with non-commercial by intention vs. within a commercial biobank)" (Lipworth, Forsyth, Kerridge 2011, p. 806). As stated by the authors, a range of research possibilities supports the development of a „more detailed and nuanced 'sociology of biobanking' (Lipworth, Forsyth, Kerridge 2011, p. 792).

Several review studies on biobanking were published in professional databases, focusing e.g. on participants' perceptions and preferences on consent types (D'Abramo, Schildmann, Vollmann 2015; Garrison et al. 2016), or public attitudes toward biobanking (Domaradzki, Pawlikowski 2019; Shabani, Bezuidenhout, Borry 2014), as well as on qualitative biobanking research studies (Lipworth, Forsyth, Kerridge 2011).

This study brings findings on various types of expectations of donors and the public in biobanking in relation to their mediating variables based on review studies in examined area, in order to contribute to the awareness of the expectations of the donors and public in biobanking and to the information flow among biobanking research participants.

OBJECTIVE

Participation in biobanking can be analysed in the optics of donors, of medical professionals as well as in the optics of public. In this study, various expectations of participants — actual donors and the public (potential donors) have been followed based on a systematic research of quantitative and qualitative studies published in the PubMed database in the period May-June 2021.

Using the terms „expectations of donors in biobanking", 41 studies were identified and 493 studies were identified using the search term „expectations in biobanking" in the PubMed database. Subsequently, review studies focused on genomic data sharing and participants' expectations in biobanking were also included in the meta-analysis. Studies that did not contain an abstract and those that were identified after the initial review of the abstract as focusing on specific problems in the field of professional medical research, were not included in the meta-analysis. Finally, 91 studies were included and analysed in the area of expectations of donors and the public in biobanking.

The research questions were set as follows: 1. What kinds of expectations of biobanking participants (donors, public) can be identified based on review of studies in examined area? 2. What mediating variables of participants' expectations can be identified? 3. What practical conclusions and recommendations for the further research can be drawn?

FINDINGS

Expectations of participants in biobanking represent one of the key factors of biobanking participation, e.g. in the area of perception of threats or consent types preferences. According to the UTAUT model of acceptance and use of innovations (Venkatech *et al.* 2003), factors of biobanking participation also may include a) perception of concerns and possible risks and threats associated with donation, b) supporting factors e.g. public discourse, availability of information sources and c) social factors e.g. membership in the patient or support community, family and friends support.

Based on the review of the studies in examined area, expectations of donors and public in biobanking include

a) expectations of donors and public in area of overview, transparency and awareness of biobanking research, b) expectations of donors and public in the area of individual and family benefits of biobanking, c) expectations of donors and the public in the area of the common good, d) expectations of donors and public regarding the type of consent, controllability and clarity of data.

Based on the available findings of expectations in biobanking, also mediating variables need to be considered in participants' expectations such as sociodemographic variables of age, education, nationality, religiosity, perception of legitimacy of participation in biobanking, trust in research institutions and a type of a tissue.

Expectations in the field of information, overview and transparency of biobanking research

According to the authors (Shabani, Bezuidenhout, Borry 2014), the main areas of research in biobanking expectations include expectations of controllability and overview of personal data as well as the concerns regarding data protection and their sharing.

Biobanks have become a source of biological data, data on phenotypes, clinical aspects, but also on lifestyle, exercise or nutrition (D'Abramo, Schildmann, Vollmann 2015). As the authors state, „the most anticipated benefit resulting from biobanking was the increase in knowledge about many diseases and the development of new therapies" (Domaradzki, Pawlikowski 2019, p. 4). As presented by the focus group participants of a study, „there does have to be an open exchange of information in order for some of these really significant things to happen for people's benefit" (Trinidad, Fullerton, Bares 2010, p. 4). Participants declared the requirement of sufficient transparency of the information, the interest in more specific information about the method of storing tissue samples, the storage of genomic data itself, and the ways in which the obtained data will be used in the future.

According to the authors, perception of the legitimacy of the proposed way of using the data is related to how the respondent understands what will happen with his data — as stated by the authors, „the large majority of these participants were interested in understanding study goals, finding out about what might be learned along the way, and being kept abreast of how their contributions may be used to advance knowledge" (Trinidad, Fullerton, Bares 2012, p. 9). Similarly, also in other cultural environments, participants who are willing to donate samples for social benefit and good expect more information about the intentions of biobanks (Heredia *et al.* 2017).

Respondents differ in their attitudes towards the end use of the data and the degree of controllability of the provided data, especially with regard to their possible future commercial use. A specific issue in the field of informing participants is the ethical and psychosocial aspect of informing parents about their children's samples data. According to a qualitative study of the authors, parents considered genomic information to be important, expecting this information to be recorded in a child's health record and used to protect their child's health (Kulchak *et al.* 2018).

As stated by the authors, „a possible way to inform about the risks associated with research is to inform about several possible alternative types of consent to tissue donation" in addition to the broadly defined type of participant consent to tissue donation and the sharing of their genomic data even in repeated research projects (D'Abramo, Schildmann, Vollmann 2015, p. 8).

Expectations of participants in the field of individual and family benefits of biobanking

Benefits of biobanking were perceived as significant with respect to future generations, families of participants as well as donors themselves (Kettis-Lindblad Å *et al.* 2006; Toccaceli V *et al.* 2009; Mezinska, Kaleja, Mileiko 2020; Etchegary *et al.* 2015; Tith *et al.* 2020). The potential benefit to family members is an important motivation for potential donors as „the relatedness to relatives or other types of close relationships played a significant role in the donors' motivation to be involved in a biobank, risk-benefit assessment, and decisions on sharing information on research and its results (Mezinska, Kaleja, Mileiko 2020, p. 1).

Donors' relationships with friends and relatives has been examined in relation to decision-making in biobanking participation (Mezinska, Kaleja, Mileiko 2020). The importance of family and friends support in decision to participate in biobanking is related to the fact that" for some (potential donors) it is easier and more meaningful to assess the risk-benefit ratio of participating in a biobank in the context of personal benefits or benefits to their relatives or friends, who in some cases may even be members of the research team" (Mezinska, Kaleja, Mileiko 2020, p. 2).

Family membership can also affect expectations of feedback on research findings (Barazzetti *et al.* 2017). Similarly, according to a study in a Chinese setting on a sample of 508 parents of children with heart disease, the most common expected benefit was a potential benefit to the children, with 86 % of parents wanting to be informed about the results of research involving their children's samples (Gao *et al.* 2018, p. 1).

Perception of the benefits of genomic information open sharing may prevail over concerns of loss of privacy (Lipworth *et al.* 2009, D'Abramo, Schildmann, Vollmann 2015, Trinidad, Fullerton, Bares 2010) when even those who expect benefits from participation in biobank activities also perceive possible threats and risks. However, the collection of data on a large scale among some participants reduced the degree of concern about possible risks from the identifiability of individual data (Trinidad *et al.* 2010).

Expectations of donors and the public in the area of the common good

One of the significant issues of biobank expectations studies is to what extent the benefits of donation are understood on an individual level, and to what extent it is rather understood as a contribution to the common good. For example, according to the qualitative findings of review studies, „people can be motivated to donate by a broader sense of citizenship, altruism and pragmatism” (Lipworth, Forsyth, Kerridge 2011, p. 7), as well as by „altruism, solidarity, reciprocity and gratitude” (Richter *et al.* 2017, p. 5).

