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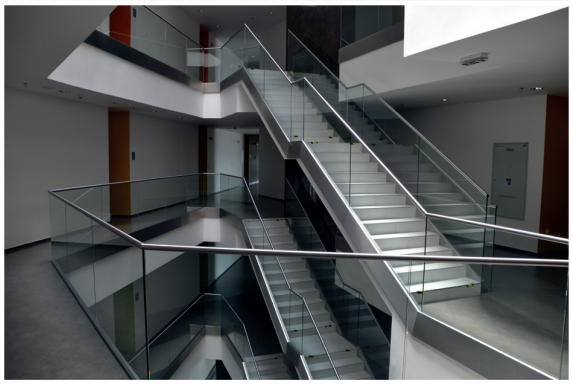

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CONTENT / OBSAH

EDITORIAL

Dear Readers,

The journal Zdravotníctvo a sociálna práca (*Health and Social Work*) was established in 2006 at Faculty of Health and Social Work of blessed P.P. Gojdič in Prešov, St. Elizabeth University College of Health and Social Work in Bratislava. In 2020, the 15th year of the journal was published.

Previously professional journal, within 5 years developed into an international, peer-reviewed scholarly journal, published quarterly (4 issues per year). The journal is published by the St. Elizabeth University of Health and Social Work in Bratislava. The journal became international in 2009. The journal is 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 and www.zdravotnictviasocialniprace.cz. 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. In 2020, the conference was planned, similarly to last year, in Ustroń, Poland. Due to the unfavorable epidemiological situation, the conference was postponed by the organizers to March 2021.

Our long-term effort is to gradually acquire for the journal Central European significance and be included in international databases. Starting by 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, the journal is moving this year from issue 3 to the publication of articles in English only. The journal will be renamed next year.

Prof. Miron Šramka, MD, DSc.
Redactor-in-Chief

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INDICATIONS FOR ENUCLEATION AND EVISCERATION OF THE EYE GLOBE

INDIKÁCIE K ENUKLÉACII A EVISCERÁCII OČNEJ GULE

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ABSTRACT **Aim:** The aim of this retrospective study was to evaluate the number of enucleations realized at the Department of Ophthalmology of the Faculty of Medicine of Comenius University in the period from 2009 to 2019.

Material and methods: Retrospective study includes patients 244 patients in period 2009 - 2019, who were indicated for enucleation or evisceration of the eye globe.

Results: Out of a total of 244, 214 were enucleated eyeballs and 30 were eviscerated. Enucleation was indicated in 141 (65.8%) patients for the malignant process and 73 (34.2%) patients underwent enucleation for non-tumor causes (condition after repeated operations, condition after acute injury, condition after trauma in the past, secondary glaucoma, bulb atrophy, corneal ulceration. The mean age of the patients in the cohort was 70 years.

Conclusion: The ophthalmologist always seeks to improve or maintain visual functions, and we perform primary enucleation or evisceration only in the event of a serious devastation injury or to prevent the spread of an infection that could endanger the patient's life. In acute conditions, the ophthalmologist always seeks primary suture, but out of a total of 214 patients over the 11 years it was necessary to proceed with enucleation or evisceration in 8 patients.

Key words: enucleation of the eye globe, anophthalmus, phtisis bulbi, avulsion of the eye globe, uveal melanoma

ABSTRAKT **Cieľ:** Cieľom tejto retrospektívnej štúdie je zhodnotiť počet enukleácii a evisceráciivykonaných na Klinike oftalmológie LF UK za obdobie v rokoch 2009 až 2019.

Materiál a metodika: Retrospektívna štúdia zahŕňa pacientov hospitalizovaných a operovaných v období 2009 – 2019 na Klinike oftalmológie LFUK a UNB v Bratislave, ktorí boli indikovaní na enukleáciu alebo evisceráciu očnej gule. Spolu bolo 214 pacientov, z toho 96 žien a 118 mužov. Priemerný vek pacientov v súbore bol 70 rokov. Následne sme súbor rozdelili na enukleácie realizované z malígnej a nie malígnej príčiny.

Výsledky: Z celkového počtu 244 bolo 214 enukleovaných očných gúľ a 30 eviscerácii. Enukleácia sa indikovala u 141 (65, 8 %) pacientov pre malígny proces a 73 (34, 2 %) pacientov podstúpilo enukleáciu pre inú ako nádorovú príčinu (stav po opakovaných operačných výkonoch, stav po akútnom úraze, stav po traume v minulosti, sekundárny glaukóm, atrofia bulbu, ulcus corneae). Priemerný vek pacientov v súbore bol 70 rokov.

Záver: Snahou oftalmológa je vždy zachovať očnú guľu a k enukleácii alebo eviscerácii sa snaží pristúpiť len v prípade vážneho devastačného poranenia alebo s cieľom predísť rozšíreniu infekcie, ktorá by mohla pacienta ohroziť na živote. Pri akútnych rozsiahlych úrazoch so stratou štruktúr sa oftalmológ vždy snaží o primárnu suturu, avšak z celkového počtu 214 pacientov za sledovaných 11 rokov bolo potrebné pristúpiť primárne k enukleácii alebo eviscerácii u 8 pacientov.

Kľúčové slová: enukleácia očnej gule, anophthalmus, ftíza bulbi, avulzia očnej gule, uveálny melanóm

INTRODUCTION

Enucleation is a radical surgical procedure in ophthalmology that involves the permanent removal of the eyeball and is irreversible. Enucleation is usually the last surgical solution that an ophthalmologist reaches when all the therapeutic options for a given diagnosis were done before. It is mostly associated with the radical removal of predominantly intraocular tumors, but there are also separate groups of diseases where it is necessary to proceed with enucleation, which in this case was important to improve the patient's life (Cihelková *et al.* 2005).

Enucleation is most commonly performed in the case of an intraocular tumor. It is standardly used in the treatment of malignant uveal melanoma, which is one of the most common primary intraocular tumors in adulthood. In contrast, enucleation for retinoblastoma is most commonly performed in childhood. Furthermore, we can encounter a case of basal cell carcinoma, which grows into the orbit, or the bulbar conjunctiva, and the only treatment option is enucleation, sometimes exenteration of the orbit. However, it is used for any intraocular tumor with a malignant potential that does not respond to conventional treatment or has metastatic potential, causing eye pain or blindness (Cihelková *et al.* 2005; Damato 2018; Damato 2020). Enucleation of the eyeball in tumors is indicated only in advanced stages. Each enucleated eyeball, resp. each material removed during the operation must be examined in detail histologically.

Although enucleations are more often associated with severe traumatic injuries to the ocular structures, or with intraocular tumors, anterior segment diseases can also lead to such radical surgery (Damato, Heimann 2013; Furdová 2007; Furdová, Oláh 2010; Kanski, Bowling 2011).

Such diseases also include corneal ulcer that begins as a defect of the epithelium on the surface of the cornea. If the inflammation is not detected in time, there is a progression of inflammation; descemetocele, when an opening is made in the cornea, communication occurs with the ventricular space, which can result in endophthalmitis. In this case, enucleation is a life-saving treatment of first choice (Svozílková *et al.,* 2016).

Acanthamoeba infection, which is common in contact lenses users, can cause small microtrauma and subsequently cause descemetocele under the influence of collagenolytic enzymes, with possible corneal perforation. As a result, endophthalmitis may develop. In such severe cases, enucleation is the only possible solution (Kuchynka *et al.* 2016; Laurik *et al.* 2019).

Absolute glaucoma is the terminal stage of glaucoma disease, when the values of intraocular pressure are increased several times, visual functions are disappeared. In this case, if pain is present, the diagnosis is made as bulbus dolorosum - a painful eyeball. With medical treatment, the condition is no longer affected. Enucleation represents a radical solution (Drews 1978).

Eye trauma is a group that includes a wide range of involvement of individual eye structures. This is one of the most common causes not only of emergency department visits, but also causes of loss of visual function. The most common types of injuries are perforation injuries with foreign intraocular bodies, open wounds and bruises or burns. The most common indications for enucleation of the eye are perforation injury, rupture of the eyeball, and the resulting hypotonia, irreversible damage to anatomical structures, loss of visual function. Rupture is characterized by hypotension and collapse of the eyeball with tissue prolapse, hemophthalmus and subsequent severe visual impairment (Hirt *et al.* 2011; Zheng, Wu 2013). In the past, rupture of the eyeball

was a clear indication of primary enucleation; nowadays, as far as possible, revision and suture are used primarily (Reed *et al.* 2020).

In the contusion of the eyeball, the entry and exit wounds are not present as in the case of perforation injuries of the eye. However, rupture of the eyeball may occur. In severe contusions, where the anatomical structures are irreversibly damaged, enucleation is the primary solution if the patient has a permanent loss of visual function (Manandhar 2011).

The phtisis of the eye globe is a terminal stage of the disease, which is characterized by shrinkage of the eye with complete loss of vision. In this case, enucleation is the primary solution, as the eye has no visual potential and does not have the desired cosmetic effect (Tripathy *et al.* 2018).

MATERIAL AND METHODS

We retrospectively analyzed data from examinations in patients of the Department of ophthalmology LF UK an UNB in Bratislava, who underwent enucleation or evisceration. All preoperative and postoperative examinations, including the operation itself, were performed in the period from January 2009 to December 2019.

We included a total of 244 patients in the cohort, a total of 244 eyes. Of the total number of patients, 214 enucleations and 30 patients eviscerated. The mean age of the patients in the group was 70 years. The mean age of the patients in the enucleation group for malignant origin was 63 years and in the enucleation group for non-malignant origin of enucleation 77 years. The average age of women who underwent enucleation for another reason was 58 years and of men 55 years. The mean age of the patients who underwent evisceration was 59 years. The ratio of lateralization of the eyes is more or less balanced - in men the enucleation of the right eye was performed 25 times, the left 20 times. In women, the right eye 16 times and the left eye 13 times. We divided the group into two, a group of enucleations and a group of eviscerations in patients with 11 years of follow-up. We divided the enucleation group into enucleations indicated for a malignant process and enucleations indicated from a non-malignant process.

RESULTS

From the total number of 214 enucleated resp. a total of 141 (65.8%) and 73 (34.2%) patients underwent enucleation for non-tumor causes, such as postoperative surgery, post-acute injury, or a history of secondary glaucoma, bulbar atrophy or ulcus cornae. The number of eviscerations was a total of 30 times. (Figure 1)

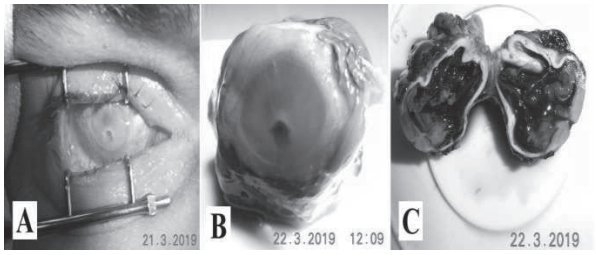
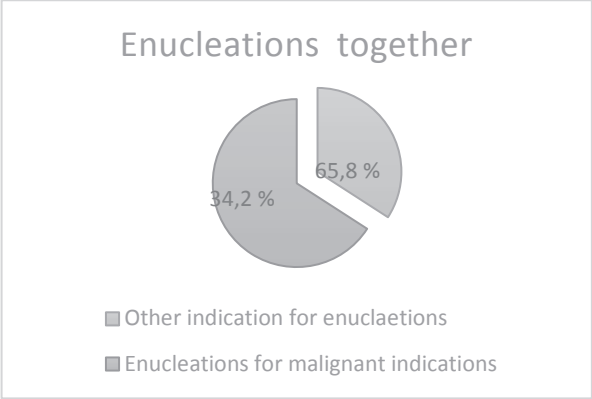


Figure 1. A) Patient´s pre operation status of the right eye before enucleation with perforated cornea - clinical condition after recurrent uveitis, pars plana vitrectomy, phakofragmentation, basal iridectomy and silicone oil implantation and post-silicone oil release with persistent secondary glaucoma; B) eye globe with corneal perforation; C) detail of intraocular structures after incision of enucleated eye globe
(Photo A. Furdová)
Obrázok 1. A) Pacient pred enukleáciou pravého oka s perforovanou rohovkou – ide o klinický stav po opakovaných uveitídach v minulosti, stav po Pars plana vitrectomii, fakofragmentácii, bazálnej iridektómii a implantácii silikónového oleja a následne stav po vypustení silikónového oleja s pretrvávajúcim sekundárnym glaukómom; B) enukleaovná očná guľa s perforáciou rohovky; C) detail vnútroočných štruktúr po narezaní enukleovanej očnej gule
(foto A. Furdová)

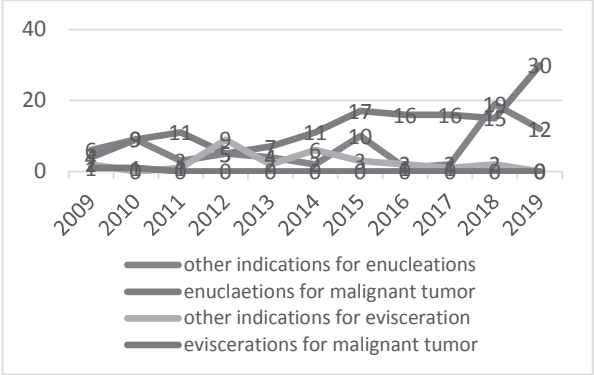
Graph no. 1 is divided into a set of enucleations and eviscerations according to the percentage for the malignant process and for a non - malignant process for the period 2009-2009.

Graph no. 2 is divided into enucleations for benign cause according to the occurrence of diagnoses – percentage.

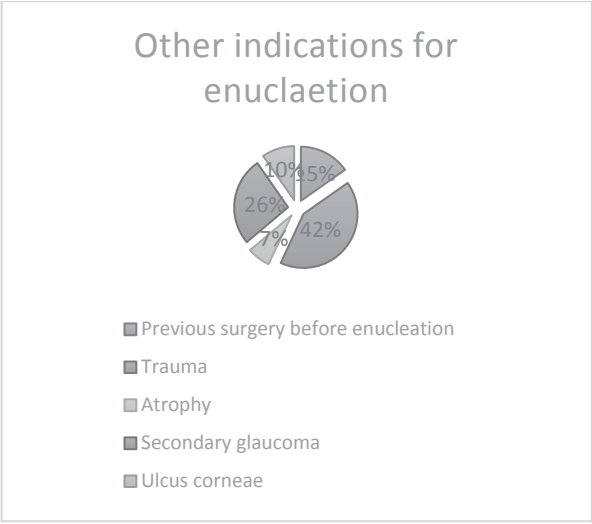
Graph no. 3 shows the period from 2009 to 2019, in which we clearly see the number of enucleations or eviscerations in patients who had an indication from a malignant process but also from another reason, like benign process. In recent years, we have seen an increase in the number of indications for enucleation for the malignant process (up to 30 cases in 2019). The number of post-injury eviscerations has been on a declining trend in recent years.



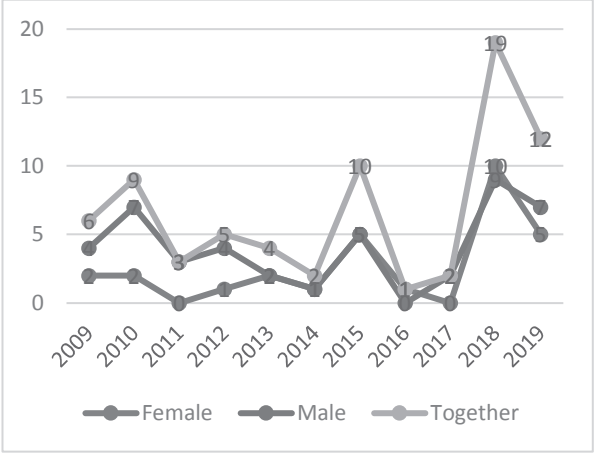
Graph 1. Enucleations divided into 2 bacis files for the period 2009 - 2019
Graf 1. Rozdelenie enukleácii na 2 základné súbory za obdobie 2009 – 2019



Graph 3. Group of patients after enucleation and evisceration in 2009 – 2019
Graf 3. Súbor pacientov po enukleácii a eviscerácii od obdobie 2009 – 2019



Graph 2. Enucleations divided for benign cause according to the occurrence of diagnoses – by percentage
Graf 2. Rozdelenie enukleácii z benígnej príčiny podľa výskytu diagnóz – percentuálne zastúpenie



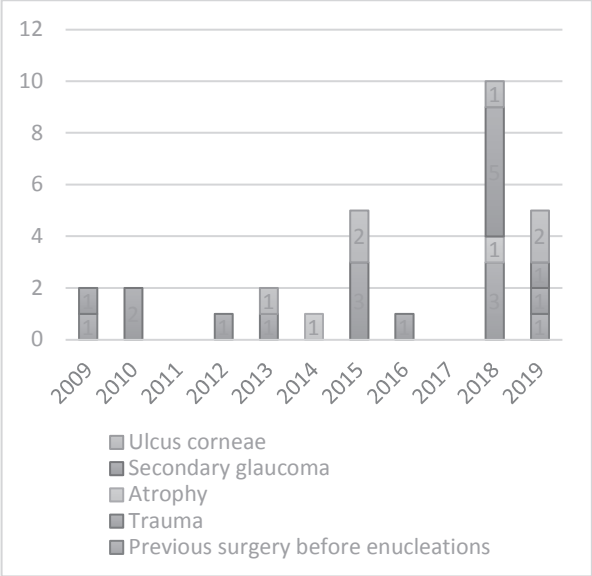
Graph 4. Other indications for enucleation
Graf 4. Iné indikácie enukleácie

Graph no. 4 shows the number of enucleations in the period from 2009 - 2019 by sex and together in individual years separately. We do not see a significant difference between the sexes or recent differences.

