

PREOPERATIVNI, INTRAOPERATIVNI I POSTOPERATIVNI PREDIKTORI POVEZANI SA KOMPLIKACIJAMA I PREŽIVLJAVANJEM PACIJENATA NAKON RESEKCIJE KOLOREKTUMA

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SAŽETAK

Kolorektalni karcinom je treća najčešće dijagnostikovana forma svih karcinoma, a drugi najsmrtonosniji karcinom na svetu. Međunarodna agencija za istraživanje raka (engl. International Agency for Research on Cancer - IARC) smatra da će se globalno opterećenje društva kolorektalnim rakom povećati za 60%, što predstavlja više od 2,2 miliona novih slučajeva i 1,1 milion smrtnih ishoda do 2030. godine. Cilj ovog preglednog rada jeste da prikaže koji prediktori, u kom delu toka bolesti i na koji način utiču na nastanak postoperativnih komplikacija, kao i na samo preživljavanje pacijenata sa kolorektalnim karcinomom. Povišeni nivoi inflamatornih markera, loš nutritivni status, viša kategorija ASA klasifikacije fizičkog statusa (*American Society of Anaesthesiologists*) i loše životne navike predstavljaju značajne nezavisne prediktore lošeg preživljavanja i povećavaju rizik od nastanka postoperativnih komplikacija nakon resekcije. Intraoperativno doprinos lošim ishodima daju duže trajanje operativnog zahvata i veliki gubitak krvi tokom operacije. Postoperativne komplikacije (popuštanje anastomoze, postoperativno krvarenje, intraabdominalni apsces, komplikacije stome, opšte komplikacije) samostalno povećavaju rizik od mortaliteta nakon operativnog zahvata.

Ključne reči: kolorektalni karcinom preoperativni faktori, intraoperativni faktori, postoperativni faktori, komplikacije, preživljavanje

Uvod

U svetu, kolorektalni karcinom je treća najčešće dijagnostikovana forma svih karcinoma (1). Češće se javlja kod muškaraca nego kod žena, i 3-4 puta je češći u razvijenim zemljama nego u zemljama u razvoju (1). Prema podacima Alijanse za kolorektalni kancer 2024. godine dijagnostikovano je 152.810 novih slučajeva karcinoma u Americi (2). Prema podacima Svetskog fonda za istraživanje kancera 2022. godine je bilo 1.926,425 novih slučajeva kolorektalnog karcinoma u svetu (3). Najveća procenjena standardizovana stopa incidencije na 100.000 stanovnika je 2020. godine bila u Evropi (30,4), zatim Okeaniji (29,8) i Severnoj Americi (26,2), a najmanja u Aziji (17,6), Latinskoj Americi (16,6) i Africi (8,4) (4). Prema podacima Međunarodne agencije za istraživanje raka (engl. International agency for research on cancer - IARC), 2020.

godine, kolorektalni karcinom je bio drugi najčešći uzrok smrti među karcinomima, odmah posle karcinoma pluća (4). Globalno, standardizovana stopa mortaliteta (engl. age-standardized mortality rate - ASMR), kolorektalnog kancera je iznosila 9,0/100.000 u 2020. godini (4). Kada se posmatraju regioni, najveća ASMR (na 100.000) je bila u Evropi (12,3), a najniža u Africi (5,6) i Mediteranskoj oblasti (5,3) (4). Prema podacima za 2022. godinu (1), zemlja sa najvećom stopom incidencije kolorektalnog karcinoma (na 100.000) u muškoj populaciji je bila Mađarska, a u ženskoj Norveška.

Praćenjem trenda obolevanja od kolorektalnog karcinoma od 2010. do 2021. godine, pokazano je da se na globalnom nivou incidencija kolorektalnog karcinoma povećala za oko 35,9%, sa 1.614.410 slučajeva u 2010. godini na 2.194.143

PREOPERATIVE, INTRAOPERATIVE AND POSTOPERATIVE PREDICTORS ASSOCIATED WITH COMPLICATIONS AND SURVIVAL OF PATIENTS AFTER COLORECTAL RESECTION

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ABSTRACT

Colorectal cancer is the third most commonly diagnosed form of all cancers, and the second deadliest cancer worldwide. The International Agency for Research on Cancer (IARC) estimates that the global burden of colorectal cancer on society will increase by 60%, representing more than 2.2 million new cases and 1.1 million deaths by the year 2030. The aim of this review paper is to show which predictors, at what point in the course of the disease, and in what way they influence the occurrence of postoperative complications and the survival of patients with colorectal cancer. Elevated levels of inflammatory markers, poor nutritional status, a higher category of the ASA (American Society of Anesthesiologists) physical status classification, and poor lifestyle habits represent significant independent predictors of poor survival and increase the risk of developing postoperative complications after resection. Intraoperatively, longer duration of the operation and significant blood loss during surgery contribute to poor outcomes. Postoperative complications (anastomotic leakage, postoperative bleeding, intra-abdominal abscess, stoma complications, general complications) independently increase the risk of mortality after surgery.