The studies confirm differentiated estimates of altruistic attitudes and motivation of donors in various environments. According to the representative survey of the US population, 11.7 % of respondents were willing to donate their data altruistically, compared to 50.6 % willing to provide data in case they are financially compensated, and 37.8 % were not willing to provide data regardless of compensation (Briscoe *et al*. 2020, p. 1). Similarly in the US environment, 10 % of respondents had no expectations for individual benefits from the results of biobank research (Ormond *et al.* 2009).

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As reported by the study in the UK environment, „the public reflects the importance of biological citizenship, the contribution of knowledge to future generations or the family line, and the willingness to help others”. As presented by the authors, participants perceive helping other people with a similar problem as a benefit of sharing genomic data and contributing to cooperation for the common good, assuming that the amount of information obtained must have a positive impact for everyone (Trinidad, Fullerton, Bares 2010). However, especially in the case of acceptance of a more broadly defined type of consent, it is confirmed that „the perception of benefits prevails over the perception of risks” (Ludman *et al.* 2010, p. 2).

The concept of donation (in the context of donated tissue) is viewed critically in studies (Locock, Boylan 2016; Sharp, Randhawa 2014), with the authors pointing to the importance of reciprocity as part of the biobanking process — although „altruism has featured explicitly as an underpinning principle for biobanking, conceptualizing donation as altruistic downplays the role of reciprocity and personal or family benefit (Locock, Boylan 2016, p. 1).

Participants' expectations of benefits in the area of common good are also related to the preferred type of consent for the use of data in biobanking to a research institution. According to the authors, „the assessment of risks of a broad type of consent is associated with a perception of solidarity and an obligation to support medical research after considering the risks and benefits” (D'Abramo F, Schildmann, Vollmann 2015, p. 8). Similarly, based on the findings of qualitative studies, it is generally accepted that research results should be shared, as they are important research results associated with high trust, expectation of reciprocity and sharing of research benefits (Lipworth, Forsyth, Kerridge 2011).

In a context of „therapeutic misconception”, the empirical findings are available according to which many respondents confuse participation in the biobank with medical examinations, diagnostics or treatment To what extent are the expected individual benefits overestimated as a result of a possible misunderstanding of the nature of biobanking, or as a result of a mistaken confusion of the research intentions with a therapeutic and treatment intention (therapeutic misconception), it is investigated in studies (Vaz, Srinivasan 2015, Henderson *et al.* 2007). Attention is drawn to the fact that an informed consent should contain a clear definition of the difference between research and medical practice to avoid the mistake when „individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the participants in research may potentially benefit from the given clinical research” (Henderson *et al.* 2007, p. 2).

Expectations of donors and the public in the field of consent — type of consent, controllability and clarity of data

Several studies monitor participants' expectations regarding the preferred consent type and its subsequent use in research activities, that represent one of the most discussed topics in biobank research (D'Abramo, Schildmann, Vollmann 2015). Expectations of donors towards the open sharing of obtained data and the possible de-identification of participants are differentiated. In general, a higher willingness to participate in the activities of biobanks is associated with a higher readiness to open share of genomic data, as e.g. those who perceive possible threats in the area of privacy and the availability and security of their personal data prefer specific and more narrowly defined forms of consent (Kaufman *et al.* 2009).

The form of consent for donation can take several forms, from open (broad) consent, with providing the opportunity to freely examine the collected tissue without requiring additional consent for re-use of the tissue, to narrower, multi-layered types of consent, which allows participants to opt out of those types of research with which they will not agree. The possibility to choose different types of consent is generally perceived as positive, as e.g. respondents stated they „feel respected and involved and „feel in control" if they were asked to consent to subsequent new research activities" (Kaufman *et al.* 2009, p. 9). If there are multiple forms of consent, it can therefore be assumed that offering these options is a suitable way to form long-term and sustainable relationships between those who participate in the research and conduct it.

As presented by the authors, new innovative forms of consent are flexible and dynamic consent through ICT, which can be used to hold interactive and flexible contacts between researchers and participants (D'Abramo, Schildmann, Vollmann 2015). This form facilitates informing and obtaining renewed consent in the case of new research purposes, or sharing genomic data with other research organizations. The advantage of this type of consent is the support of public trust, effective feedback according to the individual interest of the participant and strengthening of the transparency and reliability of research processes (D'Abramo, Schildmann, Vollmann 2015, p. 12). The difficulties that may appear in relation to re-consent cover possible large costs, problems in contacting research participants (for example, because of missing or incorrect contact information), and non-return of reconsent forms, as well as emotional reactions linked to perceiving violation of privacy" (Dixon-Woods *et al.* 2017). However, the findings of the qualitative study of the authors indicate that the future consent agreements „should be sensitive to the cooperative values that participants see as guiding their relationships with longitudinal biobank" (Dixon-Woods *et al.* 2017, p. 9). Authors of the study suggest avoiding rigid models and prefer „graded initial agreement with oversight mechanisms.. (including) participant involvement, to determine when new consent is needed" (Dixon-Woods *et al.* 2017, p. 9).

Donors' expectations differ according to their attitudes towards use of data as well as their expectations of control over data use and attitudes towards commercial use of genomic data. Although donors may perceive the use of genomic data by commercial biobanks as contradictory in contrast to the altruistic motivation of donors (Shabani, Bezuidenhout, Borry 2014) and pharmaceutical industry sponsorship of biobanks has been shown to be a relevant factor in deciding the type of consent (D'Abramo, Schildmann, Vollmann 2015), a qualitative meta-analysis findings confirmed that few studies found „that donors believed that commercial researchers or entities should be completely prohibited from accessing public biobanks, provided that the benefits of their research would be shared" (Lipworth, Forsyth, Kerridge 2011, p. 800). Especially in the context of trust towards biobank institutions and researchers, a broader consent can be a way for the participant to participate in the „moral exchange" between donors, research organizations and the social environment (Lipworth, Forsyth, Kerridge 2011). The emphasize is put on the diversification of the group of donors and the specific social context of participation in biobanking:"..the tissue type, the collection situation, including who is asked to give consent, and the geographical, social and historical context of the biobank influence the attitudes of various potential donors for consent, re-consent and feedback from research results" (Hoeyer 2010, p. 345). Diversified consents could also include the possibility of expressing differentiated expectations in research results feedback, as the importance of feedback in biobanking has been confirmed in various cultural environments (Tindana *et al.* 2020; Mwaka *et al.* 2021; Murphy *et al.* 2008; Vermeulen *et al.* 2018; Porteri *et al.* 2014).

However, expectations of participants for feedback are also differentiated, varying from those emphasizing the transparent and sufficient information about the tissue research methods (Vermeulen, Boeckhout, Zielhuis 2014) to those who do not request this information at all (Vermeulen *et al.* 2018). For example, according to the findings of a study in the Dutch environment, „the majority of surveyed respondents would request information on findings for both curable (92 %) and incurable (76 %) diseases, while acknowledging that the process of informing can be difficult for practical reasons" (Vermeulen *et al.* 2018, p. 178). Similarly according to a study by the authors, the request for feedback on individual findings was correlated with the willingness to donate in the German environment (Richter *et al.* 2017). The declared prosocial motivation of donors (e.g. altruism, solidarity, reciprocity, gratitude) does not appear to be mutually exclusive with the requirement for feedback and reporting on individual research findings.