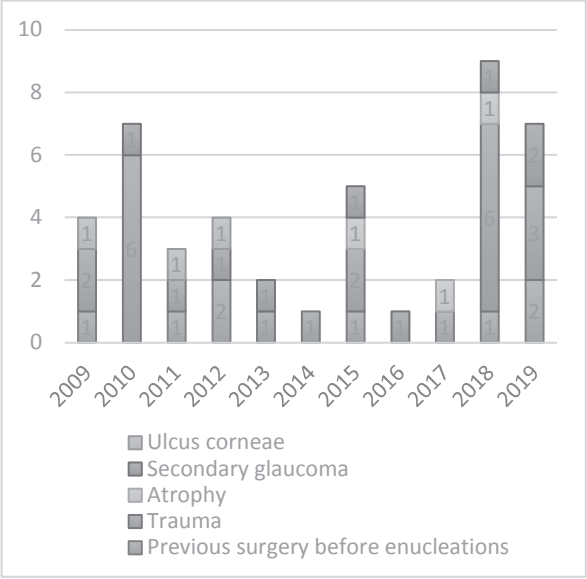
Graph no. 5 shows enucleations in women divided by number in given years, which we divided into 5 subgroups. The most common cause of enucleation was secondary glaucoma after previous operations, e.g. in r. 2018.

Graph no. 6 shows the numbers of enucleations in men in the period 2009-2019 divided by the number of operations in the given years. We divided the file into 5 subgroups. In men, the most common cause of enucleation for the benign process was injury, e.g. in r. In 2018 there were up to 6 cases.

Graph no. 7 shows eviscerations in women divided by number in given years, which we divided into 5 subgroups. In women, the most common cause of evisceration for the benign process was phtisis after previous operations, e.g. in r. 2012 or in 2014.

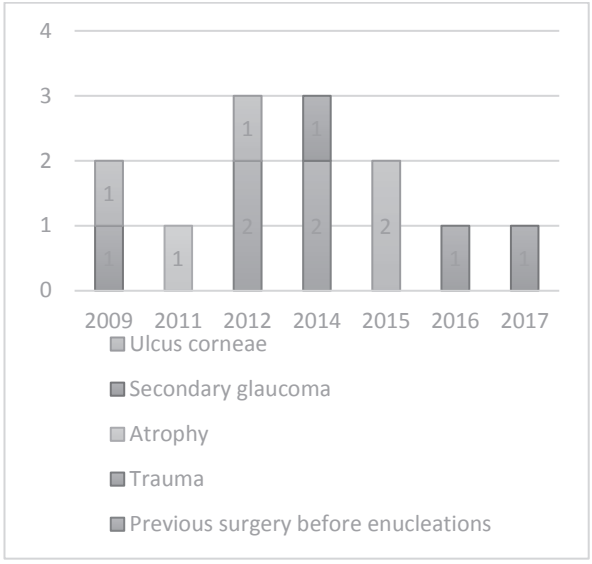


Graph 5. Enucleations in female patients for non malignant indications
Graf 5. Enukleácie u žien pre benígny proces

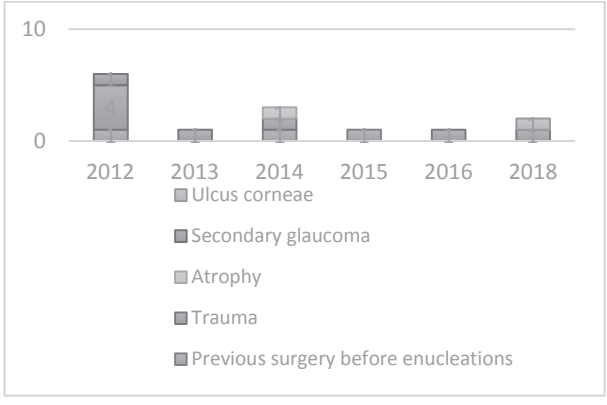


Graph 6. Enucleations in male patients for non malignant indications
Graf 6. Enukleácie u mužov pre benígny proces

Graph no. 8 shows eviscerations in men divided by number in given years, which we divided into 5 subgroups. For example, in men, the most common cause of evisceration for the benign process was post-injury phthisis - up to 4 cases in 2012. Enucleation of the eyeball from a suspected malignant process was most often indicated for malignant intraocular tumor – melanoma of the uvea, which met the indications for enucleation. In 7 patients, enucleation or partial exenteration of the orbit was performed for consequences for previous treatment, resp. in patients with advanced stage basal cell carcinoma with infiltration into the orbit and surrounding structures (Figure 2), in 1 case for epidermoid conjunctival carcinoma infiltrating to surrounding tissues, in 2 cases for malignant melanoma originating primarily from the conjunctiva, but also in 1 case for malignant meningioma.



Graph 7. Evisceration in female patients for non malignant indications
Graf 7. Eviscerácie u žien pre benígny proces



Graph 8. Evisceration in male patients for non malignant indications
Graf 8. Eviscerácia u mužov pre benígny proces

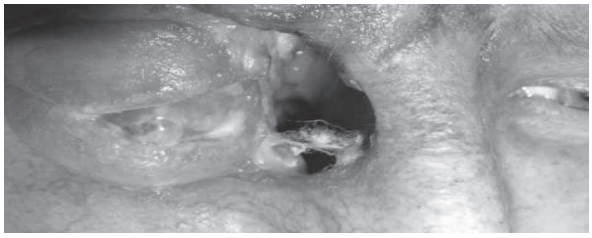


Figure 2. Patient before enucleated right eye due to complications of cornea for large infiltrative basocellular carcinoma, which caused defect of nasal part of orbit with communication to paranasal sinuses (Photo A. Furdová)
Obrázok 2. Pacient pred enukleáciou pravého oka pre komplikácie na rohovke pre rozsiahly infiltratívny bazocelulárny karcinóm, ktorý spôsobil defekt nazálnej časti očnice s komunikáciou do paranazálnych dutín (foto A. Furdová)

DISCUSSION

Ophthalmology has made significant progress in solving injuries, as well as cancer, but radical surgery such as enucleation or evisceration still has its place in indicated cases. Even in today's modern age of medicine, we still do not have to use such radical surgical procedures, but sometimes it is based on an acute condition, but it also happens that patients seek out a cosmetic ophthalmologist after injuries or repeated operations. The loss of an organ has a significant effect on the patient's psyche. In our work, we analyzed the results of enucleations and eviscerations in a group of our patients, and we found, as in other workplaces, a higher number of enucleations for injuries in men than in women, which may be related to their work or sports activities (Zheng, Wu 2013; Farokhfar *et al.* 2017).

The surgeon's decision in severe injuries for enucleation or evisceration can be determined by several factors; however, several workplaces prefer evisceration mainly for cosmetic reasons in patients, where patients are reliably followed up in order to reduce the incidence of sympathetic ophthalmia (Zheng, Wu 2013).

In acute conditions, we always strive for primary suture, but out of the total number of 11 years, we had to proceed primarily with enucleation or evisceration in 8 patients. Three patients underwent enucleation for injury and one eviscerated, one eviscerated the day after cataract surgery for endophthalmitis, and two for perforated ulcus cornae engraved the eyeball. One patient was specific in that he was admitted to our hospital with a diagnosis of eyeball avulsion (Figure 3). One of the patients with enucleated eye had histologically confirmed intraocular neurofibroma. Of the total number, a mobile prosthesis was sutured during enucleation in 13 patients and in 3 with evisceration.

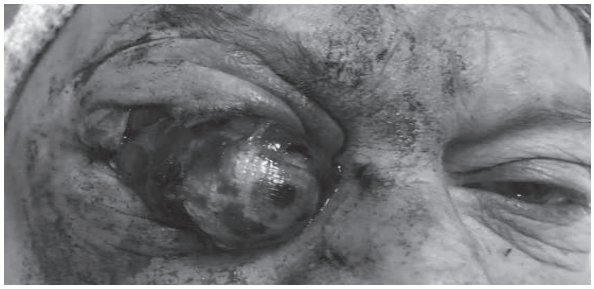


Figure 3. Patient few hours after trauma with avulsion of the right eye globe
(Photo K.Horkovičová)
Obrázok 3. Pacient niekoľko hodín po úraze s avulziou očnej gule vpravo
(foto K. Horkovičová)

In patients with military injuries, the proportion of enucleations and eviscerations is the same in severe devastating eye injuries, but the percentage of sympathetic ophthalmia is very low in both surgical procedures (Holmes *et al.* 2019).

Despite significant advances in the treatment of corneal ulcer and new techniques and procedures in eye microsurgery in some cases, it is necessary to approach a radical solution in the final stage (evisceration, enucleation). In his study, Hongyok described 100 patients who underwent this radical solution, all of whom had visual acuity worse than 5/200 (Hongyok, Leelaprute 2016).

Enucleation in patients with primary intraocular tumors has been replaced in recent decades by various forms of radiotherapy and combined procedures with local tumor resection. Uveal melanomas affect 2 to 8 million Europeans each year. Approximately 35% are treated by enucleation. Proton beam radiotherapy may be an alternative to enucleation in patients who do not consent to enucleation (Hope-Stone *et al.* 2019). Despite radical enucleation therapy, the number of patients who develop metastases and end fatally is still as high as 50% (Jager *et al.* 2020). There remains a concern that if choroidal malignant melanoma is small and undiagnosed because of its size, it may cause the tumor to metastasize and the patient will die sooner compared to if the tumor is larger and diagnosis and

therapy faster. The survival of patients after primary enucleation for the tumor process - malignant uveal melanoma or after radiosurgical procedures is not different (Brovkina 2018; Furodvá *et al.* 2018; Shields, Shields 2015; Zahorjanová *et al.* 2020; Damato 2010). The quality of life after eye loss is also determined by the cosmetic effect and is very important for the patient. In a study in Ireland of 138 patients out of 206 patients who completed a quality of life questionnaire after enucleation or brachytherapy for uveal melanoma, there were no significant differences between the two groups (Scannell *et al*. 2020). It should not be forgotten that in addition to proper diagnosis and treatment, it is necessary to pay attention to the psychological consequences in patients after enucleations or eviscerations (Hope-Stone *et al.* 2019; Fini *et al.,* 2012; Furdová, Lukačko 2017; Justusová *et al.* 2016; Furdová *et al.* 2020; Ilavská, Kardoš 2011).

In a retrospective study in from 1990 to 2000, Cohen et al. 198 patients with choroidal melanoma who were treated with stereotactic radiosurgery - 78 patients or enucleation - 118 patients (Cohen *et al.* 2003).

In all patients with confirmed metastases in the follow-up interval from treatment, liver metastases were confirmed by sonography or CT examination - 53 patients (27%). Enucleation was required in 8 patients after treatment with stereotactic radiosurgery. The duration of follow-up ranged from 1 month to 10 years, 7 patients dropped out of the study group in the group of enucleated patients, in the group of patients after stereotactic radiosurgery one dropped out of the follow-up. This study was the first analysis of patient survival after enucleation and after stereotactic radiosurgery. There was no significant effect on the interval without metastasis after treatment depending on age, gender, presence of extrascleral spread or secondary retinal detachment. This study confirmed that the largest tumor size and tumor location are independent prognostic factors in patient survival (Seregard, Kock 1995). In the study of Furdova et al. there was no difference in the prognosis of patients after radical surgery (enucleation) and after irradiation with a radiosurgical method (Furdová *et al.* 2018; Furdová *et al.* 2010; Furdová *et al.* 2017; Furdová *et al.* 2011).

Enucleation for melanoma from the corpus ciliare is less common and in some patients, enucleation occurs after prior irradiation for subsequent complications. In the group of authors Furdova et al. reported secondary enucleation for post-radiation complications in 3 (17.64%) patients, all of whom had histopathologically confirmed malignant melanoma arising from the ciliary body (Furdová *et al.* 2017).

CONCLUSION

For each patient, our aim is the primary salvage of the eyeball, if it is possible also for the preservation of visual functions, and we approach primary enucleation or evisceration in cancers at an advanced stage, where this method is indicated. We perform enucleation or evisceration primarily, only in the case of a serious devastating injury or in order to prevent the spread of infection, which could endanger the patient's life. it is always necessary to instruct the patient before the operation about the severity of the condition and give him time to be able to prepare sufficiently, as it is a removal of the eye.

CONFLICT OF INTEREST

The authors hereby declare that the origin of the topic of the professional article and its publication is not in conflict with interests, is not supported by any pharmaceutical company and has not been assigned to another journal or printed elsewhere, except for congressional abstracts and recommended procedures.

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TRABECULECTOMY IN GLAUCOMA SURGERY
TRABEKULETÓMIA V CHIRURGICKEJ LIEČBE GLAUKÓMU

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ABSTRACT

Aim: Retrospective analysis of surgical outcomes in glaucoma patients during 5 years, focusing on importance of the trabeculectomy in the surgical treatment of glaucoma, taking into account the latest European glaucoma Society recommendations.

Materials and Methods: The sample consists of 304 subjects who underwent 368 surgeries on 368 eyes in a time interval of 5 years. An exploratory-type retrospective study was used. The group includes patients with the main diagnosis of primary or secondary glaucoma, coded according to the international classification of diseases H40.1-H40.9, H42.0 and H42.8 hospitalized in a time interval of 5 years at the Department of Ophthalmology, Faculty of Medicine, Comenius University in Bratislava. Inclusion criteria were glaucoma surgery with decompensated values of intraocular pressure despite maximum antiglaucoma treatment and patients who have signs of progression in ophthalmoscopy, perimetry and other imaging modalities.

Results: In the analyzed sample of 368 eyes, trabeculectomy with basal iridectomy was performed in 188 eyes (51.1%). The remaining 180 eyes (48.9%) underwent other surgeries. Simple trabeculectomy as the only procedure was performed in 152 eyes (80.9%), antimetabolites were used in 25 eyes (13.3%), in which mitomycin C was used in 13 (6.9%) and 5-fluorouracyl in 12 eyes (6.4%). As a combined operation, trabeculectomy and basal iridectomy with phacofragmentation of the lens and implantation of an artificial intraocular lens was performed in 11 eyes (5.8%). The initial operation of trabeculectomy with basal iridectomy was performed in 143 eyes (94.1%). Reoperation was required in 9 eyes (5.9%).

Conclusion: By analyzing the data of our patients, we confirmed the recommendations of the European Glaucoma Society, where trabeculectomy is the most commonly used surgery in the treatment of primary forms of glaucoma. In secondary forms of glaucoma, the position of trabeculectomy is less clear.

Key words: trabeculectomy, primary and secondary glaucoma, glaucoma treatment, glaucoma surgery, antimetabolites

ABSTRAKT

Cieľ: Retrospektívna analýza chirurgických výsledkov u pacientov s glaukómom počas 5 rokov so zameraním na význam trabekulektómie v chirurgickej liečbe glaukómu s prihliadnutím na najnovšie odporúčania Európskej glaukómovej spoločnosti.

Materiál a metódy: Súbor tvorí 304 pacientov, ktorým bolo realizované 368 operácií na 368 očiach v časovom intervale 5 rokov. Použila sa retrospektívna štúdia exploratívneho typu. Do súboru boli zaradení pacienti s hlavnou diagnózou primárny alebo sekundárny glaukóm,

s kódovým označením diagnózy podľa medzinárodnej klasifikácie chorôb: H40.1-H40.9, H42.0 a H42.8, hospitalizovaní v časovom intervale 5 rokov na oftalmologickej klinike Lekárskej fakulty Univerzity Komenského v Bratislave. Kritériom pre zaradenie bola operácia glaukómu s dekompenzovanými hodnotami vnútroočného tlaku napriek maximálnej antiglukomatóznej liečbe a pacienti, u ktorých bola zaznamenaná progresia v objektívnom náleze, perimetrii a iných zobrazovacích modalitách.

Výsledky: V sledovanom súbore 368 očí bola trabekulektómia s bazálnou iridektómiou realizovaná u 188 očí (51,1%). U zvyšných 180 očí (48,9%) bol realizovaný iný operačný výkon. Trabekulektómia ako samostatný výkon bol realizovaný u 152 očí (80,9%), s použitím antimetabolitov sa realizovala u 25 očí (13,3%) z toho antimetabolit mitomycín C bol použitý 13 krát (6,9%) a antimetabolit 5-fluorouracyl 12 krát (6,4%). Ako kombinovaný operačný výkon, trabekulektómia a bazálna iridektómia s fakofragmentáciou šošovky a implantáciou umelej vnútroočnej šošovky bola realizovaná u 11 očí (5,8%). Prvotný operačný výkon trabekuletómia s bazálnou iridektómiou bol realizovaný u 143 očí (94,1%). U 9 očí (5,9%) bola nutná reoperácia.

Záver: Analýzou dát našich pacientov sme potvrdili odporúčania Európskej glaukómovej spoločnosti, kde trabekulektómia predstavuje najčastejšie používaný chirurgický zákrok v liečbe primárnych foriem glaukómov. Pri sekundárnych formách glaukómu je už postavenie trabekulektómie menej jednoznačné.