Keywords: colorectal cancer, preoperative factors, intraoperative factors, postoperative factors, complications, survival.

Introduction

Colorectal cancer is the third most commonly diagnosed cancer worldwide (1). It occurs more frequently in men than in women, and it is 3-4 times more common in developed countries than in developing countries (1). According to the data of the Colorectal Cancer Alliance, 152,810 new cases of colorectal cancer were diagnosed in the U.S. in 2024 (2). According to the World Cancer Research Fund, there were 1,926,425 new cases of colorectal cancer in the world in 2022 (3). In 2020, the highest estimated standardized incidence rate per 100,000 was in Europe (30.4), followed by Oceania (29.8) and North America (26.2), while the lowest rate was in Asia (17.6), followed by Latin America (16.6) and Africa (8.4) (4). According to the International Agency for Research on Cancer (IARC), in 2020, colorectal cancer was the second

most common cause of cancer deaths, after lung cancer (4). Globally, the age-standardized mortality rate (ASMR) of colorectal cancer was 9.0/100,000 in 2020 (4). When different regions are observed, the highest ASMR (per 100,000) was in Europe (12.3), while the lowest was in Africa (5.6) and the Mediterranean region (5.3) (4). According to the data for 2022 (1), the country with the highest incidence rate of colorectal cancer (per 100,000) in the male population was Hungary, while in the female population it was Norway.

The observation of trends in colorectal cancer incidence between 2010 and 2021 showed that globally the incidence of colorectal cancer increased by 35.9%, from 1,614,410 cases in 2010 to 2,194,143 cases in 2021 (5). However, when the mortality rate of colorectal cancer is considered,

slučaja u 2021. godini (5). Međutim, kada govori-mo o stopi mortaliteta kolorektalnog karcinoma, ona je sa 13,37 na 100.000 u 2010. godini sman-jena na 12,40 na 100.000. u 2021. godini. Kada govorimo o trendu kretanja broja izgubljenih godina „zdravog života“ (engl. *Disability adjusted life years* - DALYs) u periodu od 2010. do 2021., on se do 2021. godine povećao za 23,9%, među-tim stopa DALY standardizovana prema uzrastu je smanjena za 6,9% (5). U 2021. godini najveća inci-dencija kolorektalnog karcinoma je bila u Holandiji 69,8 na 100.000, a mortaliteta u Urugvaju 27,46 na 100.000 stanovnika (5). Prema podacima Globalne opservatorije za rak (engl. *Global cancer observa-tory*), broj novootkrivenih slučajeva kolorektalnog karcinoma na globalnom nivou će se sa 1.931,590 u 2020. povećati na 3.154.674 u 2040. godini, što predstavlja povećanje stope incidencije kolorektal-nog karcinoma za čak 63,3% u narednih dvadeset godina (4). Procenjene promene novootkrivenih slučajeva kolorektalnog karcinoma (4) će procen-tualno biti manje zastupljene u visoko razvijenim u odnosu na srednje i nisko razvijene zemlje. To je potvrđeno i poslednjih decenija (4), gde je za-beležen pad u trendu obolevanja u zemljama koje su ranije imale veće rizike od kolorektalnog karci-noma (Danska, Švedska, Australija, Kanada i USA), a u zemljama u razvoju (Brazil, Kosta Rika, Kuvajt i Indija), sa ranije manjim rizikom od kolorektalnog karcinoma, prisutan je trend porasta. Procenje-ni broj novih slučajeva kolorektalnog karcinoma 2020. u odnosu na 2045. godinu, za oba pola, sta-rosne dobi do 85 godina, biće povećan za 77,4% u Aziji, 26,7% u Evropi, 77,8% u Latinskoj Americi, za 36% u Severnoj Americi i 112,8% u Africi (6). IARC smatra da će se globalno opterećenje od kolorek-talnog karcinoma očekivano povećati za 60%, što predstavlja više od 2,2 miliona novih slučajeva i 1,1 milion smrtnih ishoda do 2030. godine (6).