In the part of the studies, the majority of participants studies preferred one of the more narrowly defined types of consent emphasizing understanding of research details and individual rights of donor, especially if they were offered these options (Oliver *et al.* 2012; McGuire *et al.* 2011; Valle-Mansilla, Ruiz-Canela, Sulmasy 2010). On the contrary, the findings confirm the preference for a broad type of consent by the authors, „with 85.9 % of blood donors as research participants who stated that they would accept research supervision by ethics committees within a broad type of consent and did not insist on individual supervision in this area", accepting the transferred responsibility for the use of biological data (Hoeyer *et al.* 2005, p. 97). High levels of trust in professionals and willingness to donate were documented on a sample of oncology patients (Yip *et al.* 2019). Similarly, a case study of the biobank closure confirmed the interest of the respondents in providing samples to another biobank especially for research purposes (Peppercorn *et al.* 2019), however not for the purposes of commercial profit (Allen *et al.* 2017). According to the authors' analysis, participants should be asked for their consent „in a sensitive way that takes into account their expectations and concerns, and should not be burdened with too much technical detail or asked for project-specific consent before they themselves express an interest, provided that they know about this possibility" (Lipworth, Forsyth, Kerridge 2011, p. 802).

Participant expectations include access to up-to-date information on biobank research and the possibility of contact researchers and of communication via social networks and the Internet. Dynamic interactions between participants and researchers using ICT technologies can have a practical impact on the efficiency of the biobanking recruitment process, as e.g. based on findings that sending a message about the use of donated plasma increased the subsequent repeat donation of plasma by 3.6 % compared to a group of donors who were not informed about the use of their samples (Fosgaard *et al.* 2020, p. 460).

Empirical findings on incomplete awareness of the details the consent content granted by participants over time has been identified (Watanabe *et al.* 2011; McCaughey *et al.* 2016), e.g. in the area of possibility of withdrawal of donation consent (Watanabe *et al.* 2011).

Social context of donation — embedding donation in relation to the highest cultural values — legitimizing participation in biobank activities as a mediating variable

The concept of expectations in biobanking requires the specification of how these expectations are distributed in various social environments. Although donation is an individual act, it needs to be perceived in its social context — e.g. cultural patterns may presuppose different preferences for types of informed consent, as documented by the authors' findings on expectations of patients with rare diseases from different countries (McCormack *et al.* 2016).

A stated by the authors, „the appropriateness of using the term participation to reflect donation as a highly social process with many meanings" (Lipworth, Forsyth, Kerridge 2011, p. 801). Pointing to the variety of social contexts of people's decisions to donate and its ethical dimension, donors can e.g. understand the act of donation as a moral „negotiation" between the donor and the medical professional (Hoeyer, Lynöe 2006; Hoeyer 2010). In the motivation of donors in this context, „there is an emphasis on self-discipline, solidarity, trust, in which patients combine their own personal expectations with consideration of societal benefits — thus viewed, the motivation for transfer exposes an inter-subjective negotiation" (Hoeyer, Lynöe 2006, p. 5).

Based on a meta-analysis of qualitative studies, participants do not always require narrowly defined consent and are willing to provide their data without further participation in the responsibility for reuse of donated tissue (Lipworth, Forsyth, Kerridge 2011). Thus, perception of the legitimacy of participation in biobanking and perception of its societal benefits both act as a mediating variable of the preferred type of consent — donor do not always require personal benefit, being motivated by a"broader sense of citizenship" (Lipworth, Forsyth, Kerridge 2011, p. 8).

When deciding on participation in biobanking, the effect of embedding the relationship to symbolic totality should be considered. As the nature of the normative order is related to the anchoring of relations to the highest reality — when legitimizing a social system, religious values take precedence over cultural, political and economic subsystems, than „any given value system is characterized by a certain type of pattern, which, if institutionalized, creates a situation where the general type of social of the system is desirable" (Parsons 1971, p. 48). According to the authors. „religious and philosophical factors are among the factors of influence in participation in biobanking, but to a lesser extent than the factor of confidentiality of health and genetic information and fears of research results not being available to participants and of commercial abuse" (Goddard *et al.* 2009, p. 3).

Qualitative findings suggest that the sanctity of the body is not perceived as a significant factor in Western countries (Hoeyer, Lynöe 2006). However, greater part of the studies were conducted in majority Western-type societies, and less so within migrant or indigenous communities, where a tissue can be perceived in a different context (Lipworth, Forsyth, Kerridge 2011, p. 801).

Mediators of genomic data donation and sharing — tissue type

Tissue samples collected, stored and examined in biobanking research are usually samples such as serum (plasma), solid tissue samples, blood cells, bone marrow cells, cord blood derivatives, body fluid samples, saliva, urine, stool, hair and nails (Henderson *et al.* 2013, p. 6). As reported by the authors, respondents of the sample were generally more inclined „to donate their blood (82 %), saliva (77 %) or urine (70 %)… (while) a deceased family member's organs or tissues were the least desired for donation (25 %)" (Merdad *et al.* 2017, p. 6).

As reported by the authors, type of donated tissue acts as a special mediating variable in relations to ethical attitudes, the perception of the sanctity of the body, the common good and the legitimization of participation in the activities of biobanks (Shabani, Bezuidenhout, Borry 2014).

Tissue types as „brain post mortem, eyes post mortem, embryos, spare eggs and sperm were seen controversial, as well as animal research, research conducted outside the UK and research conducted by pharmaceutical companies" (Lewis *et al.* 2013, p. 1), as well as cloning, stem cell research and genetic engineering (Schwartz *et al.* 2001; Goodson, Vernon 2004), and research with presumed eugenic or commercial potential (Lemke *et al.* 2010). For example, in the review study of tissue donation, the collection of reproductive tissues (embryos, gametes) as well as tissues for genealogical research were excluded of the analysis, since, as the authors state, "the scientific, ethical and legal aspects of this type of biobanking are specific" (Lipworth, Forsyth, Kerridge 2011, p. 4).

Age, education and religiosity as mediating variables of participation in biobank activities

Gender and age act as mediating variables of the willingness to participate in biobanking with as e.g. empirical findings confirming middle-aged participants with higher degree of willingness to participate in biobank activities to compare younger and older participants (Goddard *et al.* 2009; Lewis *et al.* 2013). However, according to a study, the majority of elderly people of different ethnic origins were willing to provide organ samples, preferring biobanks focused on cancer research (Ewing *et al.* 2020). Participants with higher education often prefer closer access to their data and closer agreement based on findings on public perceptions of biobanks in Europe (Gaskell *et al*. 2013).

According to a review study of religious values in biobanking decisions, it is „an international phenomenon occurring across cultures" (Eisenhauer, Arslanian-Engoren 2016, p. 104), however, research studies have brought mixed findings on how religiosity factors act, e.g. depending on different confessions.

Various religious, moral, social and cultural settings are reflected in differentiated prosocial motives for donation. According to a study in a Jordanian setting, „the perception of sample donation as a good deed on a religious level was positively correlated with the willingness to donate bio-specimens for future research" (Makhlouf *et al.* 2019, p. 23). As reported by a study in the Malaysian environment, „although the producers, scientists and the Christian scholars' attitudes were inclined towards the positive side compared to other stakeholders.. they also seemed to reserve some considerations when it comes to issues of data and specimen protection" (Hasrizul *et al.* 2017 p. 12). However, „no significant differences of attitudinal variables across education levels and religion have been conformed" (Hasrizul *et al.* 2017, p. 13).

The effect of religiosity was not confirmed by the authors (Pulley JM, Brace MM, Bernard GR et al. 2008), other findings confirmed that „respondents who wanted to be asked to donate HBSs were significantly more likely to had no religious affiliation (86.4 % vs 77.9 %) (Lewis *et al.* 2013, p. 3). Several studies emphasize societal benefits of biobanking research (De Vries *et al.* 2016, Gornick, Ryan, Kim 2014), suggesting that „limiting the scope of consent can help accommodate religious values and preferences..(and) the need to respect the religious values of patients by fully explaining the implications of research procedures in biobanking" (Eisenhauer, Arslanian-Engoren 2016, p. 104).