Kľúčové slová: trabekulektómia, primárny a sekundárny glaukóm, liečba glaukómu, chirurgia glaukómu, antimetabolity.

INTRODUCTION

Glaucoma is a multifactorial disease characterized by progressive optic neuropathy. This disease has been known in medicine since the Middle Ages. Already in ancient Greece, Hippocrates described the condition "glaykoseis", translated as "green color of sea water", as a blindness that occurs in the elderly. Worldwide, glaucoma is the second leading cause of blindness and a serious health and socio-economic problem (Grewe 1986; Oláh 1998; Gerinec 2005).

Glaucoma is characterized by irreversible damage of the optic nerve, which and without appropriate treatment leads to gradual impairment of visual function, which eventually results in irreversible and complete loss of visual function. However, glaucoma is not just about local changes. These also occur in the basal ganglia of the brain and heart activity (Mlčák 2009; Mlčák *et al*. 2009; Ferková 2012).

Glaucoma treatment aims to maintain the patient's visual functions in the context of quality of life. We have a choice of many methods that are gradually evolving and constantly improving. Surgical treatment is usually performed in the event of failure of the conservative method of therapy and its main goal is to reduce intraocular pressure and thus stop the ongoing glaucoma progression and thus improve the patient's quality of life (European Glaucoma Society 2014; Rozsíval *et al.* 2017; Lešták *et al.* 2019).

Trabeculectomy is currently the gold standard in the surgical treatment of glaucoma (Gerinec 2005). The first description of trabeculectomy (TE) dates back to 1830 and is attributed to William McKenzie of Glasgow, who created a connection between the anterior chamber of the eye and the outer space by sclerotomy behind the corneal limbus. Peripheral iridectomy was first described by Albrecht von Graef in 1857. The surgical procedure was gradually modified and developed, and in 1968 Cairns first described and used the term trabeculotomy. The technique of trabeculectomy, despite several variations, has remained similar to Cairnsen's original description to this day (Morgan 2012).

The indication of filtration surgery - trabeculectomy is the amount and duration of increased intraocular pressure (IOP), the extent and progression of the visual field defect, the extent of damage to the optic nerve head, the condition and course of the disease if trabeculectomy was performed the patient's general condition, life prognosis and, last but not least, the patient's own view of the loss of visual functions and his expectation from surgery. Despite the effect of

surgery on stabilization progressive neuropathy, complications are relatively common. The most significant include decreased central visual acuity because of edema of the optic nerve head or macula, irregular astigmatism, photophobia, cataract formation, foreign body sensation, eye pain, choroidal effusion due to, shallowing or disappearance of anterior chamber, failure of the hypotensive mechanism, subchoroidal haemorrhage, filter pad inflammation (blebitis) leading to bulbar atrophy (Rozsíval *et al.* 2017; Jiang *et al.* 2018). A drawback to the effectiveness of trabeculectomy is the subsequent process of scarring in the area of the Tenon's fascia or sclera, which leads to the closure of the filter channel and an increase in intraocular pressure. In these cases, the scarring process can be prevented by using antifibrotic substances - mitomycin C and 5-fluorouracil (5-FU), which suppress the production of fibroblasts and thus the whole scarring process after TE (Heng Hah *et al.* 2012; Jiang *et al.* 2018).

METHODOLOGY

In our work, we chose a retrospective exploratory-type study with a time interval of 5 years, from January 1, 2015 to December 31, 2019. We used methods of univariate, (one-dimensional) and bivariate (two-dimensional) descriptive (descriptive) statistical analysis on categorical data. Categorical data are expressed as absolute numbers and relative numbers (percentages) of statistical units in a given category. We also monitored the time development in selected characteristics. Our sample includes subjects hospitalized at the Department of Ophthalmology of the Medical Faculty of Comenius University in Bratislava with the main diagnosis of primary or secondary glaucoma, according to the international classification of diseases coded H40.1-H40.9, H42.0 and H42.8. Inclusion criteria were glaucoma surgery with decompensated values of intraocular pressure despite maximum antiglaucoma treatment and patients who have signs of progression in ophthalmoscopy, perimetry and other imaging modalities.

Our sample included 304 patients, 158 men and 146 women, who underwent 368 surgeries on 368 eyes during 5 years. Age and gender were not taken into account when enrolling patients. The mean age of patients is 55 years with a median of 66.5 years with a maximum of 91 years and a minimum of 19 years. We analyzed the data using Microsoft Excel and Microsoft Word 2010 and displayed the data into clear tables and graphs.

RESULTS

The analyzed sample consists of 304 patients, 158 men and 146 women, who underwent 368 operations (eyes) in a time interval of 5 years.

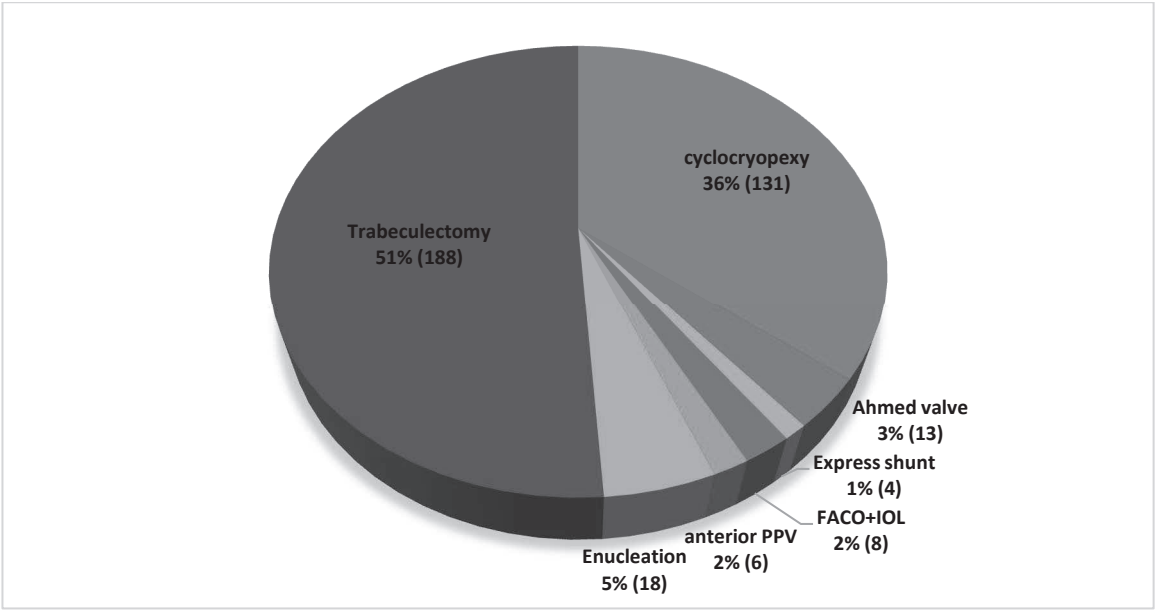
Based on the available data, we found that in the monitored group of 368 eyes, trabeculectomy with basal iridectomy was performed in 188 eyes (51.1%). The remaining 180 eyes (48.9%) underwent other surgery - cyclocryopexy, implant application (Ahmed valve, Express Shunt), phacoemulsification with intraocular lens implantation (FAKO + IOL) without previous or subsequent TE, anterior pars plana vitrectomy (PPV) or enucleation. The data obtained are clearly shown in graph 1 and table 1.

Based on the data summarized in tab. 2, we found that in the monitored group of eyes, trabeculectomy with basal iridectomy was performed in 188 eyes (51.1%).

Table 1. Individual surgical procedures

n = 368	**TE**	**Cyclocryopexy**	**Ahmed valve**	**Expres shunt**	**FACO + IOL**	**Anterior-PPV**	**Enucleation**
Number of operated eyes	188	131	13	4	8	6	18
Percentage (%)	51,1	35,6	3,5	1,1	2,2	1,6	4,9

n = absolute number; TE = trabeculectomy, FACO = facofragmentation, IOL = introcular lens, PPV = pars plana vitrectomy

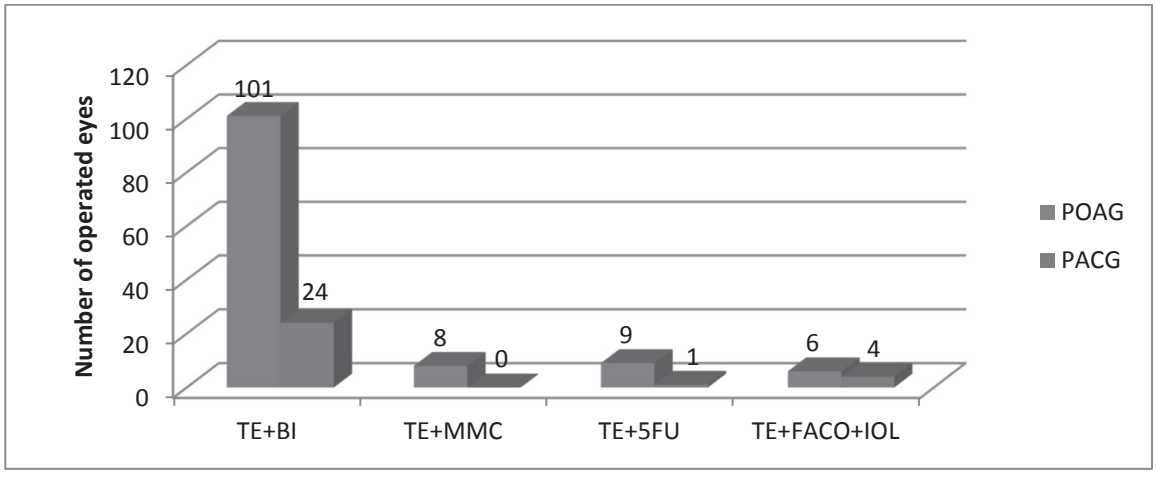


Graph 1. Percentage and absolute values of individual glaucoma operations

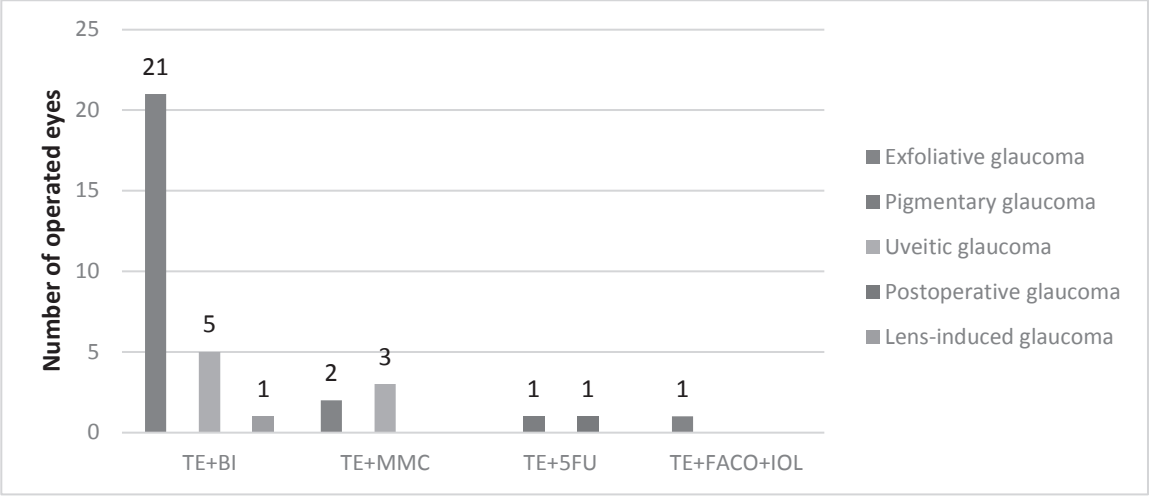
Table 2. Trabeculectomy with basal iridectomy

	TE+BI	TE+BI +Mitomycin C	TE+BI + 5FU	TE+BI + FACO+IOL
POAG	101	8	9	6
PACG	24	0	1	4
Exfoliative glaucoma	21	2	0	1
Pigmentary glaucoma	0	0	1	0
Uveitic glaucoma	5	3	0	0
Postoperative glaucoma	0	0	1	0
Lens-induced glaucoma	1	0	0	0
Together	**152**	**13**	**12**	**11**

POAG = primary open angle glaucoma; PACG = primary angle closure glaucoma;



Graph 2. Primary glaucoma - trabeculectomy with basal iridectomy



Graph 3. Secondary glaucoma - trabeculectomy with basal iridectomy

Of these, trabeculectomy as a single surgery was performed in 152 eyes (80.9%). Trabeculectomy with basal iridectomy using antimetabolites was performed in 25 eyes (13.3%), of which mitomycin C was used 13 times (6.9%) and 5-fluorouracyl 12 times (6.4%). As a combined operation, trabeculectomy and basal iridectomy with phacofragmentation of the lens and implantation of an artificial intraocular lens was performed in 11 eyes (5.8%). Initial TE + BI surgery after previous unsuccessful conservative and laser treatment was performed in 143 eyes (94.1%). The remaining 9 eyes (5.9%) were reoperations after previous failed surgery, which did not bring the desired effect, in which 5 cases were with primary glaucoma and 4 cases were with secondary glaucoma. Antimetabolites (MMC or 5-FU) were used in reoperation in all 9 eyes. The data are summarized in Graphs 2 and 3.

DISCUSSION

Glaucoma is a serious eye disease. Over time, the patient develops damage to the optic nerve and subsequent impairment of visual function. If we do not start adequate treatment in time, the patient will experience irreversible loss of vision. We have several options to treat the patient. We have conservative and laser treatment available, but in some cases we have to resort to surgery. According to the European Glaucoma Society (2014), the most commonly used surgery in the treatment of POAG is trabeculectomy (European Glaucoma Society 2014). Trabeculetomy is a filtration surgery in which a communication is formed between the anterior chamber and the subconjunctival space (BMJ Publishing Group Ltd. BMA House 2017). Indications for surgery are conditions where other forms of therapy, such as medication or laser fail to produce the desired effect, as well as when other forms of treatment are not suitable because of patient compliance or other reasons. It is also an indication to prevent further progression of the disease, which cannot be achieved with medication or by laser, and in the case of advanced disease diagnosis, when other methods would not be successful (Krásnik, Furdova and Oláh 2014; BMJ Publishing Group Ltd. BMA House 2017; Oláh *et al.* 2017).

In our group of patients, trabeculectomy subgroup represented 51.1% (188 eyes) of all surgical procedures in patients with glaucoma. Of these, 154 eyes (81.4%) were patients with the primary form of glaucoma (POAG and PACG).

For a more accurate comparison of results, a Goldman applanation tonometer was used to measure IOP in all subjects. Tonometers are calibrated to measure pressure in millimeters of mercury (mmHg). There are many different types of tonometers, including Schiotz, Goldmann, Perkins, Marg-MacKay, Air-Puff = American Optical, and the new "Triggerfish" wireless contact lens = Sensimed AG (Cridland 1917; Goldmann 1954; Mackay, Marg and Oechsli 1960; Perkins 1965; Myers and Scott 1975).

When analyzing the data in our follow-up in table 1 and 2 and graphs 1 to 3, we found that trabeculectomy in the study group represents 124 operations out of a total of 148 operations in POAG in 5 years, which represents 83.8% of POAG operations. In the case of

PACG, trabeculectomy also represents the majority of operations, namely 24 eyes (50.9% of PACG surgery). In the remaining 16.2% for POAG and 49.1% for PACG, other surgical modalities are represented. In his study, Landers (2012) also evaluates trabeculectomy as the most widely used surgical technique and method of choice in primary glaucoma. Repeated trabeculectomy was performed in 4 patients with POAG (3.2%), in all cases using antifibrotic agents. In PACG, repeated TE was performed in 2 cases (6.7%), but without the use of antifibrotic agents (Landers *et al.* 2012).

The use of antifibrotic agents significantly reduces the risk of postoperative scarring but brings complications due to their toxicity (Khaw *et al.* 2017). In our group of patients, out of 25 cases of trabeculectomy combined with an antimetabolite (MMC or 5FU), this procedure was performed in 18 eyes with primary glaucoma and in 7 eyes with secondary glaucoma. In primary glaucoma, the procedure was performed as a reoperation after a previous trabeculectomy in 4 eyes (22.2%). In the remaining 14 eyes, this method was chosen on the basis of a preoperative examination of a patient without a previous trabeculectomy in the past. In secondary glaucoma, the antimetabolite together with trabeculectomy was used in 6 eyes (85.7%) as the primary choice, in cases of post-inflammatory, postoperative, pigmented or pseudoexfoliative glaucoma. In 1 case, an antimetabolite with TE was used after a previous unsuccessful cyclocryopexy. In all 25 cases, the need for further reoperation has not yet been identified.

Khandelwal *et al.* (2015) in their work on the combined surgery of glaucoma and cataracts speak of the high safety and efficacy of this procedure with a minimum of postoperative complications (Khandelwal *et al.* 2015). In our group, a combined surgical procedure of trabeculectomy with cataract surgery was performed in 11 patients with primary or secondary glaucoma. In all 11 cases, the postoperative outcome was without complications, intraocular pressure was within the normal range (≤18 mmHg) and reoperation or additional conservative therapy was not necessary.