U cilju redukcije kolorektalnog karcinoma neophodno je raditi na uvođenju i adekvatnom organizovanju skrining programa. Trenutno dos-tupni skrining testovi za ranu dijagnostiku, koji su u širokoj upotrebi jesu gvajak FOBT (engl. *Guaiac Fecal occult blood test*) i imunohemijski FOBT (engl. *Fecal Immunochemical Test* - FIT)(1). Iako gFOBT test zadovoljava osobine skrininga, iako dostupan, jednostavan i jeftin, to je test koji ima malu specifičnost i veliki broj lažno pozitivnih re-zultata. Da bi se smanjio broj lažno pozitivnih rezu-ltata, potrebno je analizirati više od jedne stolice,

promeniti način ishrane (izbaciti iz ishrane crveno meso, određeno voće i povrće) i prekinuti primenu nekih lekova (aspirin, NSAID, antikoagulant) (7). Is-traživanje u Minesoti je pokazalo efikasnost gFOBT testa odnosno da njegova primena smanjuje in-cidenciju kolorektalnog karcinoma (8). U opser-vacionim studijama je pokazano da FIT ima veću senzitivnost u ranom otkrivanju kolorektalnog karcinoma i uznapredovalih adenoma u odnosu na gFOBT (7). Takođe je meta analiza 12 kohort-nih studija otkrila da je FIT test, sa graničnom vrednošću 20g hemoglobina po gramu stolice, senzitan 79%, a da mu je specifičnost 94% (9). Kolonoskopija iako omogućava ranu detekciju prekanceroznih lezija i kolorektalnog karcinoma, njegovu vizualizaciju i mogućnost ekscizije prome-na, se najčešće koristi kao dijagnostički test nakon pozitivnih rezultata gore pomenutih neinvazivnih skrining testova (FOBT i FIT) (7). Međutim u nekim zemljama poput Sjedinjenih Američkih država, može se koristiti kao „prva linija skrininga“ (7). Kolonoskopija se smatra "zlatnim standardom" zbog svoje visoke pouzdanosti, ali zbog visokih troškova, potrebe za obukom stručnjaka, rizika i neprijatnosti za pacijente, ne koristi se svuda kao masovni skrining test.

Cilj ovog preglednog rada jeste da prikaže koji prediktori, u kom delu toka bolesti i na koji način utiču na nastanak postoperativnih komplikacija, kao i na samo preživljavanje pacijenata sa kolorek-talnim karcinomom. Identifikacijom prediktora i njihovom kontrolom bilo bi moguće smanjiti broj postoperativnih komplikacija i obezbediti una-pređenje kvaliteta života i bolje preživljavanje.

Metod

U okviru ovog preglednog rada za pretraživanje literature koristili smo PUBMED. Ključne reči koje su korišćene za pretraživanje su: preoperativni, intraoperativni i postoperativni faktori, postop-erativne komplikacije, preživljavanje, incidencija, mortalitet i kolorektalni karcinom. Uključeni su svi oni radovi koji su bili na engleskom jeziku i koji su publikovani za poslednjih 30 godina.

Komplikacije nakon kolorektalne hirurgije

Kolorektalni karcinom obično počinje kao prekancerozna proliferacija epitelnih ćelija slu-zokože, najčešće u obliku adenoma ili polipa. Smatra se da samo oko 10% svih adenoma napredu-je do invazivnog karcinoma, najčešće nako 10-20

it decreased from 13.37 per 100,000 in 2010 to 12.4 per 100,000 in 2021. As far as the trend in the number of disability adjusted life years (DALY) is concerned between 2010 and 2021, it increased by 23.9% until 2021, however, age-standardized DALY rate decreased by 6.9% (5). In 2021, the highest incidence of colorectal cancer was in the Netherlands, 69.8 per 100,000, while the highest mortality was in Uruguay, 27.46 per 100,000 (5). According to the Global Cancer Observatory data, the number of newly discovered cases of colorectal cancer will increase globally from 1,931,590 in 2020 to 3,154,674 in 2040, which represents an increase in the incidence of colorectal cancer by 63.3% in the next twenty years (4). The estimated changes in the number of newly discovered cases of colorectal cancer (4) will be lower in highly developed countries compared to countries with low and medium HDIs. This has been confirmed in recent decades (4), when a decline in the incidence trend has been recorded in countries that previously had a higher risk of colorectal cancer (Denmark, Sweden, Australia, Canada and the USA), while an increasing trend has been observed in developing countries, which previously had a lower risk of colorectal cancer (Brazil, Costa Rica, Kuwait and India). The estimated number of new cases of colorectal cancer in 2020 compared to 2045, for persons of both sexes, aged up to 85 years, will increase by 77.4% in Asia, 26.7 in Europe, 77.8% in Latin America, by 36% in North America and 112.8% in Africa (6). According to the IARC, the global burden of colorectal cancer is expected to increase by 60%, with more than 2.2 million new cases and 1.1 million deaths by 2030 (6).