Family status, support groups and support of friends and family as a mediating variable of biobanking participation

The need for family and friend support and emotional closeness has been confirmed as important in relation to the perception of risks in data and research findings sharing (Yip *et al.* 2019, Mezinska, Kaleja, Mileiko 2020). Donors perceive benefits and risks of donation in perspective of their family and close ones, so perception of possible risks of data sharing when determining family anamnesis is the main reason why some authors require obtaining informed consent from relatives of donors as well (Robinson *et al.* 2016; Minari *et al.* 2014).

According to the authors, membership in a supportive community has been identified as important in biobanking participation, as e.g. in case of parents of children with cancer, who appreciated „how the tissue embedded them within the childhood cancer community" (Dixon-Woods *et al.* 2008 p. 1). Also, the sense of belonging to the patient community was identified as *a consequence* of participation in biobanking, e.g. as an „act of solidarity and reciprocity, which makes patients part of a community" (Pellegrini *et al.* 2014, p. 523).

According to the findings of the authors, participants may also feel pressure to donate from family members, or due to their respect or sympathy for a certain clinician or researcher (Haddow *et al.* 2008, Hansson *et al.* 2006).

Trust in research institutions and sensitivity of genomic data as a mediating variable of participants' expectations

Participants' attitudes towards genomic data sharing are influenced by the their perception of data sensitivity and controllability, as well by the overall trust in biobanking and perceived altruism (Shabani, Bezuidenhout, Borry 2014). The feelings of possible threats to personal data sharing were identified e.g. in groups of patients with rare diseases in an international comparison (although patients generally declared a willingness to participate in biobanking) (McCormack *et al.* 2016), also in the case of a lower willingness to participate in biobanking of patients with hepatitis B compared to healthy patients (Ma *et al.* 2012).

As reported by the authors, „healthy trust and distrust require an understanding of which expectations are reasonable and which are not" (Hawley 2015, p. 798). Participants' expectations include also an overview and control over the activities of the research organization. In this context, the institution's ability to supervise the biobanking process and of the internal control within the research process is expected, as well as the selective approach of a biobank when cooperating with other research organizations. The trust in biobank institution includes the trust that biobanks can ensure the supervision of compliance with the rules and, if necessary, can ensure the use of sanctions. However, the question of a real possibility of de-identification of personal data is raised (Wallace 2016; Shabani, Bezuidenhout, Borry 2014).

According to studies in various environments (Ma *et al.* 2012; Kettis-Lindblad *et al.* 2006; Munung, de Vries 2020), trust in government and scientific institutions is one of the important factors involved in decisions to participate in biobanking. Although some studies have found low trust in biobanks, overview study confirmed a high degree of trust in biobanks and researchers — as the authors state, „the general public surveyed considered academic researchers in biobanks and their institutions to be highly trustworthy" (Lipworth *et al.* 2009, p. 119).

Psychosocial benefits in biobanking were rated as key by participants according to the current findings of the authors, when „the most important factors related to the willingness to donate material to biobanks seemed to be trust towards scientists and doctors" along with „selected preferred values such as knowledge, self-development and tradition" (Pawlikowski, Wiechetek, Majchrovska 2022, p. 1). According to the qualitative findings on a sample of oncology patients, „contribution to biobanks was perceived as a strengthening individual experience associated with feelings of hope, associated with research because it makes the relationship with researchers and clinicians less asymmetrical" (Pellegrini *et al.* 2014, p. 523).

Practical measures to strengthen trust in biobank activities include e.g. supporting the sensitivity of researchers to ethical aspects, ensuring the transparency of the identity of researchers and possible commercial use of research, supporting opportunities for participants to communicate with researchers, as well as providing feedback on research results or socially responsible distribution of research benefits (Hoeyer 2010; Goddard *et al.* 2009; Gaskell *et al.* 2013; Kettis-Lindblad *et al*. 2006; Briscoe *et al.* 2020; Dove *et al.* 2015). Based on review study findings, public engagement is considered to be a means of produce and maintain public trust and legitimacy, which are essential for the functioning of biobanks (Luna Puerta *et al.* 2020), understanding involvement as „mechanisms whereby there can be meaningful and legitimate public input into policy that involves dialogue between relevant publics with scientists, policy makers, and other stakeholders…" (Luna *et al.* 2020, p. 4).

An example of a good practice is a cooperation of a biobank with organizations of patients with rare diseases (Baldo *et al.* 2016). The recommendations to support trust in biobanking process are aimed at e.g. changing the language used or the environment so that people feel as comfortable as possible during the tissue sample collection process, or „involving older people as consultants so that participants better understand the value of biobanking research for individuals from various populations" (Ewing *et al.* 2020, p. 683). Finally, a qualitative study of the authors that participants were sensitive to the quality of information, the moment of asking for consent, as well as the recruiter's behavior and attitudes (Bosisio *et al.* 2021), including also white coat-playing a role in a patient's decision regarding medical treatment (Brase, Richmond 2004).

CONCLUSION

In this study, expectations of participants in the biobanking were followed as one of the factors biobanking participation. Expectations of biobanking participants — actual donors and public — were identified in areas of a) expectations of donors and public in the field of information, overview and transparency of biobanking research, b) expectations of donors and public in the field of individual and family benefits of biobanking, c) expectations of donors and the public in the area of the common good and d) expectations of donors and the public in the field of consent — type of consent, controllability and clarity of data, the feedback on research results.

When studying expectations in biobanking, it is necessary to consider mediating variables, e.g. sociodemographic variables of age, education, nationality, religiosity, also the perception of the legitimacy of participation in biobanks, trust in scientists and institutions as well as a specific tissue type.

Based on findings in biobanking studies, the diversity of different types of biobanking institutions and the different social contexts of donation, in which the term biobank and donation can take on different meanings can be emphasized. Especially in recent years, the interest in research of specific sub-populations, or populations from different social and cultural environments in the context of their participation in biobanking, in order to strengthen the representativeness of the findings in the given area.

Although the expectations of biobanking participants are one of the factors in biobanking process — in addition to institutional support, awareness, information sources and perception of risks in biobanking — we believe that findings in expectations of donors and public in biobanking and data sharing are important part of the information flow among biobanking participants.

Several current research questions in biobanking process can be emphasized. Sociology of biobanking can focus on participants' expectations of data transparency and feedback of research results, ensuring supervision of data security and protection, or the precise and unified communication when informing about the method of data anonymization, as well as on new current dynamic consent types.

Practical measures to support biobank research activities thus include mechanisms of control and supervision over the safety of biobanking. Other research questions include expectations of experts, public and donors of trust and reliability of the relationship of researchers, donors and institutions in biobanking process. Identifying the segments of population with a specific interest in feedback on research results or in the types of consent that various groups of potential and actual donors may prefer, is relevant with regard to promoting willingness to participate in biobanking. As the authors suggests, when planning the activities of a biobank, it is possible to consider alternative processes or the purposes, e.g. as a source of information and part of a network supporting development in this area, a source of „best practices" examples, training and workshops, etc. (Stephens, Dimond 2015).

Research questions in expectations in biobanking also cover the analysis of the current state of biobank functioning (types, size), analysis of biobanking participation in relation to demographic indicators, family history of diseases and donor motivation, values and experiences, preferred type of consent to share genomic data, perception of risks, trust in scientists, research institutions as well as researchers', experts', donors', and public attitudes and expectations in the context of long term relationship between funders, experts, donors and researchers.