In a retrospective analysis of data on surgical treatment of glaucoma at our clinic, we confirmed the important role of trabeculectomy with basal iridectomy in the treatment of primary open-angle or closed-angle glaucoma, in case of progression of glaucoma neuropathy despite maximum conservative or laser therapy, as well as hypersensitivity to conservative and laser possibilities.

The use of antimetabolites, especially in repeated trabeculectomies, leads to a reduction in postoperative scarring and the risk of further reoperation is thus lower. However, due to their high corneal toxicity, we recommend their use only when necessary. In secondary glaucoma, cyclocryopexy plays a major role in the analysis, which, despite the declining European trend of use, represents an important method for us in the treatment of refractory secondary glaucoma with high VOT values, not responding to conservative therapy (Khaw *et al.* 2017; Sanchez *et al.* 2018; Lanza *et al.* 2019; Sarrafpour *et al.* 2019). In secondary glaucoma, the treatment of the underlying diagnosis as a causal cause of the condition should not be forgotten either (Ferková 2012; Furdova *et al.* 2018).

CONCLUSSION

Glaucoma is the second most common cause of vision loss and a serious problem in ophthalmology. Clinical care for patients with glaucoma must be individual, tailored to the patient's needs, taking into account its socio-economic status. If we identify risk factors in time, establish an accurate diagnosis and implement the most appropriate method of treatment based on the latest knowledge and recommendations, we will prevent the development of structural and functional glaucoma changes. The goal of glaucoma treatment is to maintain the best possible visual functions of the patient and improve his quality of life. In the management of a glaucoma patient, we must not forget about further follow-up of the disease in order to be able to respond in time to any changes by adjusting and adapting the therapy using the latest knowledge.

Glaucoma is a specific problem in ophthalmology. In its treatment, but especially in the surgical one, it is necessary to take into account the fact that individualization and adequate choice of technique, taking into account the current state and degree of the disease, its local and general comorbidities and the expected perioperative and postoperative course. Last but not least, the patient's "compliance" and his approach and responsibility for postoperative treatment as well as his willingness to cooperate in postoperative care and regular check-ups at the glaucoma outpatient clinic are important.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest in connection with the published article.

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MMRP (MISMATCH REPAIR PROTEINS) AND SURVIVIN IN TUBULAR COLON ADENOMAS

MMRP (PROTEÍNY OPRAVUJÚCE NEZHODY) A SURVIVIN V TUBULÁRNYCH ADENÓMOCH HRUBÉHO ČREVA

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ABSTRACT **Objective:** The aim of our study was to observe the immunohistochemical expression pattern of mismatch repair proteins (MMRP), mutl homolog 1 (MLH1), mutl homolog C 2(MSH2), mutl homolog C 6 (MSH6) and mismatch repair endonuclease 2 (PMS2), as well as survivin, in colon polyps.
Methods: We assessed above mentioned proteins in a unified group of 124 tubular adenomatous colon polyps with regard to the presence of dysplastic abnormalities in order to explore their relationship. Furthermore, we studied their relation to such clinicomorphological parameters as the age of patients, size of adenoma, degree of dysplastic changes and localization of the lesion.
Results: Survivin was expressed in 97 cases (78.2%), MLH1 was found in 111 cases (89.5%), MSH2 in 115 cases (92.7%), MSH6 in 118 cases (95.2%) and PMS2 in 105 cases (84.7%). The majority of absent MMRP cases was detected where the adenoma size was less than 10 mm with LGD (low-grade dysplasia). Survivin expression significantly correlated with the adenoma size and dysplasia grade. Subcellular survivin compartmentalization was statistically associated with the adenoma size, dysplasia grade and adenoma localization. Furthermore, we confirmed a significant relation between survivin expression and MMRP. In general, the intensity of immunoreaction was stronger in the MMRP than in survivin.
Conclusions: Our recent results suggest that MMRP may suppress the antiapoptotic activity of survivin in LGD and HGD (high grade dysplasia) colon adenomas.

Key words: mismatch repair proteins, survivin, colon adenoma

ABSTRAKT **Cieľ:** Cielom našej štúdie bolo pozorovať imunohistochemický profil expresie opravy nezhody (MMRP) MLH1, MSH2,MSH6 a PMS2 ako aj survivínu v polypoch hrubého čreva.
Metódy: Vyššie uvedené proteíny sme hodnotili v 124 tubulárnych adenomatóznych polypoch hrubého čreva s dôrazom na prítomnosť dysplastických abnormalit s cieľom preskúmať ich vzťah. Ďalej sme študovali ci vzťah k takým klinickomorfologickým parametrom ako sô vek pacientov, veľkosť adenómu, stupeň dysplastických zmien a lokalizácie lézie.
Výsledky: Survivin bol prítomný v 97 prípadoch (78,2%), MLH1 da zistil v 111 prípadoch (89,5%), HSH2 v 115 prípadoch (92,7%), MSH6 v 118 prípadoch (95,2%) a PMS2 v 105 prípadoch (84,7%). Zistili sme vo väčšine adenómoch, ktorých veľkosť bola menšia ako 10 mm s LGD (dysplázia nízkeho stupňa) chýbal MMRP. Expresia prežitia významne korelovala s veľkosťou adenómu a stupňom dysplázie. Distribúcia subcelulárneho survivínu štatisticky korelovala s veľkosťou adenómu, stupňm dysplázie okalizáciou adenómu. Ďalej sme potvrdili

významný vzťahmedzi expresiou survivínu a MMRP. Intenzita imunoreakcie bola silnejšia v MMRP ako v prípade survivínu.
Záver: Naše výsledky naznačujú, že MMMRP môže potlačiť aktivitu survivínu v adenómoch hrubého čreva s LGD a HGD (dysplázia vysokého stupňa).

Kľúčové slová: proteíny oprvujúce nesúlad, survivín, adenóm hrubého čreva.

INTRODUCTION

Mismatch repair (MMR) system is utilized by the proliferating cells to correct errors (mutations) that may develop during DNA replication (Hassen and, Chowdhury 2012). DNA MMR also controls the cell cycle checkpoints, thus genomic stability, and play an important role in apoptosis in response to DNA damage (Cejka *et al* 2003). MMR genes are ubiquitous genes encoding mismatch repair proteins (MMRP). There is a tendency to heterodimerization of MMRP to functional doublets. MSH2 form a heterodimer with MSH6 (or MSH3), which is involved in the diagnostic recognition of misaligned nucleotides and mispaired insertion-deletion loops. Furthermore, MSH2-MSH6 (MSH3) doublet recruits and activates proteins MLH1 and PMS2 (Peltomäk 2003). Subsequently, the MLH1-PMS2 protein complex recruits nucleases, polymerases and other assorted proteins, which initiate downstream repair functions such as the excision of the mismatched DNA strands or microsatellite instable (MSI) sequence repeats (Scherer *et al.* 2005). Defects in the MMR cause an increased spontaneous mutation rate, which is known as the "mutator phenotype" (Charames and Bapat 2005). In addition to elevated mutation rate, loss of MMR function may also lead to instability in simple sequence repeats (microsatellites). During mono-, di-, tri-, and tetranucleotide repeats replication, a new forming strand may slip along the original template, resulting in a bulged mispaired insertion-deletion loop. MMR mutations, predominantly in MLH1, MSH2, MSH6 and PMS2, may initiate the production of inactivated or abnormally short proteins that cannot perform their normal function. Loss of protein expression may suggest a defective MMR.

Protein survivin is a unique member of the inhibitors of apoptosis protein (IAP) family. IAP proteins play a key role in the negative regulation of apoptosis (programmed cell death). Multifunctional survivin possesses a number of distinct features not shared with other IAP family members. Its outstanding position in the IAP family is emphasized by its role in the cell cycle regulation, apoptotic cascade inhibition and angiogenesis stimulation. Survivin is highly expressed in embryonic and fetal tissues as well as in human malignancies (Li and Brattain 2006). On the other hand, it is almost undetectable in most terminally differentiated normal cells. Furthermore, survivin appears to be localized in different subcellular compartments: in the nucleus, in the cytoplasm, or there is a combined immunohistochemical positivity in both the nucleus and cytoplasm (Oh 2009).

Survivin expression is significantly lower in normal adult tissue than in corresponding malignant tumors, furthermore, in tumors it shows different subcellular compartmentalization. Therefore survivin could represent a promising tumor biomarker and prognostic factor (Ge *et al*. 2013).

Basically, MMRPs and survivin are known to be diametrically opposed signals, which may regulate the apoptotic pathways, and both represent a powerful prognostic marker. Therefore, we analyzed the immunohistochemical expression of these proteins in sporadic colorectal adenomas with respect to the degree of dysplastic changes in order to explore their relationship. Moreover, we correlated these proteins with clinicomorphological parameters.

MATERIALS AND METHODS

Archival formalin-fixed paraffin-embedded tissue samples from 124 cases of sporadic colon adenomatous polyps were enrolled in the present study. The study was approved by the Ethics Committee of Jessenius Faculty of Medicine, Comenius University in Martin. All methods were carried out in accordance with the approved guidelines. All patients that participated in this study provided a written informed consent.

Pathology reports from all patients were reviewed and their age, sex, localization and size of polyps recorded. Hematoxylin and eosin stained slides from each patient were reviewed to confirm the degree of dysplasia. The cecum, ascending and transverse colon were regarded as the right or proximal colon, whereas the descending colon, sigmoid and rectum were referred to as the left or distal colon (Pino *et al.* 2009).

Our adenoma group included 87 males (70.2%) and 37 females (29.8%). The average age of males was 60.9 ±10.1 years and of females it was 68.7 ±9.1 years. The polyps were located in male/female patients in 33/13 (26.6% / 10.5%) cases in the right colon and in 54/24 (43.6% / 19.3%) cases in the left colon.

Each paraffin block was cut into three-micrometer thick sections and subjected to immunohistochemical staining. For a greater adherence of the tissue sections to the glass surface, we used Flex slides (Dako, Glostrup, Denmark) baked for two hours in an oven at 59°C. The slides were then treated in a PT Link System (Dako). The endogenous peroxidase activity was quenched with 3% hydrogen peroxide for ten minutes. The immunohistochemical reactions for MMRP were performed using Flex monoclonal mouse anti-human MLH1 and MSH2 antibodies (Dako, Clone ES05 and Clone FE1, respectively), and Flex monoclonal rabbit anti-human PMS2 and MSH6 antibodies (Dako, Clone EP51 and Clone EP49, respectively). For survivin, immunohistochemical staining was performed using monoclonal mouse anti-survivin antibody (Dako, Clone 12C4, dilution 1:50). For MMRP immunoreactions, the sections were incubated for 20 minutes with a primary antibody at room temperature, and sections for MSH2 reaction were treated by Linker / Mouse for 20 minutes. The MLH1, MSH2, PMS2 and MSH6 proteins were visualized by means of the EnVision™ Flex / HRP System (Dako) using 3,3´ - diaminobenzidine (DAB) chromogen as substrate. After a one hour incubation with a primary antibody and Linker / Mouse treatment for 20 minutes, survivin was visualized by means of the EnVision™ Flex / HRP System using 3-amino-9-ethylcarbazole (AEC) chromogen as substrate, according to the manufacturer´s instructions. All sections were counterstained with Mayer´s hematoxylin (Dako). Negative controls were obtained by omitting the primary antibody.

In all cases, the intensity of immunoreaction (weak +, moderate ++, and strong +++) was assessed and in case of survivin also its subcellular localization (nucleus – N, cytoplasm – C, or both – NC).

Analyzed data

The expression and staining intensity of the mismatch repair proteins and the antiapoptotic protein survivin in 124 cases of sporadic colorectal adenomas.

Compared parameters

In all cases, the immunoreaction intensity for survivin and MMRP was assessed and in the evaluation of survivin also its subcellular localization. Further, the expression and staining intensity of MMRP MLH1, MSH2, MSH6, and PMS2 vs. the age of patients, size of adenomas, degree of dysplasia and colon localization; relation between MMRP and survivin.

Statistical analysis

χ^2-test was used for statistical analysis of survivin, MLH1, MSH2, MSH6 and PMS2 expression with the age, size of tumor, dysplasia grade and tumor localization and for comparison of mutual relations between mentioned proteins. The Cochran-Armitage test for trend was used to evaluate whether the intensity of survivin, MLH1, MSH2, MSH6 and PMS2 immunoreactivity correlates with the tumor size, dysplasia grade and tumor localization. Statistical analysis was performed using Microsoft® Excel 2010/XLSTAT©-Pro (Addinsoft, Inc., Brooklyn, NY, USA); the significance level was set at $p<0.05$.

RESULTS

In our panel of 124 colorectal adenomas, survivin was expressed in 97 cases (78.2%) (Table 1), MLH1 in 111 cases (89.5%) (Table 2), MSH2 in 115 cases (92.7%) (Table 3), MSH6 in 118 cases (95.2%) (Table 4), and PMS2 in 105 cases (84.7%) (Table 5).

In the evaluation of absent cases in group of MMRP, majority of them was found in adenoma size <10 mm: 10/13 cases (76.9%) for MLH1 (Table 2), 7/9 cases (77.8%) for MSH2 (Table 3), 4/6 cases (66.7%) for MSH6 (Table 4), and 16/19 cases (84.2%) for PMS2 (Table 5). In parameter "Dysplasia", absent cases were mainly associated with low grade dysplasia: 11/13 cases (84.6%) for MLH1 (Table 2), 7/9 cases (77.8%) for MSH2 (Table 3), 5/6 cases (83.3%) for MSH6 (Table 4), and 15/19 cases (78.9%) for PMS2 (Table 5). In colon localization, absent cases were more frequent in distal colon: 9/13 cases (69.2%) for MLH1 (Table 2), 7/9 cases (77.8%) for MSH2 (Table 3), 5/6 cases (83.3%) for MSH6 (Table 4), and 15/19 cases (78.9%) for PMS2 (Table 5).

Table 1. Relationship between survivin expression and clinicomorphological parameters in colon adenomas

survivin expression	negative	positive	subcellular localization		intensity of immunoreactivity	
			C	NC/N	+	++/+++
age						
≤ 50	1	10	5	5	8	2
51-70	20	59	30	29	51	8
>70	6	28	15	13	23	5
comparison - negative vs positive	P=0.375					
correlation with subcellular localization			P=0.730			
trend test in the intensity of immunoreactivity					P=0.919	
size						
≤5mm	17	26	23	3	25	1
6- 10 mm	9	43	21	22	34	9
>10 mm	1	28	6	22	23	5
correlation with survivin expression (negative vs positive)	P=0.0008					
correlation with subcellular localization			P<0.0001			
trend test in the intensity of immunoreactivity					P=0.165	
dysplasia grade						
low	24	44	42	2	41	3
high	3	53	8	45	41	12
correlation with survivin expression (negative vs positive)	P<0.0001					
correlation with subcellular localization			P<0.0001			
trend test in the intensity of immunoreactivity					P=0.032	
localization						
proximal	9	37	10	27	27	10
distal	18	60	40	20	55	5
correlation with survivin expression (negative vs positive)	P=0.647					
correlation with subcellular localization			P=0.0006			
trend test in the intensity of immunoreactivity					P=0.013	

C – cytoplasmic, N – nuclear, NC - combined cytoplasmic and nuclear
+ weak intensity, ++ / +++ moderate / strong intensity

Table 2. Relationship between MLH1 expression and clinicomorphological parameters in colon adenomas

MLH1 expression	negative	positive	intensity of immunoreactivity	
			+	++/+++
age				
≤ 50	0	11	3	8
51-70	8	71	22	49
>70	5	29	8	21
comparison - negative vs positive	P=0.378			
trend test in the intensity of immunoreactivity			P=0.900	
size				
≤5mm	6	37	18	19
6- 10 mm	4	48	14	34
>10 mm	3	26	1	25
correlation with survivin expression (negative vs positive)	P=0.611			
trend test in the intensity of immunoreactivity			P=0.0001	
dysplasia grade				
low	11	56	27	29
high	2	55	6	49
correlation with survivin expression (negative vs positive)	P=0.019			
trend test in the intensity of immunoreactivity			P<0.0001	
localization				
proximal	4	42	6	36
distal	9	69	27	42
correlation with survivin expression (negative vs positive)	P=0.618			
trend test in the intensity of immunoreactivity			P=0.005	

+ weak intensity, ++ / +++ moderate / strong intensity

Survivin

χ^2-test confirmed that the presence of survivin expression (Table 1) significantly correlates with the tumor size (p=0.0008) and dysplasia grade (p<0.0001). However, correlation with the age of patients and tumor localization was statistically insignificant (p=0.375, p=0.692 respectively).

As for the survivin distribution, our results revealed that the subcellular localization of survivin (Table 1) significantly correlates with the tumor size (p<0.0001), dysplasia grade (p<0.0001) and tumor localization (p=0.0006).

Cochran – Armitage test confirmed a trend that survivin intensity of immunoreactivity increases with higher dysplasia grade (p=0.032) and more proximal localization (p=0.013) of colon adenomas (Table 1).