In order to reduce colorectal cancer, screening programs should necessarily be introduced and adequately organized. Currently available screening tests for early diagnosis, which are widely used, are Guaiac Fecal Occult Blood Test (FOBT) and Fecal Immunochemical Test (FIT) (1). Although gFOBT test meets screening criteria and it is easily available, simple and inexpensive, it is a test that has low specificity and a great number of false positive results. In order to reduce the number of false positive results, it is necessary to analyze more than one stool, change dietary habits (eliminate red meat, certain fruits and vegetables from the diet) and stop the use of some drugs (aspirin, NSAIDs, anticoagulants) (7). The research in Minnesota showed the effectiveness

of gFOBT test, that is, that its application reduced the incidence of colorectal cancer (8). It has been shown in observational studies that FIT had higher sensitivity in the early detection of colorectal cancer and advanced adenomas compared to gFOBT (7). Also, it was found in a meta-analysis of 12 cohort studies that the FIT test, with the threshold of 20 µg hemoglobin per one gram of feces, demonstrated a sensitivity of 79% and a specificity of 94% (9). Although colonoscopy enables early detection of precancerous lesions and colorectal carcinoma, its visualization and the possibility of excision of changes, it is most often used as a diagnostic test after positive results of the aforementioned non-invasive screening tests (FOBT and FIT) (7). However, in some countries, such as the United States of America, it can be used as “the first line of screening”. Colonoscopy is considered to be “the gold standard” due to its high reliability, but due to high costs, the need for expert training, risks and discomfort experienced by patients, it is not used everywhere as a mass screening test.

The aim of this review article is to show which predictors, at what point of the course of the disease and in which way, influence the occurrence of postoperative complications, as well as the survival of patients with colorectal cancer. By identifying the predictors and controlling them, it would be possible to reduce the number of postoperative complications and ensure the improvement of the quality of life and better survival.

Methods

As part of this review article, we used PUBMED to search the literature. Key words used for the search were the following: preoperative, intraoperative and postoperative factors, postoperative complications, survival, incidence, mortality and colorectal cancer. All studies that were written in the English language and published in the last 30 years were included.

Complications after colorectal surgery

Colorectal cancer usually begins as a precancerous proliferation of mucosal epithelial cells, usually in the form of adenomas and polyps. It is believed that only about 10% of all adenomas progress to invasive carcinoma, usually after 10-20 years of gradual growth (10). Invasive

godina postepenog rasta (10). Invazivni karcinom, koji potiče iz pomenutih pre-karcinoznih promena jeste po tipu adenokarcinom, koji čini 96% svih kolorektalnih karcinoma. Operativno lečenje karcinoma predstavlja prvi izbor kada je reč o lečenju lokalizovane bolesti, jer nudi najveću šansu za izlečenjem i preživljavanjem. Petogodišnje preživljavanje pacijenata sa kolorektalnim karcinomom je usko vezana za stadijum u kojem je bolest otkrivena. Ako je karcinom otkriven u stadijumu I bolesti (lokalizovana bolest) stopa petogodišnjeg preživljavanja je 90-93%, a za regionalnu bolest (stadijum II) je 70-85%. U trećem stadijumu bolesti kreće se 50-70%, a kada postoje udaljene meta promene (IV stadijum bolesti) 10-20%. Svako odlaganje dijagnoze i napredovanje karcinoma u viši stadijum drastično smanjuje šanse pacijenta za dugoročno preživljavanje (11). Iako su hiruške tehnike dosta uznapredovale, kao i preoperativna i perioperativna nega pacijenata, postoperativne komplikacije i dalje predstavljaju veliki izazov nakon operativnog zahvata, koje utiču na dalji tok bolesti tj. oporavak pacijenata, dužinu boravka u bolnici, kao i na samo preživljavanje pacijenata. Inače sve komplikacije posle resekcije kolorektalnog kancera mogu da budu hirurške (npr. popuštanje anastomoze, infekcija hirurške rane, intra-abdominalni apsces, postoperativno krvarenje, komplikacije stome itd.) i sistemske (pneumonija, plućna embolija, srčani udar, duboka venska tromboza, ileus, bubrežna insuficijencija, urinarne infekcije itd.) komplikacije (tabela 1).