As biobanks may become a requirement for medical practise (Kajo *et al.* 2016), it may become a relevant issues to follow the prerequisites for a sustainable functioning of biobanking system also in Slovakia to the future,

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Periocular non-melanoma skin tumours of the eyelids – review

Periokulárne nemelanómové kožné nádory mihalníc – review

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ABSTRACT

Introduction: Basal cell carcinoma (BCC) is the most common tumour of the eyelids and periocular region. The incidence of BCC of the eyelids (C44.1 ICD-10-CM) is gradually increasing worldwide. Basal cell carcinoma represents 90 % of malignant tumours of the eyelids, predominantly in the male population Squamous cell carcinoma, sebaceous carcinoma, Merkel cell tumour, Kaposi's sarcoma or primary lymphoma are found less often in the periocular area.

Research objectives: The aim of this article is to analyse the epidemiology, aetiopathogenesis, clinical attributes, diagnostics, histopathology, recurrence, prognostic factors and management of BCC.

Core of work: Non-melanoma skin tumours are the most widespread malignancies in the Caucasian population. Standardised incidence of diagnosis C44 (dg. C44.) in the period 1997–2 012 in Slovakia ranged from 35.05 to 73.9 cases per 100,000 inhabitants. Dependency on gender, age, and tumour incidence have been demonstrated in several studies. A definitive diagnosis can only be established on the basis of a histopathological examination. The primary treatment modality for BCC is surgical resection. Advanced lesions require extensive surgical interventions and other available treatment modalities. We can consider the apoptotic index, the expression of Bcl-2, as an unexplained prognostic factor of BCC recurrence.

Conclusion: Within the context of onco-ophthalmology, increased attention must be given to periocular malignant tumours. Multidisciplinary and patient co-operation in the field of cancer is essential, improving early diagnosis, treatment and survival of patients. Patient management requires an individualised approach.

Keywords: Basal cell carcinoma. Non-melanoma tumours. Oncoophtalmology. Recurrence of BCC.

ABSTRAKT

Úvod: Bazocelulárny karcinóm je najčastejšie sa vyskytujúci nádor mihalníc a periokulárnej oblasti. Incidencia nádorov mihalníc (C44.1 v MKCH 10 klasifikácii) má celosvetovo stúpajúcu tendenciu. Bazocelulárny karcinóm predstavuje 90 % malígnych nádorov mihalníc, s prevahou v mužskej populácii. Spinocelulárny karcinóm, sebaceózny karcinóm, nádor z Merkelových buniek, Kaposiho sarkóm, či primárny lymfóm sa v periokulárnej oblasti nachádzajú menej často.

Ciele práce: Cieľom tejto práce je analýza epidemiológie, etiopatogenézy, klinických vlastností, diagnostiky, histopatológie, recidivovania, prognostických faktorov a manažmentu BCC.

Jadro práce: Nemelanómové periokulárne nádory sú najrozšírenejšími nádormi v kaukazskej populácii.

Na Slovensku sa štandardizovaná incidencia dg. C44. v období r. 1997 — 2012 pohybovala od 35,05 do 73,9 prípadov na 100 000 obyvateľov. Vo viacerých štúdiách je preukázateľná závislosť medzi pohlavím, vekom a incidenciou BCC. Definitívnu diagnózu možno stanoviť len na základe histopatologického vyšetrenia. Primárnou liečebnou modalitou BCC je chirurgická resekcia. Pokročilé lézie vyžadujú rozsiahle chirurgické intervencie a využitie iných dostupných liečebných modalít. Za neobjasnený prognostický faktor recidivovania BCC môžeme zaradiť apoptotický index, expresiu Bcl-2.

Záver: V rámci onkooftalmológie sa problematike periokulárnych malígnych nádorov musí venovať zvýšená pozornosť. Multidisciplinárna spolupráca a spolupráca pacienta v oblasti nádorových ochorení je nevyhnutná, zlepšuje včasnú diagnostiku, liečbu a prežívanie pacientov.

Kľúčové slová: Bazocelulárny karcinóm. Nemelanómové nádory. Onkoftalmológia. Recidivovanie BCC.

INTRODUCTION

Non-melanoma skin tumours are the most widespread malignancies in the Caucasian population, comprising more than one-third of adult cancers, with 18–20-times higher incidence than malignant melanoma and representing 5–10 % of all skin tumours (Furdova A, Horkovicova K, Furda R et al. 2021). The most common malignant tumour of the eyelid is basal cell carcinoma (BCC), which is responsible for 90 % of malignancies in this area. It arises from pluripotent cells localised in the stratum basale of the epidermis and in the area of the outer hair sheath. Squamous cell carcinoma (SCC) is a much less common but more aggressive tumour than BCC, with eventual metastases into regional lymph nodes (Prídavková, Bieliková, Ferková et al. 2021). Squamous cell carcinoma comprises 5–10 % of eyelid malignancies and may occur *de novo* or from actinic keratosis. It arises from the layer of the epidermis called the stratum spinosum (stratum Malpighii). Sebaceous carcinoma (SGC) is a very rare tumour that usually affects the elderly. Merkel cell carcinoma is a rapidly growing tumour that arises from cells in the dermis and typically affects the elderly, and Kaposi's sarcoma can occur in immunocompromised patients (Furdova, Kapitanova, Kollarova et al. 2020).

CORE OF WORK

EPIDEMIOLOGY

We analysed data of 68,516 patients with dg. C44. in the period 1997–2 012. The standardised incidence ranged from 35.05 to 73.9 cases per 100,000 inhabitants. The development of the incidence of clinical stages of malignant skin tumours in the period from 2000–2 012, regardless of age, is shown in figures 1, 2. Standardised mortality ranged from 0.2 to 0.9 cases per 100,000 population. Specific data on the diagnosis of C44.1 (Malignant tumour of the skin of the eyelid, including the canthus — the third position of the C44 reporting code) cannot be obtained (NOR 2022).

The first data on the detected disease are in the age category of 10–14-year-olds. The incidence then gradually increases up to the maximum in the age category of 70–74-year-olds. Age-specific incidence (or mortality) is the number of cases per 100,000 patients in a given age category and shows a rising tendency for the monitored diagnosis (Fig. 3).

Basal cell carcinoma

Basal cell carcinoma arises from the basal cells of the epidermis and hair follicles. It is characterised by invasive growth, low mortality and a low tendency to metastasise (Ondrušová M, Pleško I, Safaei-Diba Ch et al. 2007). The aetiology is linked mainly to exposure to UV radiation in people with pale skin. This fact is founded on extensive studies conducted in Europe, Australia and North America (Prídavková, Bieliková, Ferková et al. 2021). The greatest significance is attributed to UVB radiation (290–320 µm), which is capable of damaging cellular DNA, thus causing mutations with the occurrence of thymidine dimers. Molecular, genetic, ionizing radiation, immunosuppression and other factors are also applied to the aetiopathogenesis of cancer (Furdová A, Oláh Z 2010). In several studies, a demonstrable dependence between sex, age and the incidence of BCC can be seen. This occurs most often in patients in the sixth to eighth decade of life, with a median age of 62 years (46 % were at least 65 years old).