Table 3. Relationship between MSH2 expression and clinicomorphological parameters in colon adenomas

MSH2 expression	negative	positive	intensity of immunoreactivity	
			+	++/+++
age				
≤ 50	0	11	1	10
51-70	6	73	19	54
>70	3	31	6	25
comparison - negative vs positive	P=0.607			
trend test in the intensity of immunoreactivity			P=0.854	
size				
≤5mm	4	39	14	25
6- 10 mm	3	49	11	38
>10 mm	2	27	1	26
correlation with survivin expression (negative vs positive)	P=0.801			
trend test in the intensity of immunoreactivity			P=0.002	
dysplasia grade				
low	7	60	21	39
high	2	55	5	50
correlation with survivin expression (negative vs positive)	P=0.138			
trend test in the intensity of immunoreactivity			P=0.001	
localization				
proximal	2	44	4	40
distal	7	71	22	49
correlation with survivin expression (negative vs positive)	P=0.337			
trend test in the intensity of immunoreactivity			P=0.006	

+ weak intensity, ++ / +++ moderate / strong intensity

MLH1

MLH1 expression (Table 2) significantly correlates with dysplasia grade (p=0.019). High-grade adenomas expressed MLH1 in 96% of cases, while low-grade ones only in 83% of cases. The intensity of immunoreactivity of MLH1 increased significantly with an increased tumor size and higher dysplasia grade (p=0.0001, p<0.0001 respectively). Interestingly, proximally located adenomas were statistically associated with a stronger immunoreaction intensity (p=0.005).

MSH2

Table 3 shows MSH2 expression in adenomatous polyps. Comparison between MSH2 positive and negative adenomas did not reveal any significant relation to the observed clinicopathological parameters (p>0.05). However, intensity of immunoreactivity in MSH2 positive samples significantly increased with the increasing tumor size and higher dysplasia grade (p=0.002, p=0.001 respectively). Furthermore, the intensity of immunoreactivity was significantly higher in adenomatous polyps with proximal localization (p=0.006).

Table 4. Relationship between MSH6 expression and clinicomorphological parameters in colon adenomas

MSH6 expression	negative	positive	intensity of immunoreactivity	
			+	++/+++
age				
≤ 50	0	11	3	8
51-70	1	78	20	58
>70	5	29	8	21
comparison - negative vs positive	P=0.007			
trend test in the intensity of immunoreactivity			P=0.920	
size				
≤5mm	2	41	19	22
6- 10 mm	2	50	11	39
>10 mm	2	27	1	26
correlation - negative vs positive	P=0.826			
trend test in the intensity of immunoreactivity			P<0.0001	
dysplasia grade				
low	5	62	25	37
high	1	56	6	50
correlation with survivin expression (negative vs positive)	P=0.139			
trend test in the intensity of immunoreactivity			P=0.0003	
localization				
proximal	1	45	8	37
distal	5	73	23	50
correlation with survivin expression (negative vs positive)	P=0.288			
trend test in the intensity of immunoreactivity			P=0.100	

+ weak intensity, ++ / +++ moderate / strong intensity

MSH6

MSH6 expression (Table 4) showed characteristics similar to MSH2. We confirmed a relation between MSH6 expression and age (p=0.007), but other clinicopathological parameters did not reveal any significant relation (p>0.05). However, the intensity of immunoreactivity in MSH6 positive samples significantly increased with the increasing tumor size and higher dysplasia grade (p<0.0001, p=0.0002, respectively).

PMS2

PMS2 expression (Table 5) significantly correlates with the dysplasia grade (p=0.019). PMS2 positivity increased with the higher dysplasia grade. Furthermore, the intensity of immunoreactivity in PMS2 positive samples also significantly increased with the increasing tumor size and higher dysplasia grade (p=0.008, p<0.0001, respectively). Sixty-six % of adenomatous polyps with proximal localization, but only 43% polyps with distal localization, demonstrated a strong intensity of immunoreactivity (p=0.017).Relation between survivin and mismatch proteins (Table 6).

Table 5. Relationship between PMS2 expression and clinicomorphological parameters in colon adenomas

PMS2 expression	negative	positive	intensity of immunoreactivity	
			+	++/+++
age				
≤ 50	2	9	3	6
51-70	11	68	34	34
>70	6	28	13	15
comparison - negative vs positive	P=0.848			
trend test in the intensity of immunoreactivity			P=0.742	
size				
≤5mm	9	34	20	14
6- 10 mm	7	45	24	21
>10 mm	3	26	6	20
correlation - negative vs positive	P=0.420			
trend test in the intensity of immunoreactivity			P=0.008	
dysplasia grade				
low	15	52	35	17
high	4	53	15	38
correlation with survivin expression (negative vs positive)	P=0.018			
trend test in the intensity of immunoreactivity			P<0.0001	
localization				
proximal	4	42	14	28
distal	15	63	36	27
correlation with survivin expression (negative vs positive)	P=0.116			
trend test in the intensity of immunoreactivity			P=0.017	

+ weak intensity, ++ / +++ moderate / strong intensity

We confirmed a significant relation between survivin expression and all of the mismatch proteins ($p<0.05$). The following analysis shows that adenomatous polyps in which survivin intensity was lower than the intensity of mismatch protein - MLH1, MSH2, MSH6 and PMS2 formed the following percentages of all samples: 64%, 72%, 71% and 52%, respectively. Adenomas with identical intensity of survivin and mismatch protein - MLH1, MSH2, MSH6 and PMS2 formed 24%, 21%, 24% and 29% of all samples, respectively.

DISCUSSION

Many molecular abnormalities have been described in adenomatous polyps, including defects in MMR, which cause an increased spontaneous mutation rate, known as the mutator phenotype. Loss of MMR function may accelerate the development and accumulation of mutations in genes, which are responsible for the control of cell growth. This fact supports a reasonable hypothesis for a rapid enlargement of colon adenomatous polyps and their progressive structural transformation to carcinomas (Molaei *et al.* 2011). In our series, vast majority of MMRP absent cases were found in adenomas <10 mm. In general, the size of adenoma is considered as a valuable prognostic marker, large adenomas >10 mm are associated with worse histomorphological features

Table 6. Relationship between survivin and mismatch proteins expression in colon adenomas

expression	MLH1			MSH2			MSH6			PMS2		
	A	+	++/ +++	A	+	++/ +++	A	+	++/ +++	A	+	++/ +++
survivin A	1	13	13	1	14	12	0	16	11	1	20	6
survivin +	12	17	53	8	11	63	6	15	61	18	25	39
survivin ++/+++	0	3	12	0	1	14	0	0	15	0	5	10
comparison	survivin vs MLH1 P=0.019			survivin vs MSH2 P=0.0002			survivin vs MSH6 P<0.0001			survivin vs PMS2 P=0.0002		

A - absent, + weak intensity, ++ / +++ moderate / strong intensity

(Toll *et al*. 2011). On the other hand, Sheridan *et al.* (2006) suggest that small sized sessile serrated adenomas (SSA) may develop into carcinomas despite their relatively small size. Molecular abnormalities develop through MSI (microsatellite instability).

Either a decreased or completely absent immunostaining for MMRP was described in many SSA (Lee *et al*. 2005). Recently, several studies demonstrated that immune-histochemical detection of MMRP abnormal expression is able to identify defective MMR genes. Molecular testing of MSI status consists of polymerase chain reaction and gel electrophoresis to examine the DNA sequences (Khoo 2013). There is an excellent correlation between the immunohistochemical results and MSI analysis. Both of these approaches are recommended to diagnose the abnormal status of MMR (Lanza 2011). Based on our recent results, we point out that the loss of MMRP expression is also related to small sized sporadic adenomas <10 mm and an increased risk of malignancy should be taken into consideration in these colon lesions. Data regarding the expression absence of MMRP in large vs. small sporadic colorectal adenomas is scarce. Most papers describe and study these proteins in adenomas associated with the Lynch syndrome (Walsh *et al*. 2012).

Furthermore, in our adenoma group, absent cases were mainly associated with low-grade dysplasia. The degree of dysplastic changes is an important histomorphological and prognostic parameter. High-grade dysplasia is the strongest predictor for the development of a malignant tumor. Interestingly, we found a higher prevalence of abnormal staining for four MMRP in the low-grade adenoma cases as opposed to the high-grade cases. Currently, there is a heated discussion within the scientific literature concerning the expression of MMRP and the severity of dysplasia. Some authors conclude that the loss of MMRP expression is also detected in the absence of high-grade dysplasia. On the other hand, a significant correlation was found between MSI and high-grade dysplasia in adenomas. Pino *et al.* (2009) observed a significant association between absent immunohistochemical staining of MMRP and high-grade dysplasia. Study by Walsh *et al.* (2012) demonstrated a mismatch repair deficiency in 12/12 adenomas with high-grade dysplasia (100%) and in 60/79 adenomas with low-grade dysplasia (76%). However, all of the above mentioned research groups dealt with hereditary non-polyposis colorectal cancer (HNPCC) adenomas.

In sporadic colorectal adenomas, the predominant MMRP loss is MLH1. Silencing of the MLH1 gene by promoter hypermethylation results in either partial or complete immunohistochemical absence of the protein in question (Hawkins and Ward 2001). We found the loss of MLH1 protein in 13/124 cases (10.5%). Typically, all absent MLH1 cases were accompanied by the loss of immunohistochemical positivity for PMS2. PMS2 protein is probably unstable without its heterodimer twin (Young *et al*. 2001). The absence of more than one MMRP demonstrates progression via MSI pathway and this pattern may suggest a progressive transformation through adenoma-dysplasia-carcinoma sequence in some portion of the assessed cases. Interestingly, Nakagawa *et al.* (2001) concluded that normal colonic mucosa may also represent a possible precursor lesion by the spread of MLH1 promoter methylation with subsequent

development of sporadic MSI+ colorectal cancer. Methylation of MLH1 promoter was also described by Kuniyasu *et al.* (2001) in hyperplastic mucosa adjacent to colon cancer in athymic mice. Thus, our findings indicate that the expression abnormalities in MMRP system may play a critical role in the early stages of development of premalignant and malignant colon lesions.

In our present study, sporadic adenomas located distally displayed a loss of immunostaining for four MMRPs more frequently. Our results are consistent

Taking into account the key role of survivin in the regulation of apoptosis, it is not surprising that in a wide spectrum of malignant tumors, premalignant lesions and cancer-cell lines elevated survivin levels were described. In our series of dysplastic adenomas, survivin was detected in 78.2% of cases. In general, the immunohistochemical survivin over-expression in malignant biopsy samples indicates a worse prognosis, relapse and/or decreased response to chemotherapeutic treatment (Muto *et al.* 1975). Moreover, a proliferative fenotype of survivin is associated with poor prognostic histomorphological parameters, such as vascular invasion and tumor grade 3 (Talbot 2006).

The correlations of survivin immunoreactivity with other clinicomorphological parameters are shown in Table 1. As expected, the presence of survivin expression significantly correlates with the adenoma size and the degree of dysplasia, statistically significant differences were observed between the subcellular localization of survivin and the adenoma size, dysplasia grade and its localization. Furthermore, there is a significant trend between the intensity of survivin immunoreaction and the dysplasia grade and localization. These recent results suggest that survivin expression pattern in colon adenomas is also associated with worse prognostic features. In general, the incidence of focal malignant changes is increased in larger adenomas and in HGD adenomas (Muto *et al.* 1975). This may represent a definitive relationship between adenomas and colorectal carcinomas (the adenoma-carcinoma sequence) (Talbot 2006).

Both MMRP and survivin are involved in apoptotic cascades. Abnormalities in the regulation of apoptosis may influence the development of early and developed malignant tumors (Yurgelun 2012). On the one hand, the main functions of survivin and MMRP are well described in numerous papers (Sun 2014), but on the other hand, their relation is studied very rarely. To the best of our knowledge, the relation between MMRP and survivin was not so far elucidated in dysplastic colon adenomas.

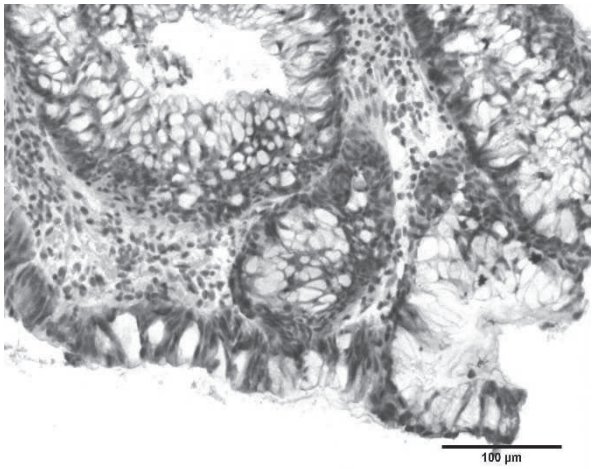

Figure 1. Strong intensity of survivin immunoreaction in HGD colon adenoma

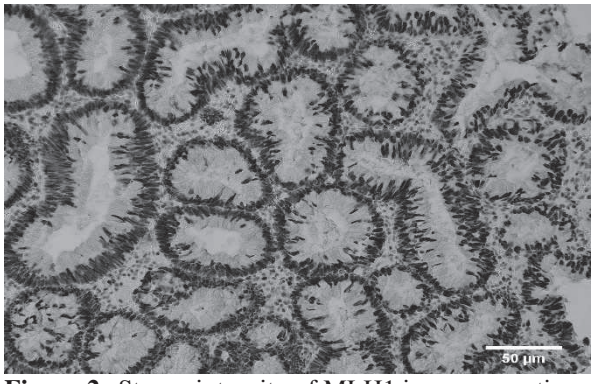

Figure 2. Strong intensity of MLH1 immunoreaction in HGD colon adenoma

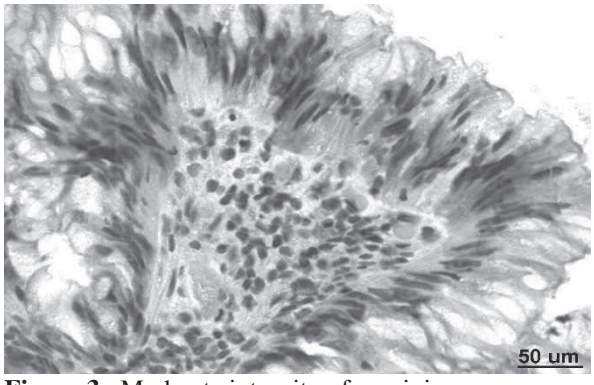

Figure 3. Moderate intensity of survivin immunoreaction in LGD colon adenoma

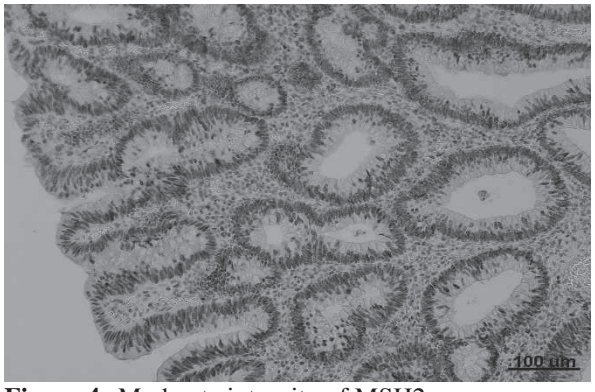

Figure 4. Moderate intensity of MSH2 immunoreaction in LGD colon adenoma.

Briefly, MMRPs are responsible to correct mutations during DNA replication, and the antiapoptotic survivin with its basic functions is an ideal protein for the development of premalignant and malignant lesions. Our analysis revealed a significant relation between the expression of MMRPs and survivin (Table 6). Furthermore, interesting findings were detected by evaluating the immunoreaction intensity. As described in our recent results, the majority of adenomatous polyps showed a lower intensity of survivin immunoreaction in comparison to the intensity of MMRPs. In addition, some percentage of cases revealed identical immunoreaction intensity for both the MMRPs and survivin. This may slightly uncover the relation of these proteins.

MLH1, MSH2 and PMS2 MMRPs are also linked with apoptotic cascade via p53 or its homologue p73 (Stojic *et al.* 2004), e.g. p73 protein is directly stabilized by PMS2 protein and this interaction enhances its pro-apoptotic function (Shimodaira 2003). Other studies, Luo *et al.* (2004) and Hassen *et al.* (2002), described the key role of MLH1 and PMS1/PMS2 heterodimerization. Nuclear accumulation of this complex may increase the activation of p53 by ataxia-teleangiectasia mutated (ATM) protein kinase. Köster *et al.* (2007) reported a significant correlation between the immune-histochemical expression for MSH2 and p53 and apoptosis in cervical carcinoma. Zhang *et al.* (1999) showed that overexpression of MSH2 and MLH1 may induce apoptosis and they demonstrated that MSH2-deficient cells do not display apoptotic features. The expression of functional activity of p53 may regulate the expression of MSH2, since a binding site for p53 was discovered in the promoter region of the MSH2 gene (Scherer 1996). Thus, it seems, that the common denominator between MMRP and apoptosis is the p53 protein. P53 protein can either activate the apoptotic cascade by the up-regulation of several various associated genes or suppress the genes with antiapoptotic functions (Hoffman *et al.* 2002). Survivin is known to be suppressed by wild type p53, because it interacts with the survivin promoter, which is shown as the first promoter to confer p53-dependent repression (Mirza 2002). In addition, p53 may interfere with bcl-2 proteins in mitochondria with a subsequent release of cytochrome c (Halasova *et al.* 2010) and formation of a proapoptotic multi-protein complex apoptosome.