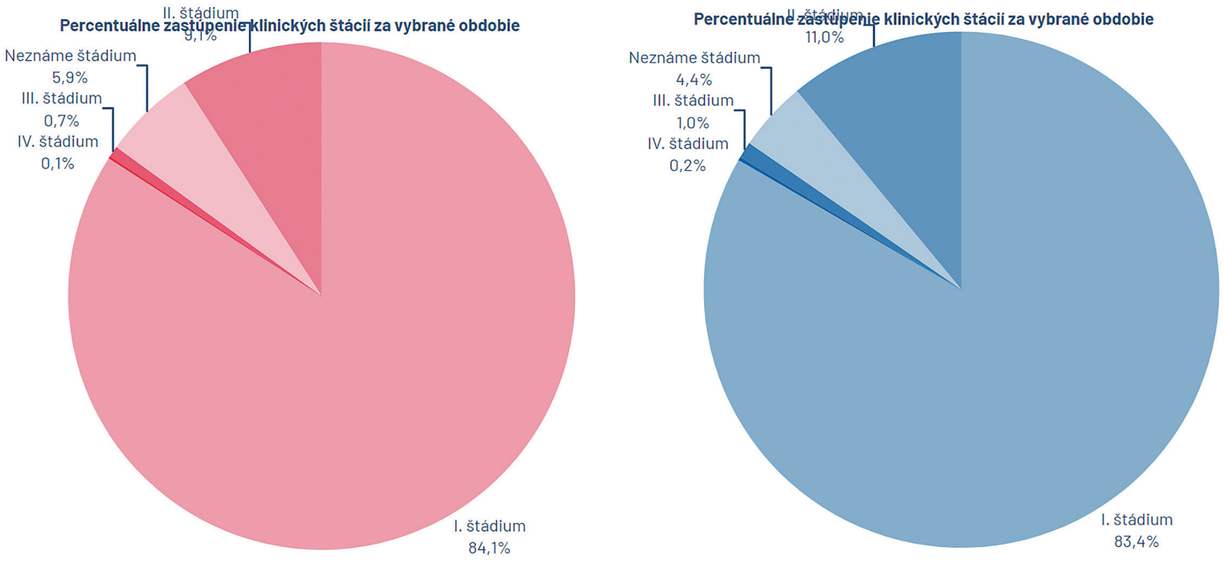

Fig. 1, 2: Malignant tumours of the skin of the eyelid, including the canthus — the third position of the C44 reporting code — percentage of clinical stages for the selected period in women and men (NOR SR).

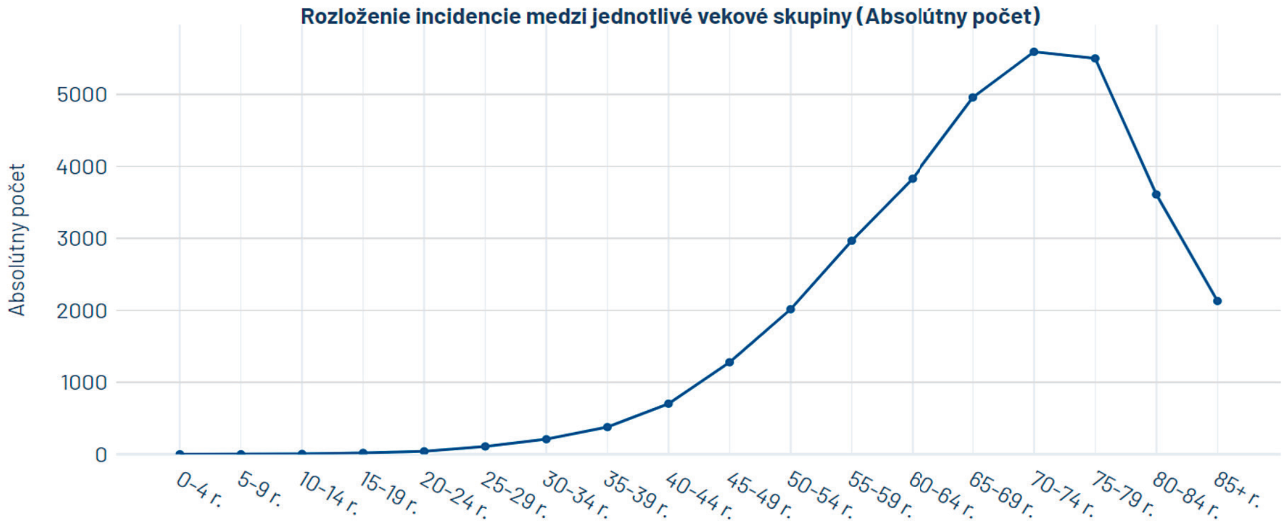

Fig. 3: Malignant tumours of the skin of the eyelid — age structure of patients in the period 1997–2 012 (NOR SR).

A moderate predominance occurs in the male population; i.e. 61 % is male. The relationship of the sex of patients to the risk of BCC recurrence is still controversial. In Silverman's studies, no relationship between sex and tumour recurrences was evident. The most frequent localisation of basal cell carcinoma is the area of the lower eyelid, the inner and outer corners. Activation of the Hedgehog signalling pathway with inactivating PTCH1 mutations was identified in 90 % of sporadic BCCs and activating SMO (smoothened protein) mutations in approximately 10 %. In the background of 4–100 % of basal cell carcinomas is an inactivating mutation of the tumour suppressor gene p53, which is located on chromosome 17 (Pricl S, Cortelazzi B, Dal Col V, et al. 2015). Viral oncoprotein E6 from beta HPV has the ability to bind to the p53 protein and inactivate it, which results in limiting the induction of apoptosis of cells damaged by UV radiation through the reduction of the pro-apoptotic protein Bcl-2. Oncoprotein E7 interferes with p16, and these mechanisms lead to an accumulation of mutations and oncogenic transformation of keratinocytes, which are more sensitive to UV-induced carcinogenesis (Poláková K, Murárová Z 2021). Included in the genetic syndromes associated with a higher incidence of BCC is the syndrome of non-acute basal cell tumours, xeroderma pigmentosum, where the risk of developing skin tumours is 1000-times higher than in the general population. The 5-year cumulative risk of a new BCC in patients with at least one previous BCC is 41–45 % compared with a 5 % risk in the Caucasian population without BCC (Prídavková, Bieliková, Ferková et al. 2021).

CLASSIFICATION

For determining the stage of advancement of a tumour, the TNM „staging" classification is used, as well as determining the histopathological degree of „grading" differentiation. Grading is based mainly on the cytological characteristics of the tumour, whereby we distinguish 4 grades: differentiated (G1), moderately differentiated (G2), poorly differentiated (G3) and anaplastic (G4). The classification and stages of basal cell carcinoma in the eyelid region are shown in Fig.4 (Furdová A., Strmeň P., Oláh Z 2000).

CLINICAL FEATURES

The clinical manifestations of BCC are diverse. It is most often expressed as erythema, induration, a palpable lesion, recurrent bleeding, or a cystic nodule (Fig. 5, 6, 7). Patients are often without symptoms and without subjective problems (Basset-Seguin, Herms 2020). In one study Lebowitch describes 35.7 % as being fixed to bone. Limited mobility of the eye bulb can be another significant clinical finding, and the incidence ranges from 30–76.5 %. In these patients, symptoms such as diplopia are often presented, and 35.7 % of them had only a visual or palpable lesion without bone fixation or orbital manifestations (Leibowitch, McNab, Sullivan et al. 2005).

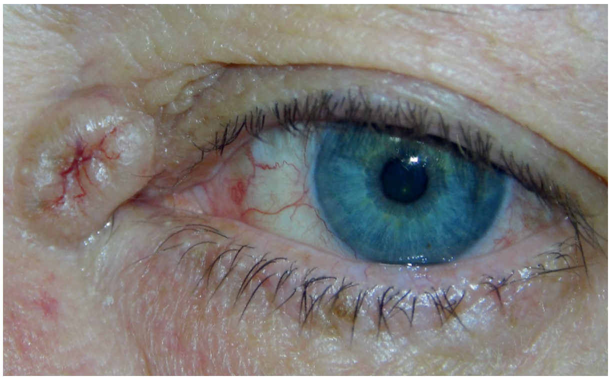

Fig. 5: Basal cell carcinoma of the medial canthus
Photo: Peter Žiak, Archive of Eye Clinic, Jessenius Faculty of Medicine, Comenius University in Bratislava, Martin

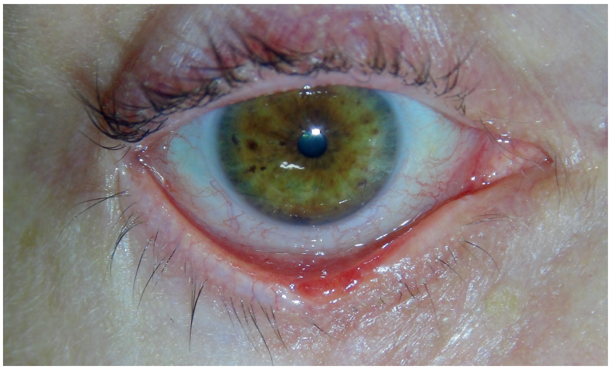

Fig. 6: Basal cell carcinoma of the lower eyelid — subtile manifestation
Photo: Peter Žiak, Archive of Eye Clinic, Jessenius Faculty of Medicine, Comenius University in Bratislava, Martin

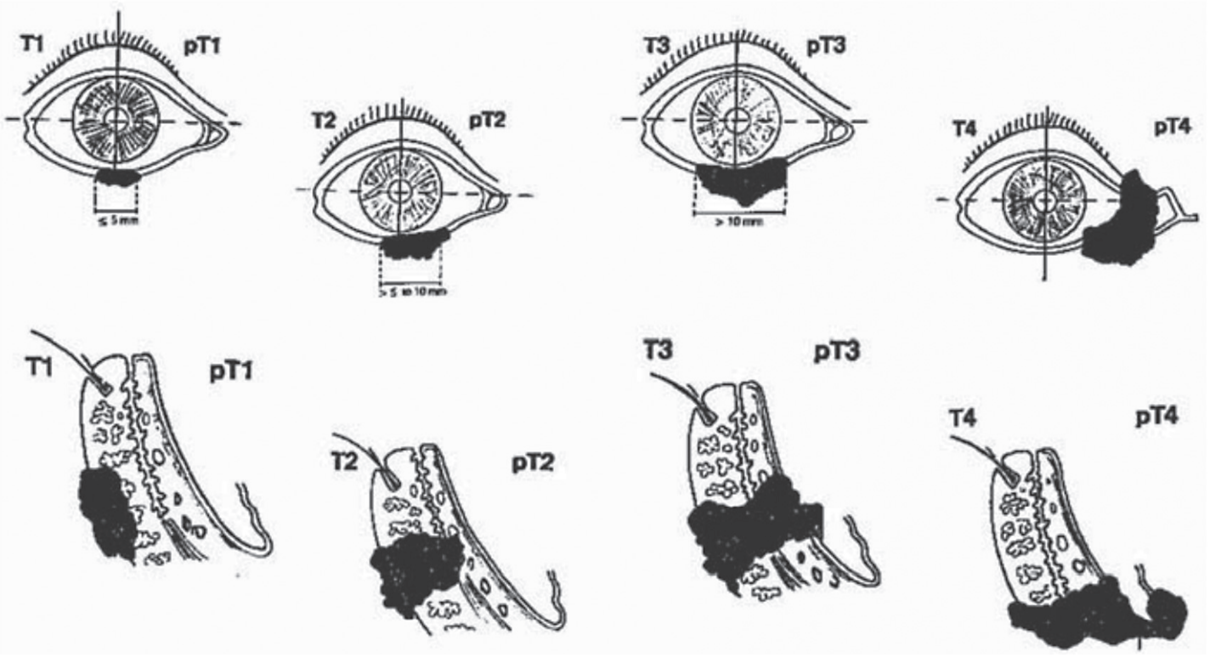

Fig. 4: TNM classification of basal cell carcinoma of the eyelids

Fig. 7. Basal cell carcinoma of the lower eyelid — ulceration with bleeding
Photo: Peter Žiak, Archive of Eye Clinic, Jessenius Faculty of Medicine

The result of tumour histology has been clearly demonstrated as being a prognostic factor for the invasive and malignant potentials of BCC (Marzuka AG, Book SE 2015).

Nodular BCC (50–80 %) is the most common type of BCC. It manifests as a slowly growing greyish-white, shiny papule to skin-coloured nodule with a thinned epidermis and telangiectasias. *Cystic BCC* is often a multilobular lesion made up of transparent nodules with telangiectasias. Both are considered to be low-risk forms of BCC. *Superficial BCC* (10–30 %) (multicentric basal cell carcinoma) are easily infiltrated brown-red lesions, with fine peeling or scabs on the surface; the epidermis in the extent of the tumour lesion has an atrophic appearance. The edges of the frequently irregular lesions are formed by a raised beaded border comprised of small shiny and sometimes pigmented nodules. Among the high-risk subtypes of basal cell carcinoma is *sclerodermiform BCC* (6–10 %) — morphea-like basal cell carcinoma. It can grow deep into the dermis and spread perineurally. This type of basal cell carcinoma rarely ulcerates. *Infiltrative BCC* (5 % of cases) is a locally destructive aggressive subtype with a higher risk of local recurrence, and *Micronodular BCC* (14–15 %) is an aggressive and locally destructive subtype with subclinical spread and a higher risk of recurrence. Basal squamous cell carcinoma (so-called metatypical carcinoma) is a tumour that includes mixed regions with typical basaloid differentiation and regions approaching squamous cell carcinoma (Poláková, Murárová 2021).

TREATMENT

Surgical resection

The primary treatment modality for BCC is surgical resection (Quazi, Aslam, Saleem et al. (2020). With respect to the tumour's location, tissue-sparing methods are often used, which increase the risk of recurrence. BCC in the area of the medial and lateral canthus thus has a significantly higher risk of intraorbital and perineural growth (Weesie, Naus, Vasilic, et al. 2019). The need for orbital exenteration in basal cell carcinoma may be significantly higher if the lesion includes the medial canthus (Furdová, Horkovičová, Babál et al. 2015).

Data on recurrences after surgical treatment of basal cell carcinoma differs depending on the surgical technique used. The incidence of recurrence in patients treated without using Mohs micrographic surgery or „en-face" frozen sections intraoperatively ranged from 1.8 to 39 %, and the proportion of recurrence increased with longer follow-up of patients (Poignet, Gardrat, Dendale et al. 2019). The recurrence rate of BCC is approximately 95 % after treatment, depending on the stage and location, and the incidence rate after primary surgery is 1–5 % per year (Paavilainen, Tuominen, Aho et al. 2007). Mohs micrographic surgery was considered to be the best method of BCC removal with minimal recurrence (Furdova A, Kapitanova K, Kollarova A et al. 2020). The most common cause of recurrence is non-compliance with the recommendation for radical excision of the basal cell carcinoma 0.3–1 cm from the clinically visible edges of the tumour (Smeets, Kuijpers, Nelemans, et al. 2004). In many patients orbital exenteration is the approach selected after the failure of previous therapeutic modalities. Given that recurrence after exenteration can be as high as 50–75 %, it is very important not to underestimate the timely management of these lesions (Furdová A, Horkovičová K, Krčová I, et al. 2015).