Köster *et al.* (2007) indicated that the MMRP system may be more active in the early stages of cancer development. The presence of dysplastic changes in colon adenomas provides evidence for their malignant potential. In our group of colon adenomas, we detected both moderate and strong intensity of immunoreaction for MMRPs in the majority of positive cases. Furthermore, we found a statistically significant relation and marked differences in the intensity of immunoreactions between the MMRPs and survivin.

Taking into account our current study results and the above mentioned interactions among the proteins in question, we suggest that the MMRPs may influence the antiapoptotic function of survivin by an indirect mechanism via the activation of p53 in LGD and HGD colon adenomas.

CONCLUSIONS.

Our recent results suggest that MMRP may suppress the antiapoptotic activity of survivin in LGD and HGD (high grade dysplasia) colon adenomas

Authorship

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

Conflict of Interest

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

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NEW CLASSIFICATION OF LOW GRADE MALIGNANT CARTILAGE MATRIX-PRODUCING BONE TUMOURS AND THEIR BRIEF MORPHOLOGICAL DIFFERENTIAL DIAGNOSIS

NOVÁ KLASIFIKÁCIA LOW GRADE MALÍGNYCH CHRUPKU TVORIACICH NÁDOROV KOSTÍ A ICH STRUČNÁ MORFOLOGICKÁ DIFERENCIÁLNA DIAGNOSTIKA

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ABSTRACT

Introduction: The new edition of the WHO Classification of Tumours of Soft Tissue and Bone re-classifies cartilage matrix-producing bone tumours. Within malignant lesions, a group of locally aggressive lesions and malignant tumours has been specified. The group of G1 chondrosarcomas has changed the most. They are divided into atypical central/peripheral cartilaginous tumours and central/peripheral G1 chondrosarcomas.

Core: Chondrosarcomas are malignant tumours of the hyaline cartilage, very often with myxoid changes, calcifications or ossification, but without the bone formation. The local recurrence of low grade chondrosarcomas is determined by the adequacy of surgical resection of the tumour – the so-called complete tumour resection does not affect the histological grade. The histological grade determines the risk of distant metastasis.

Conclusion: Despite the new classification, the morphological diagnosis of benign and malignant cartilage matrix-producing bone tumours has remained very challenging. In terms of diagnosis in practice, virtually all chondromatous tumours should be considered as chondrosarcomas until the benignity of given lesions is demonstrated.

Key words: Cartilaginous tumour – Chondrosarcoma – Cartilaginous bone tumours

ABSTRAKT

Úvod: V novej WHO klasifikácii tumorov mäkkých tkanív a kostí došlo preklasifikácii chrupku tvoriacich nádorov kostí. V rámci malígnych lézií sa vymedzila skupina lokálne agresívnych lézií a malígnych tumorov. Najviac sa zmenila skupina chondrosarkómov G1. Rozdelili sa na atypické centrálne / periférne kartilaginózne tumory a na centrálne / periférne chondrosarkómy G1.

Jadro: Chondrosarkómy sú malígny tumor hyalinnej chrupky, veľmi často s myxoidnými zmenami, kalcifikáciami alebo osifikáciou, ale bez tvorby kosti. Vznik lokálnej recidívy low grade chondrosarkómov určuje dostatočnosť chirurgickej resekcie tumoru – tzv. kompletná

resekcia tumoru, neovplyvňuje histologický grade. Histologický grade určuje riziko vzniku vzdialenej metastázy.
Záver: Morfologická diagnostika benígnych a malígnych chrupku tvoriacich kostných tumorov aj napriek tejto novej klasifikácie zostáva veľmi ťažká. Z hľadiska praktickej diagnosticky v podstate všetky chondromatózne tumory až po dokázanie benignity konkrétnej lézie by sa mali považovať za chondrosarkómy.

Kľučové slová: Kartilaginózny tumor – Chondrosarkóm – Chrupkové tumory kostí

INTRODUCTION

The new edition of the WHO Classification of Tumours of Soft Tissue and Bone re-classifies cartilage matrix-producing bone tumours. Within malignant lesions, a group of locally aggressive lesions and malignant tumours has been specified (WHO 2020).

CORE

Locally aggressive lesions include chondromatosis (M-9220/1), atypical cartilaginous tumour (M-9222/1). Malignant lesions include chondrosarcoma, grade 1 (M-9222/3), chondrosarcoma, grade 2 (M-9220/3), chondrosarcoma, grade 3 (M-9220/3), periosteal chondrosarcoma (M-9221/3), clear cell chondrosarcoma (M-9242/3), mesenchymal chondrosarcoma (M-9240/3), de-differentiated chondrosarcoma (M-9243/3) (WHO 2020).

Within the morphological description, the atypical cartilaginous tumour represents one group with chondrosarcoma, grade 1, and is referred to as central or secondary atypical cartilaginous tumour (ACT)/chondrosarcoma G1 (CS1), and the following applies to central lesions:

- they originate in the absence of a benign precursor,
- in general, these are local aggressive recurrent lesions with essentially no metastatic potential,
- a lesion is referred to as central atypical cartilaginous tumour when it is located in the bone marrow of the long or short bones of limbs,
- a lesion is referred to as central G1 chondrosarcoma when it is located in the axial skeleton, flat bones of the scapula, pelvis, and cranial base.

The acceptable name for these lesions also is low-grade central chondrosarcoma.

Secondary conventional ACT/CS1 occur in the bone marrow on the background of pre-existing benign lesions (e.g. on the background of enchondroma, osteochondroma), and are divided as follows:

- secondary atypical cartilaginous tumour – in the skeleton of the limbs,
- secondary chondrosarcoma G1: in the axial skeleton, flat bones of the scapula, pelvis, and cranial base.

The acceptable name for these lesions also is low-grade peripheral chondrosarcoma (WHO 2020).

Chondrosarcoma or chondrosarcomas are malignant tumours of the hyaline cartilage, very often with myxoid changes, calcifications or ossification, but without the bone formation. According to the definition, osteosarcomas are malignant tumours whose cells, although only focally, directly form an osteoid or bone, and the evidence of osteoid tumour is crucial. An exception is a clear cell chondrosarcoma. In chondrosarcomas, a proliferating cartilage can be myxoidically altered, calcified, and secondary ossified. In highly malignant forms on the periphery, a fibrosarcomatous component can also be found (Freyschmidt 2010). The local recurrence of low grade chondrosarcomas is determined by the adequacy of surgical resection of the tumour – the so-called complete tumour resection does not affect the histological grade. The histological grade determines the risk of distant metastasis:

G1 tumours – no metastasis
G2 tumours metastasise in 10%
G3 tumours metastasise in 71%

Chondrosarcoma is most common in the proximal and distal femur (23%), predominantly in men, most often between 40 and 60 years of age (60%; especially around 40 years of age – 66%). Secondary chondrosarcomas occur in younger people aged 30 years and younger. Eccentric chondrosarcomas occur

in younger people under the age of 40 (55%). Highly malignant chondrosarcomas occur in similarly younger people aged 30 years and younger. From the histomorphological point of view, the benignity or malignancy of cartilage matrix-producing bone tumours is determined by the evaluation of 5 basic parameters (Freyschmidt 2010; Povýšil 2017):

- increased tumour cellularity,
- tumorous invasion of normal bones as a part of infiltrative growth,
- lighter chromatin of tumour chondrocytes,
- mucoid matrix deposits (more than 20%),
- patient's age: over 45 years.

CONCLUSION

Despite the new classification, the morphological diagnosis of benign and malignant cartilage matrix-producing bone tumours has remained very challenging. In 1975, Aegerter and Kirkpatrick said that all chondromatous tumours should be considered as chondrosarcomas until the benignity of the lesion itself is demonstrated; and it is basically true even today (Povýšil 2017).

CONFLICT OF INTERESTS:

The authors have no conflict of interests to declare.

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DEVELOPMENT OF HOSPICE CARE IN THE CONTEXT OF MODERNIZATION OF HEALTH CARE IN SLOVAKIA SINCE 1948 UNTIL COVID-19 PANDEMICS

VÝVOJ HOSPICOVEJ STAROSTLIVOSTI V KONTEXTE MODERNIZÁCIE ZDRAVOTNEJ STAROSTLIVOSTI NA SLOVENSKU OD ROKU 1948 AŽ PO PANDÉMIU COVID-19

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ABSTRACT

Introduction: The structures developed in health system in Slovakia 1948 - 1989 are important precondition of later development of hospice care, however, the period is not adequately examined.

Objective: Critical assessment of the development of institutional and legislative framework of healthcare delivery since 1948 and identification of factors that can be associated with development of its organizational forms.

Material and Methods: Historical research with use of primary and secondary historical sources and relevant current literature. Legal research, legal hermeneutics, analysis, abstraction of the corpus of legislation in Slovakia.

Results: Between 1948 and 1989, universal health coverage became available for severely ill people, but only state-controlled organizations in healthcare were legal. Development of civil society allowed spiritual care and creation of hospices. Further reforms allowed direct patients' payments for health and social care, but brought a risk, that this can be limiting factor in further increase of hospices, especially due to economic impact of COVID-19 pandemics.

Conclusion: Our research supports, that organizational forms of health care delivery to the dying can develop only in the extent that current institutional context allows. Universal health coverage based on solidarity and democratization of society are important prerequisities of hospice care development.

Key words: Hospice Care. Universal Health Coverage. Public Health Insurance. History of Medicine. Right to Health Care.

ABSTRAKT

Úvod: Štruktúry vytvorené v zdravotníctve na Slovensku v období rokov 1948 až 1989 predstavujú významný základ pre neskorší rozvoj a hospicovej starostlivosti, avšak toto obdobie nie je dosiaľ dostatočne preskúmané.

Cieľ: Cieľom je kritické zhodnotenie vývoja inštitucionálneho a legislatívneho rámca poskytovania zdravotnej starostlivosti a identifikácia faktorov súvisiacich s vývojom jej organizačných foriem od roku 1948 až do súčasnosti.
Materiál a metódy: Historický výskum primárnych a sekundárnych historických prameňov a relevantnej súčasnej literatúry. Právny výskum, právna hermeneutika, analýza a abstrakcia korpusu právnych predpisov na Slovensku.
Výsledky: Medzi rokmi 1948 – 1989 bola zavedená všeobecne dostupná zdravotná starostlivosť a a stala sa prístupnou aj pre zomierajúcich, avšak iba činnosť štátom kontrolovaných organizácií bola legálna. Rozvoj občianskej spoločnosti umožnil duchovnú starostlivosť a vznik hospicov. Ďalšie reformy umožnili súkromné platby pacientov za zdravotnú a sociálnu starostlivosť. Je tu však riziko, že hospicová starostlivosť bude dostupná iba osobám ktoré si môžu dovoliť súkromné platby, čo môže byť limitujúcim faktorom zvyšovania počtu hospicov, najmä pre ekonomické dopady pandémie COVID-19.
Záver: Náš výskum podporuje tvrdenie, že organizačné formy poskytovania zdravotnej starostlivosti zomierajúcim sa môžu rozvíjať iba v rozsahu existujúceho inštitucionálneho rámca. Všeobecná dostupnosť zdravotnej starostlivosti na princípe solidarity a demokratizácia spoločnosti boli významnými predpokladmi hospicovej starostlivosti.

Kľúčové slová: Hospicová starostlivosť. Všeobecná dostupnosť zdravotnej starostlivosti. Verejné zdravotné poistenie. História medicíny. Právo na zdravotnú starostlivosť.

INTRODUCTION

"Well designed laws can help build strong health systems" (Gostin *et al*. 2019). Access to palliative and hospice care is currently considered by WHO to be a part of universal health coverage, and integration of care between the hospital, hospice home care, inpatient hospice care and day care is essential (WHO 2016). Hospice care is currently a specific part of healthcare systems. This paper is focusing especially the development of institutional framework of healthcare delivery and its organizational forms, and factors that can be associated with this development until its current state. Development of healthcare in Slovakia, especially in the period of undemocratic political regimen between 1948 and 1989, is not yet adequately examined, however, the structures that developed during this period were important precondition for the further development of healthcare and hospice care. By establishing the rules and frameworks that shape health care organization and delivery, law is a powerful instrument of health system efficiency and modernization.

Undergoing social processes offer an explanatory context for understanding of the state and development of health system as a complex social system, which should saturate health needs of population, including needs of the dying members of society. As pointed by Inglehart, concept of modernization allows description of deep structural changes that are typical for contemporary societies, referred as modern – however, modernization process does not represent a steadily course towards predetermined state of society. Modernization, in social science, refers to the transition from a traditional, rural, agrarian society to a secular, urban, industrial society. Modernization encompasses profound economic, social, political, and cultural changes, but the process of industrialization is at its core (Inglehart 2001). Modernization can be defined also as innovations in the behavioral patterns (Bunčák 2002). The organizational forms of health care delivery and institutional framework must respond to these changes.

RESEARCH OBJECTIVE

The main objective is to assess critically the development of institutional and legislative framework of healthcare delivery and its organizational forms, and factors that can be associated with this development since 1948 until its current state. The aim is to describe, how organizational forms of health care delivery and institutional framework reflected modernization

processes in Slovakia and how it impacted development of hospice care.

MATERIAL AND METHODS

Our research was focusing the historical documents in the Slovak National Archive (hereinafter referred as SNA) and secondary historical resources as well as the national legislation in the Collection of Laws of Czechoslovak Republic and Collection of Laws of the Slovak Republic (both hereinafter referred as "Coll.") and regulations issued by the Ministry of Health of the Slovak Republic in its publication volumes called "Vestník".

The methodology of historiography (archive research, critique of sources, periodization, etc.) and legal research were applied to identify key changes in regulatory landscape and enabled modernization of health system and integration of palliative care into health system in Slovakia.

RESULTS

The institutional and legislative framework played important role in definition of the types of legal persons that are allowed to be hospice care providers, its material and personal equipment, vocational training and competences of health and social care professionals, and also definition of the mechanisms of healthcare financing. As key milestone was identified year 1989 - the period 1948-1989 and period after 1989 differ in many aspects, as presented further. Important milestone is also year 2002, when hospices and hospice care were defined in the national legislation.

DEVELOPMENT OF HEALTH CARE IN SLOVAKIA BETWEEN 1948 - 1989

Year 1948 is significant landmark in Slovakian history in many aspects. To understand the extent of changes, the baseline state of healthcare services for the severely sick have to be outlined shortly. Until 1948, the network of healthcare providers created fragmented patchwork. In segment of in-patient providers, hospitals were dominating. The basic distinction was between private and public hospitals (differentiated further into state and non-state ones). The state was the founder of the state hospitals and could directly regulate its operation. State hospitals were just six. Non-state hospitals had been established by local administration (county, district, community hospitals). There was just 17 small county hospitals until 1939. Because their funding was depend0ent on the budget of local administration – counties, their equipment and financing were very limited often (Falisová 1999). Many municipal and church hospitals did not allow the access to the broad public, as well as private hospitals and sanatories, which were run by private owners such as individuals, charity associations, sickness insurance companies (SNA, E MVZTV, box 12). Private settings prevailed over public hospitals and treated mostly patients able to pay, dispossessed patients were treated only if some public organization funded their treatment. It was mainly public hospitals that were providing health care to the sick, despite of the nationality, property or religion (Mášová 2005). The scope of services was divided into three categories. Most of patients were treated in the basic category. Other two categories offered care above standard, which was more expensive, e.g. in the Trenčín hospital as of 1.1.1919, the prices for one day of hospital care were 7 CZK in I., 10 CZK in the II. and 14 CZK in the I. category (SNA, E MVZTV, box 10).

In the whole Czechoslovakia, hospitals were overburdened. Lack of public hospitals and insufficient amount of hospital beds determined health conditions in particular regions of Slovakia. It was usual that public hospitals allowed admissions only the sick with curable diseases, for them care was available, however, there was limit related to hospital capacity. For whole decades, the burning issue was treatment of incurably ill people. Care for people with disabilities and care of not affluent sick were on the shoulders of family members and voluntary charity associations, often operating on the confessional basis. The situation of the dying and people with incurable, life limiting diseases in terminal stages and their families was hard. Hospitals refused to admit patients diagnosed as "incurable" – small exemption had patients with mental diseases, and patients with highly contagious diseases. To prevent that public hospitals will became "asylum" for these types of patients, a special type of controlling mechanisms was introduced in hospitals. After refusal of hospital treatment, many patients and families experienced suffering without any professional help, especially not affluent families with many children. Some hospital physicians who were familiar with human suffering tried to find some affiliated treatable

diagnosis in particular cases, to make hospital care available. Only in extreme cases of severe social hardship or lack of family care, a municipality had to arrange proper care for the severely ill (Falisová, Capíková 2016).

During the WWII, this insufficient number of hospitals suffered significant destruction. In 1945 Slovakia became part of Czechoslovak Republic again, however, to renew healthcare was difficult with limited appropriate buildings, lacking funding and shortage of healthcare workers (Hallon, Sabol, Falisová 2011). Healthcare issues were of main interest after the end of WWII. Consensus of all political representatives was achieved quickly in document named "Košice Government Program" of 1945. A working group to initiate universal health coverage was officially established. However, after few years of democratic renewal, a political takeover by the Communist Party in February 1948 led to change in political orientation and in health policy, too (Rákosník 2010).

The Consitution - Act No. 150/1948 Coll., declared the right of each citizen for protection of health and responsibility of the state for its assurance. Act No.185/1948 Coll. allowed to transform ownership of hospitals and other in-patient health care facilities, and state local administration bodies ("národné výbory" in Slovak) were delegated by their administration and management. Between 1948 – 1953, all types of healthcare providers were step.by-step nationalized, including pharmacies. The network of regional, district and local hospitals was created, put under governance of national committees (Rákosník 2010). Differentiation of hospital care into categories was repealed. Organizational unification of healthcare settings, social care settings and health and social insurance did not allow any private initiatives. Churches and members of congregations were severely persecuted especially during the 50.years of the 20th century, their property was nationalized (Letz 2001).

In 1951, act No.103/1951 Coll. "on unified preventive and curative care" was adopted and introduced both new system of health governance and organization of healthcare delivery. Basic element of healthcare was a health district with Institute of National Health. Semaško model of healthcare organization was adopted. Rákosník labelled these political changes by term "sovietization" of healthcare, reasoning that the design of health system and its governance were adopted following the lead given by the USSR (Rakosnik 2010).

Act No 54/1956 Coll. "on sickness insurance of employees" definitely enacted free-of-charge curative and preventive care to employees and their family members, including medicines and medical aids and spa treatment. Act No 55/1956 Coll. "on social security" enacted retirement pensions, the right to broad range of sickness benefits and social care and pension in various cases of inability to work. New public authorities of social care governance was created and authorized to create institutions of social care: retirement homes, homes for persons with disabilities who do not need health care, and homes for the sick who did not need acute healthcare but in need for in-patient care. Residents contributed for funding, depending on their economic limits.

Year 1948 was crucial for modernization of healthcare. The state representation legally formulated the obligation of the state to ensure universal health coverage and the state devoted big efforts and investments to build the infrastructure of healthcare settings, available also in the regions.

Another milestone was Act No.20/1966 Coll. "on people's health". The act introduced new structure into healthcare organization to make health care accessible in regions, with new element – polyclinic, centering under one roof general and specialist out-patient care. This act was valid almost three decades, replaced by Act 277/1994 Coll. "on health care". Based on Act No.20/1966 Coll., a Decree of the Ministry of Health No. 43/1966 Coll. "on the system of healthcare settings", was elaborated on the principle of differentiation of health care providers. Based on level of complexity, specialization and the scope of health care, the hospitals were integrated with polyclinics and pharmacies and were divided into three types, with type III. offering largest spectra of complex health services. Health system recognized specialized in-patient settings, especially oncological institutes (specialized oncological hospitals). A Decree of the Ministry of Health No. 19/1975 Coll. "on the system of healthcare settings" just supplemented the previous regulation - as a part of hospital wards, intensive care units and after-treatment units should be established. A new organizational form was introduced into legislation – treatment house for the long-term ill (in Slovak "liečebňa dlhodobo chorých"), to provide specialist in-patient nursing care and treatment to people

suffering from long-term diseases. This system of differentiated providers of curative and preventive health care persisted until the 90. years of the 20th century.

Major achievements between 1948 and 1989 were related to the strengthening of health system, introduction of universal health coverage and solidarity in state welfare as leading principles, health care and medicines were provided free of charge to the citizens. Thus, population health indicators significantly improved. To meet the needs for professional care, a network of specialized healthcare settings was supplemented by more specialized in-patient providers. Community based care was designed for older people living with life-limiting and chronic illness. However, hospital care for people and hospital regimen in hospital wards were limiting contact of patients in terminal stages with family members and deepened their social isolation. Until 1989, activity of other than state or state-controlled organizations in healthcare were illegal. Only state authorities were authorized to establish a healthcare setting. Spiritual care and social support for the terminally ill was limited.

DEVELOPMENT OF HOSPICE CARE IN SLOVAKIA SINCE 1989

Transformation of political system that started in Czechoslovakia in 1989 and since January 1, 1993 in the autonomous Slovak Republic, re-defined functions and tasks of the state and brought significant changes in state welfare and health system organization, governance and funding (Olah, Schavel 2006). Many new laws were implemented to reach deetatisation and renewal of the private sector and non-governmental sector. New legislation allowed that non-governmental organizations of different types and churches could start to work. Development of volunteering and sponsoring allowed inflow of human resources and private finances into health system.

Act No. 308/1991 Coll. "on freedom of religious faith and on the position of churches and religious societies" confirms equal position to all registered churches. The Basic Treaty between the Slovak Republic and the Holy See, signed in Vatican on November 24, 2000 (published as No. 326/2001 Coll.), formulates the right of the catholic church to develop activity of a pastoral and spiritual nature, and religious training and upbringing in all educational and medical institutions, state institutions providing social services, and persons who are under the care of these institutions have the right to participate in the Mass on Sundays and on days of obligation and are granted the liberty to fulfill all religious acts (Basic Treaty, article 16.1). The Catholic Church has the right to develop activity of a formative, training, experimental-scientific, missionary, charitable, medical and social nature. This right also includes the setting up, ownership and the management of institutions of this kind in accordance with the conditions laid down by the legal system of the Republic of Slovakia (Basic Treaty, article 17.1). The same opportunities to engage in health care and pastoral activity the national legislation also allows to other registered churches in the Slovak Republic. Today, however, the possibility of legal entry and pastoral activities of the spiritual professionals or pastoral caregivers of the state registered churches is in some healthcare and social care facilities challenged and not taken for granted. Current legislation allows to provide and to access spiritual care in hospitals, however, the realization of these rights meets a lot of practical obstacles, that should be subject of further research (Trizuljaková 2011).

It is very important, that the Constitution of the Slovak Republic (act No 460/1992 Coll.) in its Article 40 still stipulates the right to health as a human right, and right to health care free of charge under conditions defined further by national legislation (Freel 2015). National health system shifted after 1989 from the Semaško model to Bismarckian model, with mandatory health insurance and plurality of health insurance funds – currently, there exist 3 health insurance funds in Slovakia (Chandogová 2018). An important role in further development of health system started to play health insurance funds as powerful stakeholders. Financing of health system has changed significantly, however, still based on the solidarity principles (Trnkusová 2013). Process started with Act No. 7/1993 Coll. "on establishment of National Insurance Company and on financing of health insurance, sickness insurance and pension insurance", Act No. 9/1993 Coll. "on health insurance and management of Health Insurance Fund" and transformation was concluded in 2004, when six reformist bills were adopted by the parliament (and published in national collection of laws under numbers 576 – 581) and define the structure, functioning and funding of the national health system in Slovakia. Act No. 578/2004 Coll. "on

healthcare providers, healthcare workers and their professional associations" defines hospices and mobile hospices as a type of healthcare settings within health system, with specific tasks defined further by Decree of the Ministry of Health of the Slovak Republic No. 770/2004 Coll. and later replaced by Decree of the Ministry of Health of the Slovak Republic No. 84/2016 Coll., which establishes the determining features of individual types of medical facilities.

National Association of Palliative Care was established in 2000 with headquarter in Trencin, since 2005 is named "Association of Hospice and Palliative Care in Slovakia" (Krizanova, Skripekova 2015). Especially the experts associated to this organization made a big effort for integration of palliative care and it genuine organization form - hospices and mobile hospices, into national legislation and health system in Slovakia.

Opportunities for institutionalization of palliative and hospice care occurred in the early 90. years of the 20th century, but to find the proper integration of health and social services was very difficult and till today is a challenge. (Krizanova, Skripekova 2015) The first department of palliative care was established in National Oncological Institute in Bratislava in 1995, since 2009 named Department of Palliative Medicine, as a part of Clinics of Clinical Oncology of National Oncological Institute. This department performs comprehensive acute in-patient and bed-patient care of terminally ill cancer patients and is the key training organization for physicians in post-graduate specialty of palliative medicine. (Krizanova 2016)

Palliative care was defined in 2002 in the document by Slovak Ministry of Health named *The Concept of Palliative Care* as a special kind of health care that is provided in the form of outpatient health care or residential care to a person with a chronic, incurable and at the same time, the most advanced and active progressive ongoing disease with timely limited life. (MH SR 2002) After huge effort of palliative care specialists, the necessary legal basis was enacted finally, so the first hospice care providers could be established. The first non-state mobile hospice for children started to work on the basis of this document in 2002 in Bratislava, named „Flicker" (in Slovak „Plamienok"). Bed hospices (so-called "stone" hospices) were introduced gradually, as the first was founded in July 2003, the Hospice of Mother Theresa in Bardejovská Nová Ves (Krizanova, Skripekova 2015).

The conditions for the development of palliative medicine created the regulation by ministry of health - *The Concept of Health Care in the Field of Palliative Medicine including Hospice Care*, in 2006. Hospice care is defined as "palliative care provided by hospice to patients with incurable disease and to dying patients as a separate medical device. The hospice care includes all of the elements of palliative care: palliative medicine, nursing, psychological, spiritual, respite and terminal care as well as care for the survivors" (MH SR 2006).

Palliative care means work of multidisciplinary team of medical doctors, nurses, physiotherapists, occupational therapist, social workers, chaplains, clinical psychologists, etc. Palliative care provides symptom control, emotional/psychological support to the patient and the family, social support, spiritual care and bereavement care (Mojzesova 2015). Access to palliative care has been recognized as a fundamental human right be leading world experts (WHO 2016). Hospice care is a form of end-of-life care designed to minimize the sources of pain and distress, improve quality of life, and offer opportunities for growth. Hospice views the patient and family as the unit of care, with patients and their families participating actively in the care planning process. Efforts to achieve a high quality of life stresses the importance of physical, emotional, and spiritual comfort and the respect for one's dignity (Kubiak, Surikova 2010; Trizuljakova, 2011). Both hospice and palliative care approach are focusing prevention and relief of suffering of any kind. Social work is historically bounded to care for the dying and until the present it is necessarily bounded to hospice care. As pointed by many recent authors, the activities of contemporary social work especially in field of hospice care are based on theologically shaped and motivated action, in other words we find their roots in the Christian faith and a connection between hospice care and Christian values, which is confirmed by the study Šmidová and Hamarová (2018). Many of these values had been shaping recent developments in bioethics and vocational education of helping professions. The value of human dignity as central value protected by human rights is mainstreamed also in modern health law doctrine and mainstreamed within human rights' based approach to health, fostered e.g. by WHO.

Concept of palliative and hospice care from 2006 is in accordance with WHO recommendations, however, experts claim that the amount of **palliative beds** can saturate just 1/3 of the need in Slovakia (Krizanova, Skripekova 2015). Currently there works 8 "stone" **hospices** and 16 **mobile hospices**, based on the latest national data (Chandogová 2018). However, most of care for the terminally ill is covered by family members at home. Alarming is the statement of experts, that the professional care and support for the sick one and his family at home or in social services facilities is limited by shortage of trained professionals, such as general practitioners, in palliative medicine and prescription limits for out-patient treatment (Krizanova 2016). Healthcare is under governance of Ministry of Health, while social care in healthcare settings is under governance of Ministry of Labor, Social Affairs and Family, thus this divide constitutes currently also an important barrier in further development of hospice care (Capikova, Novakova 2016, Krizanova, Skripekova 2015).

The Worldwide Hospice and Palliative Care Alliance (WHPCA) created a Global Atlas of Palliative Care at the End of Life in 2014, and the Slovak Republic was classified as 4a – that is, the country had second highest level of integration of palliative care into health system (Krizanova, Skripekova 2015). Similar picture displayed the document by European Association for Palliative Care (Centano *et al*. 2013). Slovakian experts pointed to the fact, that despite of integration of the hospice into the national health system, health insurance companies cover just part of the care and prevailing majority of the expenditures in hospice for care are covered by private resources, such as patients, their families or donors (Krizanova, Skripekova 2015; Veselská 2016). In 2020, working in cooperation with the World Health Organisation (WHO), WHPCA launched a second edition of the Global Atlas of Palliative Care (WHPCA, 2020) and Slovakia is still holding the second highest position 4a, characterized as following: "Countries where hospice-palliative care services are at a stage of preliminary integration into mainstream service provision: A country in this category is characterised by the development of a critical mass of palliative care activism in a number of locations; a variety of palliative care providers and types of services; awareness of palliative care on the part of health professionals and local communities; a palliative care strategy that has been implemented and is regularly evaluated; the availability of morphine and some other strong pain-relieving drugs; some impact of palliative care on policy; the provision of a substantial number of training and education initiatives by a range of organisations; and the existence of a national palliative care association."

The formal criteria are met, however, the indicators itself do not warranty real accessibility of patients to the care they need, nor overall context of hospice care. Insufficient number of palliative beds and insufficient number of hospices and mobile hospices can be confirmed as serious barrier of availability of professional care for the dying. However, there still exist problems with integration of health and social services, and problems with funding from public budgets of necessary care, which is under current legislation considered as social care – e.g.food intake, oral hygiene, personal hygiene. The scope of social services is regulated by Act No. 448/2008 coll. "on social services", as amended. Research findings of M.Veselska (2012) revealed that a lot of economic burden for hospice care rest on the shoulders of people who work in hospices, pointing that a their professional work is often seriously underpaid so that these workers serve as involuntary "sponsors". This unfavorable feature still persists until the present. There is a risk, that funding by major share of private payments can limit establishment of new hospices, but also can reduce significantly access to hospice care, especially as the result of economic consequences of COVID-19 pandemics.

Thus, hospice care – either in in-patient, or mobile hospice care, is still not easily available to the most of patients in need, and the burden of home care for a severely ill rests on the shoulders of informal carers at home. As pointed by Trizuljakova and Sitinova (2018), palliative prenatal care and perinatal hospice care is just in its very beginnings in Slovakia. Also family members of the sick, who are delivering informal care at home to most of people, should deserve stronger social protection, such as "palliative leave" (Capikova, Novakova 2016). Palliative care has to be implemented also in the families with the specific family and ethnic approach at home, however there is lack of information and awareness about home hospice care in Roma communities (Ludvigh Cintulová 2019). Compassionate care as part of social work deserves more attention and institutional support (Hamarová

2016). There is high demand for more multidisciplinary research.

Full inclusion of palliative care into primary care could be one of promising models. Currently, general practitioners in Slovakia are not allowed to prescribe most of drugs necessary for palliative treatment, also palliative care specialist are facing restrictions. Krizanova and Skripekova (2016) see as an important barrier for operation a regulatory restriction for prescription of certain medications necessary for palliative care, so that it cannot be delivered by trained specialist out-patient palliative care providers – to the patients in their homes.

All of this points to the necessity to define new organization form of delivery and financing of hospice care. Just to mention, there was a progressive bill passed in Germany in 2007, that declares the right of patients to palliative care at home, while the duty is imposed on the particular federal states and health insurance companies to define appropriate model for its realization within state jurisdictions (Escobar Pinzón *et al*. 2010).

Slovak Republic ratified all of the most important international treaties and declared to protect the right to health and right to health care as part of its obligations (Capikova, Novakova 2016). Numbers of "stone" hospices and mobile hospices are since 2002 increasing just slowly, operating as non-government organizations, established mainly on church or municipal basis, an overview can be found at continuously updating specialised portal www.Hospice.sk. There should be strong network of well-functioning hospice care providers, sustainability cannot be warrantied by charity only, or by enthusiastic individuals. In search for the best organization of palliative care delivery, definition of new model of collaboration between the state and non-government organizations is needed. The state as the key regulator should create appropriate rules that enable increase in numbers of hospices and especially mobile hospices allowing to receive palliative care at home. Health system in Slovakia needs further modernization. Most recently, the National Health Information System with its portal eHealth was introduced by Act No.153/2013 Coll. on national health information system and its amendments, allowing electronic prescription of medicines (e-Recipe), but necessary regulatory framework for practicing telemedicine and use of artificial intelligence and novel communication technologies in health care delivery is missing. In a digital society, this is a serious gap in a legislative framework. Distant consultation with a patient or his carers, distant surveillance with use of new digital devices and technologies, distant assessment of effects of medication, could be helpful to support home care of the long-term sick and in hospice care especially. The model of reimbursement and liability for use of telemedicine is missing, although, such regulations could be helpful also for palliative care and hospice care delivery and effective use of time and personal resources for hospice care.

CONCLUSION

Living conditions of the terminally as a specific population group reflect basic social relations and social values, economic limits and achievements of the sciences and health system. The organizational forms of health care delivery and institutional framework reflected modernization processes in Slovakia. Professional health and social care for the people in terminal stage of life limiting diseases were developing slowly, systematic development started after 1948 with modernization of healthcare. Besides universal health coverage, important innovation was accessibility of professional in-patient treatment for the severely ill and those in need of long-term care, a specialised health-care organization forms developed during the 50.and 60.years of the 20th century in Slovakia. However, only change of the political regimen and transition to democracy since 1989 allowed further modernization of healthcare and development of hospice care and integration of spiritual care into health care delivery. Solidarity and universal health coverage are still cornerstones of social policy in Slovakia, however challenged by current economic development in Europe, affected by COVID-19. An important impulse for development of hospice care was development of palliative medicine as branch of medicine and hospice care movement in professional community - globalization accelerates modernization and international knowledge exchange, for benefit of hospice care. Renewal of churches in Slovakia allowed development of hospices as non-government organizations.