Vismodegib

Vismodegib is an available, orally administered specific inhibitor of the Hedgehog pathway with a small molecule. The signalisation of the Hedgehog pathway through the transmembrane protein Smoothened (SMO) leads to activation and nuclear localisation of Glioma-Associated Oncogene (GLI) transcription factors and the inducing of the Hedgehog target genes. Vismodegib has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for patients with locally advanced and metastatic basal cell carcinoma that cannot be managed with surgery or radiotherapy. The approved oral dose of vismodegib is 150 mg/day. Indications for treatment are very limited. According to a study published in the *American Journal of Ophthalmology*, vismodegib therapy for periocular and orbital BCC is effective, and the side effects are mostly manageable. In that study, Harmeet describes vismodegib as effective in the treatment of periocular and orbital BCC in about half of all cases (Prídavkova Z, Bielikova A, Ferkova N et al. 2021). The results of a pilot phase 2 clinical trial (ERIVANCE) in 104 patients with locally advanced BCC (laBCC) and metastatic BCC (mBCC) showed a response rate of 48 % (laBCC) and 33 % (mBCC), respectively, and median duration of response of 9.5 and 7.6 months. Median survival for patients with mBCC was 33.4 months. In laBCC, it is possible to discuss neoadjuvant treatment with an Hh inhibitor with the intention of shrinking the lesions, but there is no randomised data to demonstrate a favourable outcome. In a series of 15 patients treated with vismodegib for 3–6 months before surgery, only 1 patient relapsed after 22 months (Sekulic A, Migden MR, Lewis K et al. 2015).

HDR-brachyteraphy

With basal cell carcinomas significantly advanced locally, after incomplete excision, in lesions with a high risk of local recurrence or an unacceptable expected cosmetic effect, in elderly patients or with repeatedly recurring lesions, definitive radiotherapy is a suitable solution (Cisek P, Kieszko D, Bilski M 2021). The external radiotherapy standardly used in the past, in particular in 1970 s, in monotherapy for the treatment of basal cell carcinomas in the area of the lower eyelid and the inner corner has already been surpassed due to post-radiation scar-like changes in the surrounding area, and in some cases this treatment is still considered highly effective (Furdová A., Lukačko P., Lederleitner D 2013). The first reports of HDR brachytherapy in the treatment of eyelid basal cell tumours, however, appeared only in 2007. Brachytherapy has a theoretical advantage compared to surgery in that it enables the covering of larger areas of the skin with a high dose (macroscopic disease, microscopic disease, safety margin) without the need for irreversible damage to the surrounding tissues. It can be done by means of the interstitial route (the surgical introduction of brachytherapy applicators directly into the tumour tissue by puncture) or superficially. Surface brachytherapy is done by using standard applicators (e.g. Leipzig Applicator, Brock Applicator, Nucletron BV, Netherlands) or custom-made emulsions. Standard applicators are characterised by ease of use and good treatment reproducibility, but they cannot be used for irregular lesions and in a"curved" irregular terrain such as the periocular area (Leibovitch I, McNab A, Sullivan T, Davis G, Selva D 2005).

Another treatment

Local pharmacological treatment, including the immunomodulator imiquimod and 5 % 5-Fluoruracil, is less successful and is not yet widely used in localisation near the edge of the eyelid or the outer or inner corner. The principle of PDT (photodynamic therapy) is the accumulation of a photosensitizer: δ-aminolevulinic acid (ALA) or its methyl ester (MAL, Metvix® creme). PDT is the method of choice in patients with non-aggressive low risk BCC, for example, the superficial or nodular type not exceeding 2 mm in thickness, when surgery is not possible or is contraindicated (Poláková K, Murárová Z 2021). Curettage and electrocoagulation, cryotherapy and laser ablation are methods suitable for small, non-risky basal cell tumours that are not localised on the face and do not have a multifocal character. In the past, chemotherapy was also applied in the treatment of BCC, but unsuccessfully (Coker DD, Elias EG, Viravathana T et al. 1983).

THE RECURRENCE OF BASAL CELL CARCINOMA

Data on the recurrence after surgical treatment of basal cell carcinoma vary depending on the surgical technique used. In the works known to us, published during the last 10 years, the incidence of recurrences in patients treated without the use of Mohs micrographic surgery or intraoperative histopathological examination of frozen sections ranged from 1.8 % to 39 %, and with longer follow-up of patients, the proportion of recurrences increased (Prídavková Z, Bielikova A, Ferkova N 2021).

Wong et al. recorded a recurrence of 1.8 % with an average of 2.6 years of follow-up, while Finnish authors described 13.7 % of recurrences at an average of 8.6 ± 5.2 years of follow-up of 191 patients, and Ducasse et al. recorded recurrence in 5.15 % of 193 monitored patients (Wong CS, Strange RC, Lear JT 2003). Allali et al. put the more common recurrence of basal cell carcinoma in association with the type of treatment (other than surgical), tumour location (inner corner), tumour size (more than 2 cm), its infiltration into the surrounding area and histological type (Allali J, D'Hermies F, Renard G 2005).

Monitoring the relationship of the time to cancer growth and the risk of recurrence after its removal could bring interesting knowledge and help clarify the dilemma of whether long-term growing BCCs gradually acquire a more aggressive phenotype or their biological behaviour remains rather static. Based on existing knowledge, it can be assumed that the more frequent occurrence or treatment of multiple BCCs in individual patients increases the risk of recurrence. In the work of Bumpous et al. patients with multiple BCCs had a statistically higher probability of recurrence compared with persons affected by only one lesion.

At present, it is debatable whether certain forms of BCC can also show some genetic-molecular aberrations that would directly predispose them to relapse. The results of some authors indicate that „overexpression" of cyclin D1 and the aneuploidy of BCC tumour cells may predispose patients to recurrence. The assessment of these parameters, however, is usually not possible in the scope of a routine biopsy examination, and the significance of the proliferative activity of the tumour cells themselves remains unclear. Healy et al. confirmed a higher degree of immunohistochemical expression of the proliferative antigen Ki-67 in 17 primary BCCs that later recurred compared with 17 non-recurring carcinomas. In a similar work, Yerebakan et al. evaluated 26 primary BCCs, 14 of which recurred, and they stated that the percentage value of Ki-67 expression was higher in these tumours in contrast to non-recurrent tumours. On the other hand, another study showed no significant differences in Ki-67 expression in 20 primary (later recurrent) BCCs compared with 20 non-recurrent BCCs (Poláková K, Murárová Z 2021).

We can include the apoptotic index as an unexplained prognostic factor of BCC recurrence. In the work of Staibano et al. 60 BCCs were evaluated, 30 of which were BCC1 (non-aggressive type) and 30 BCC2 (aggressive type). BCC1 showed a lower apoptotic index (AI) than BCC2, with the AI of BCC1from 2.03 — 10.45 % (mean value: 5.98 %) and the AI of BCC2 from 21.91 — 43.82 % (mean value: 39.82 %). It is assumed that low AI in BCC1 could indicate a good prognosis (Staibano S, Lo Muzio L, Pannone G 2001). High expression of the Bcl-2 protein is recorded in indolent, slow-growing BCC, while low expression of Bcl-2 occurs in highly aggressive types of BCC (Pratistadevi K. Ramdial, Anil Madaree et al. 2001).

CONCLUSIONS

In the scope of onco-ophthalmology, increased attention must be paid to the issue of malignant periocular tumours. Advanced findings lead to mutilating operations, which represent a serious aesthetic problem. Early diagnosis, multidisciplinary cooperation, lifelong dispensary of the patient with early detection of recurrences are all important. Multidisciplinary cooperation and cooperation of the patient in the area of cancer tumours is essential, as it improves the early diagnosis, treatment and survival of patients. Patient management requires an individualised approach.

Conflict of Interest: None

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