Changes in organizational forms of healthcare in Slovakia in the studied period were reflecting major societal changes, that had impact on institutional and

legal framework. These changes determined the opportunities for development of hospice care as genuine type of organization of professional care for the specific group of vulnerable patients - the terminally ill. The role of various professionals including lawyers and historians is to bring the scientific evidence and professional expertise into the process of creation of regulatory framework and health policy, however, it is not the professional community, but the state authorities who is responsible for further development of hospice care in Slovakia. „Free hand of market" cannot be left unregulated, especially in health care – otherwise the danger that medicine will miss its goals can increase. Palliative and hospice care is not a luxury medicine, it is a part of human rights. It is a duty of the state to provide effective regulatory framework, that will support increase of hospices and mobile hospices and availability of palliative care. Key stakeholders and regulatory framework play important role in future efforts to react on modernization impulses, such as development of information technologies, and find appropriate, innovative models as outlined above to ensure that hospice care will be really accessible for all people in need.

CONFLICT OF INTERESTS

The authors declare no conflict of interests in connection with the published manuscript.

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PHYSICAL ACTIVITY AS ONE OF THE ELEMENTS OF OVERCOMING COVID-19 AND ITS EFFECTS ON SOCIAL DEVELOPMENT AND WELL-BEING

FYZICKÁ AKTIVITA AKO JEDEN Z PRVKOV PREKONANIA COVID-19 A JEJ VPLYV NA SOCIÁLNY ROZVOJ A ŽIVOTNÚ SPOKOJNOSŤ

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ABSTRACT

Introduction: Physical activity is one of the methods with the greatest impact on a good quality of life. The broadly understood movement is used in the prevention and / or treatment of many psycho-physical diseases. In addition, it improves the functioning of all human physiological systems.
Aim: The aim of the study is to analyse physical activity as one of the alternatives to counteract the risk of contracting the coronavirus and supporting the recovery process from Covid-19 consequences.
Findings: The study presents the main health problems and social threats caused by the Covid-19. It is focused on the physical activity including possible impacts on the most important systems of the human body in order to obtain the necessary reserves in the prevention and therapy if the coronavirus occurs. The effects of physical activity indicated in the paper clearly indicate its role in the care and therapy system of people affected by Covid-19 epidemic.
Conclusion: The spreading COVID-19 virus has very rapidly affected people's private and professional lives, disrupted global economy and increased level of unemployment and poverty. At the same time, Covid-19 caused the so-called domino effect, which modified the existing system of functioning and marks a turning point in several spheres of life.

Key words: Covid-19, physical activity, pandemic, chronic diseases

ABSTRAKT

Úvod: Fyzickú aktivitu možno považovať za jednu z mála metód, ktorá dokáže mať najväčší vplyv na dobrú kvalitu života. Všeobecne chápaná fyzická aktivita sa používa pri prevencii a / alebo liečbe mnohých psychických i fyzických chorôb. Okrem toho zlepšuje fungovanie všetkých fyziologických systémov človeka.
Cieľ: Cieľom štúdie je analyzovať fyzickú aktivitu ako jednu z alternatív na potlačenie rizík spojených s dopadmi koronavírusu a na podporu procesu uzdravenia.
Zistenia: Predkladaná štúdia popisuje základné zdravotné problémy a spoločenské ohrozenie spôsobené vírusom Covid-19. Ďalšie časti štúdie sa zaoberajú fyzickou aktivitou a jej dopadmi na najdôležitejšie systémy ľudského tela, ktorých účelom je získavanie potrebných rezerv v prevencii a liečbe v prípade nakazenia koronavírusom. Účinky fyzickej aktivity uvedené v článku jasne deklarujú jej úlohu v systéme starostlivosti a terapie u ľudí s ochorením Covid-19.
Záver: Šíriaci sa vírus COVID-19 veľmi rýchlo ovplyvnil osobný a pracovný život ľudí, obmedzil pohyb a globálnu ekonomiku. Covid-19 súčasne spôsobil takzvaný efekt domina, ktorý modifikoval doterajší system fungovania a znamená bod zlomu vo viacerých sférach života.

Kľúčové slová: Covid-19, fyzická aktivita, pandémia, chronické choroby

INTRODUCTION

World Health Organisation (WHO) spread campaigns to the world about prevention of coronavirus and asked people to follow key steps to stop the spread of the disease focused on hand washing, coughing etiquette, not touching one's face, physical and social distance. But at the quarantine time nobody highlights the risks of keeping social distance and staying home during couple of months on the mental, physical and social health. Physical activity can play a key role in the health prevention, mental harmony and it also can help to gain social development and good well-being.

Over the past several months, the coronavirus has affected the everyday lives of people all over the world. The most common symptoms of this viral infection are fever, colds, coughs, bone pain, and breathing problems, eventually leading to pneumonia. As this is a new viral disease affecting humans for the first time, vaccines are not ready to use. Therefore, emphasis is placed on comprehensive hygiene and environmental prevention measures (Haleem, Javaid 2020). While fighting against Covid-19, it is impossible not to use other available forms that increase the vitality and immune strength of the human body. Physical activity is a good way of prevention and therapy. A commonly used term in the literature is any form of exercise that increases metabolic demand. Therefore, *physical activity* includes all forms of exercise related to physical effort. They include recreational and sports activities, as well as activities performed during professional and leisure activities or activities at home (Klukowski, Nowotny, Czamara 2014, p.7). Those people with excellent physical capacity might be more intense and strenuous. In the cases of people with limited or reduced efficiency of the respiratory and circulatory systems, physical activity must be adapted to individual abilities and needs.

AIM

The research aim is to analyse physical activity as one of the few methods that makes the strongest effect on good health. Generally understood movement is used in the prevention and / or treatment of many psychophysical diseases.

FINDINGS

Impact of COVID-19 virus on the human health

Different information on health problems caused by the coronavirus is reported in the mass media and in publications. The deterioration of the physical conditions and health of the population is closely related to emotional conditions and ability to cope with stress. In a threatening situation accompanied by a pandemic, a wide range of unpleasant emotions appear as people lose control over their own health and they are afraid of their lives. They meet with fear, anger, regret and face with death of loved ones. The situation is complicated by the lack of knowledge about the term when life will return to the pre-pandemic state (Vinkers *et al.,* 2020). Polish studies highlight that emotions may be a symptom of mental disorders linked with episodes of depression and / or anxiety (Talarowska *et al*., 2020). There are the psychological factors (e.g. uncertainty, loneliness fear of epidemic) and social factors (eg. social distance, stigmatisation, lack of money, boredom) leading to stress due to the Covid-19 epidemic that might cause psychological (anxiety and depression, coronaphobia, isolation, self-mutilation) and social consequences (violence, gambling, unemployment, exclusion). (Holmes *et al*., 2020).

The problem of cardiovascular disease and coronavirus infection is associated with overburdening the body if the two conditions occur simultaneously. The most common are heart diseases associated with hypertension, high cholesterol, lung disease and concomitant diabetes. These diseases affect the general health condition of patients including resistance to viral infections. Fever combined with a marked increase in temperature increases metabolism, leading to a marked increase in oxygen demand. Inflammation caused by coronavirus infection can also lead to damage to the lining of blood vessels, myocarditis, cardiac arrhythmias, acute coronary syndrome and cardiomyopathy, and acute pulmonary heart disease.

There are scientific reports suggesting a possible infection of the Covid-19 virus in the nervous system. Covid-19 can cause, among other things, various types of disorders of the nervous system - such as taste and smell disorders, headaches and dizziness, decreased alertness, weakness, muscle pain and stroke and delirium. The above dysfunctions may occur before fever and cough. Another risk is cerebral hypoxia and blood clots leading to a stroke due to a virus that infects

the lungs, heart or kidneys. The virus can also directly infect the brain and meninges. In addition, the response of the immune system can lead to inflammation that damages the central and / or peripheral nervous system.

People with excessive obesity (BMI over 40) are more likely to become infected and have complications. Hair loss also occurs in young people infected with the coronavirus. Covid-19 infection causes kidney and liver damage, gastrointestinal symptoms (diarrhoea, nausea and vomiting, loss of appetite), eye symptoms and skin lesions.

COVID-19 carry a specific kind of virus that impacts immunity and lack of effective immune may lead to infection of people who have reduced or weak immunity due genetic, health or social factors. Patients with cancer, organ and bone marrow transplants, long-term users of corticosteroids or other immunosuppressants, and patients with HIV and AIDS are particularly at risk as well.

The scientific world is currently conducting research into the effects of new virus infection. Final formulation of conclusions requires long-term follow-up and research, but it is already argued that large numbers of patients will have physical, cognitive, and psychological impairments due to Covid-19 infection requiring long-term care. The emerging question about the long-term negative impact of Covid-19 on the human body has remained unanswered. The most frequently mentioned potential effects of the disease are pulmonary fibrosis, pulmonary and systemic vascular diseases, bronchiectasis, chronic fatigue, sarcopenia and neurological diseases. At the same time, it should be mentioned that the lack of clear symptoms does not mean that there are no changes in the body. In asymptomatic and oligosymptomatic patients, abnormalities in the lung picture and changes in the blood picture were observed (Zrozumieć COVID-19. Opracowanie zespołu ds. Covid-19 przy Prezesie Polskiej Akademii Nauk. PAN, 14.09.2020).

The impact of physical activity on human health

One of the essential determinants of a good quality of life is leading a healthy lifestyle with an appropriate level of daily physical activity. In the population dimension, a number of directives have been developed, optimal doses of preventive traffic. Physical activity should be adapted to the current capabilities of a particular person to be aware of their health condition, current lifestyle and preferred forms of spending free time. Proper and regular exercises play an important role in disease prevention. If there is a disease it accelerates the healing processes or delays the occurrence of health complications, including disability. Canadians propose a weekly exercise dose of not less than 1000 kcal (Ashe *et al.,* 2009). There is weekly physical activity at the level of 2000 kcal recommended in Poland, it should be performed at least three times a week for about 30 minutes, of moderate intensity (60-75% of the maximum heart rate) and endurance (Piotrowicz *et al.,* 2009). Walking it the simplest and good physiological form of movement at the same time walking does not require any financial expenses. The proposed level of physical activity is very important, mainly if motor passivity is generally dominant in Europe, especially in the elderly, a sedentary lifestyle. World statistics show that up to 23% of men and 32% of women are at risk of disease because they do not follow the recommended exercises of physical activity (Guthold *et al.,* 2018).

The disease processes started by the CoviD-19 virus cause degradation in the human body, organ activity is impaired or damaged and psychophysical efficiency is decreased. Therefore, in a period of full health, before the decline in efficiency and endurance of the body, it is necessary to take care of health in the range of maximum physical parameters. Exercise during this period strengthens the immune system, improves the functioning of all systems and empower well-being. In addition, participation in group activities (not recommended during a pandemic) is an excellent form of doing leisure time activities in order to provide satisfaction and mental relaxation. It should be noted that self-service and all activities related to daily activities and responsibilities also contribute to a certain level of physical activity.

During exercise, serotonin, also called as the hormone of happiness, is released. Serotonin levels and the smooth functioning of serotonin receptors play an important role in the regulation of the immune system (Patra *et al.,* 2020).

Level of physical activity also affects memory and cognitive functions, it helps to overcome stress and worry easier (Sukhov *et al.,* 2016). Positive self-esteem and a "strong sense of health" also contribute to the fight against viral diseases, and such feelings are accompanied by frequent physical activity. Occupational therapy can also be classified as a form of physical activity, it has both functional aspects

Table 1. The influence of physical activity on selected human systems with diabetes

Human system	The effect of physical activity
Cardiovascular	reduction of heart rate and blood pressure at rest and during exercise, improvement of ventricular filling and contracting force, increase in the volume of heart stroke, increased flexibility of arteries and afterload, improving the blood supply to the heart muscle, improving the lipid profile in plasma, increase physical performance, predominance of the parasympathetic system, reducing the risk of myocardial infarction and stroke, improvement of peripheral circulation, activation of the fibrinolysis process, weight reduction (shift in energy balance, acceleration of metabolism).
Respiratory	improving the vital capacity of the lungs, maintaining chest mobility, improving the exchange of gases in the body, strengthening the cough reflex, improving the movement of lashes.
Nervous system	improving the transmission of nerve impulses, improving conductivity in the peripheral system, shortening the reaction time, improving motor coordination, memory improvement improving peripheral perception, including deep perception.
Body and mobility	*Muscles* maintaining fitness, strength and muscle mass, reduction of fat content in muscles, maintaining the number of fast fibres. *Skeleton* maintaining the required bone mineral density, increased load resistance. *Joints* maintaining full joint mobility, act against degenerative changes. *Periarticular structures* maintaining the necessary flexibility and range of motion, reducing the tendency to minor injuries.
Immune system	regular activity strengthens the immune system. The weakening of the body or the appearance of symptoms of infection is a contraindication to physical activity, after the period of illness, activity should be gradually followed, increasing the intensity.
Diabetes	increasing the sensitivity of tissues to insulin, increasing the absorption of glycogen, increasing the need for sugars and better uptake from blood, weight reduction combined with increased insulin sensitivity, reduction of glycemia, improvement of the plasma lipid profile (increase of HDL, reduction of LDL and triglycerides).

(Rottermund, 2018), and is a valuable supplement to medical, professional and social rehabilitation. During therapeutic meetings, various physical and cognitive activities are forced to optimize or harmony the quality of life (Rottermund, 2016).

Physical activity and Covid-19

There are no any research results in the available literature declaring the effect of physical activity on the consequences of Covid-19. However, there is good scientific evidence on the effectiveness of exercise in combating inflammation and respiratory infections (Miles *et al.,* 2018; Lee *et al.,* 2019). Physical activity is effective in the treatment of heart and lung diseases, obesity, alleviates the course of diabetes, supports the treatment of neoplastic diseases and many other diseases called civilization [21**].**

The author's summary of the impact of physical activity on the improvement of the resilience of selected human systems and the treatment of diabetes in these areas:

People, especially those with chronic to moderate disease, should be encouraged and protected from potential exposure to the Covid-19 virus. In this way, it is possible to reduce the severity of the disease if it occurs, i.e. it will have a prophylactic effect. There is concrete evidence to improve immunity and reduce inflammation in physically active people in most cases in the above risk groups (Simpson *et al.,* 2015). Exercise, as well as taking medication every day, should become a habit, not just for high-risk people. Even in a pandemic, you should be proactive by following security rules. For those who avoid exercise, it's not too late to start trying to maintain their health with moderate-intensity physical activity.

It should be noted that during the coronavirus epidemic, physical activity must continue, but in a slightly different mode:

1. This should be done individually in order to avoid contact with other people;
2. The place of performance may be both domestic and open space;
3. Exercise and training rooms should not be used;
4. Physical training should last at least 20 minutes to achieve a therapeutic effect;
5. Physical activity should be repeated at least 3 times during the week;
6. Any physical activity should be enjoyable;
7. The main goal of physical activity (not only during the epidemic) is to improve well-being and to achieve maximum level of the health.

The coronavirus attacks the respiratory system, the immune system tries to fight the virus and causes inflammation. This inflammation causes damage to the lung tissue, restricts the exchange of gases in the body and therefore requires medical intervention. Mechanical ventilation with respirators is necessary in the critical situation (Shi et al., 2020). During exercise, muscles (30-40% of body weight) produce compounds that improve the functioning of the immune system and reduce inflammation (Hojman, 2017). For this reason, the muscular system is an effective and excellent tool in combination with the side-effects of Covid-19 infection by reducing the severity of the infection and hospitalisation.

Anxiety, stress and depression affect virtually the entire human population during pandemics, disasters and emergencies. Regular physical activity is important for mental health because it reduces the risk of symptoms of depression and anxiety (Basso *et al.,* 2017). Depression and especially mental stress upset the balance between cortisol and other hormones responsible for combating inflammation and the proper functioning of the immune system. This mechanism is particularly pronounced in the elderly people (Adam *et al.,* 2017), who have abnormal cortisol levels. Healthcare professionals should therefore support movement through a variety of forms and techniques, as this may be a partial antidote to the stress of the Covid-19 pandemic. Its effect is similar to taking prescription drugs or psychotherapy classes.

Vaccination seems to be a great way to solve the Covid-19 pandemic and according to epidemiologists, population vaccination will significantly reduce the risk of disease. Previous studies have clearly shown that physical activity increases the human body's response to vaccines (Pascoe *et al.,* 2014).

Healthy and physically active people have sufficient reserves (respiratory, circulatory) for the proper functioning of the body, while people suffering from chronic diseases has these reserves already limited (Roman et al., 2016). Improving physical fitness, regardless of medical condition and level of treatment, appears to be a key element in combating the effects of the Covid-19 pandemic. Dávidová, Hardy, Hamarová (2017) highlight a need to improve the professionalism and efficiency of the helping process to the vulnerable, especially those who are depended on the care of the others. Ludvigh Cintulová and Beňo (2018) pointed out the many ethical dilemmas within helping process of the vulnerable people that makes direct or indirect impact on their quality of life.

CONSLUSSION

Exercise and physical activity are generally recommended for the general population, and there are many research and evidence declaring that exercise in the broadest sense can contribute to reducing the health consequences of COVID-19. Physical activity helps to improve the quality of life before and after infection. The effects of physical activity reported in the study clearly declare its role in the care and therapy system of people with Covid-19 disease. The movement helps to improve the efficiency of all human systems and organs, and the reserves gained help to better overcome the negative side-effects of a pandemic. These will be prophylactic measures in a certain population and will have healing effects in infected people by coronavirus.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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