Preoperativni prediktori komplikacija i lošijeg preživljavanja nakon kolorektalne hirurgije

Kada govorimo o preoperativnim prediktorima komplikacija nakon kolorektalne hirurgije obično

se navode: demografske karakteristike (pol, godine starosti), socijalne navike u vidu konzumiranja alkohola i pušenja, kliničke karakteristike, indeks telesne mase (engl. Body mass index – BMI), klasifikacija Američkog društva anesteziologa (engl. American Society of Anaesthesiologists' - ASA) fizičkog statusa ispitanika, markeri inflamacije i komorbiditeti (dijabetes melitus i hipertenzija) (tabela 2)(1).

Demografske karakteristike

Starija životna dob je jedan od najsnažnijih prediktora komplikacija i lošijeg preživljavanja, jer stariji pacijenti obično imaju veći broj komorbiditeta, sporije zarastanje rana i oslabljen imunološki odgovor (1,4). Kod njih češće dolazi do infekcije, dehiscencije rane i kardioloških komplikacija. (12,13)

U mnogim studijama o kolorektalnom karcinomu, muški pol se nezavisno povezuje sa većom stopom postoperativnog morbiditeta i mortaliteta (1,4). Ovo se delimično može objasniti većom učestalošću loših životnih navika i težih komorbiditeta (srčane bolesti) kod muškaraca nego žena (14). Neke intervencije, npr. totalna mezorektalna ekcizija se tehnički teže izvodi kod muškaraca nego žena, što može rezultirati većim intraoperativnim stresom i komplikacijama (15).

Inflamatorni markeri

Templeton i saradnici (16) su uočili da inflamatorni markeri, kao što su odnos neutrofila/limfocita (NLR) i odnos trombocita/limfocita (PLR), mogu biti korisni za predviđanje postoperativnih komplikacija i prognozu bolesti. Identifikovano je da visok PLR predstavlja nezavisni faktor povezan sa lošom prognozom tj. preživljavanjem kod paci-

Tabela 1. Komplikacije posle resekcije kolorektuma

Hirurške komplikacije	Sistemske komplikacije
Dehiscencija anastomoze	Pneumonija
Intra-abdominalna infekcija – apsces	Plućna embolija
Infekcija hirurške rane	Srčani udar
Opstrukcija creva	Duboka venska tromboza
Komplikacije stome	Ileus
Krvarenje	Bubrežna insuficijencija
Promene u pražnjenju creva	Urinarne infekcije
Oštećenje živaca mala karlice	Drugo
Drugo	

carcinoma originating from the aforementioned pre-cancerous changes is the carcinoma of the adenocarcinoma type, which accounts for 96% of all colorectal carcinomas. Surgical treatment of cancer is the first choice when it comes to the treatment of localized disease, as it offers the greatest chance of cure and survival. The five-year survival of patients with colorectal cancer is closely related to the stage in which the disease was detected. If cancer is detected at stage I of the disease (localized disease), the five-year survival rate is 90-93%, while for the regional disease (stage II), this rate amounts to 70-85%. In the third stage of the disease, the rate is between 50 and 70%, and when there are distant meta changes (stage IV of the disease), it is 10-20%. Any delay in diagnosis and progression of cancer to a higher stage drastically reduces the patient's chances of long-term survival (11). Although surgical techniques have improved a lot, as well as preoperative and perioperative care of patients, postoperative complications still represent a major challenge after surgery, and they affect the further course of the disease, that is, the recovery of patients, the length of hospital stay, as well as the survival of patients. All complications after colorectal cancer resection can be surgical (e.g. an anastomotic leak, wound infection, intra-abdominal abscess, postoperative bleeding, stoma complications, etc.) and systemic (pneumonia, pulmonary embolism, heart attack, deep vein thrombosis, ileus, renal failure, urinary infections, etc.) (Table 1).

Preoperative predictors of complications and worse survival after colorectal surgery

As far as preoperative predictors of complications after colorectal surgery are

concerned, the following are usually mentioned: demographic characteristics (sex, age), social habits such as alcohol consumption and smoking, clinical characteristics, body mass index (BMI), the classification of the physical status of the American Society of Anaesthesiologists (ASA), markers of inflammation and comorbidities (diabetes mellitus and hypertension) (Table 2) (1).

Demographic characteristics

Older age is one of the strongest predictors of complications and worse survival, because older patients usually have a greater number of comorbidities, slower wound healing and weakened immunological response (1,4). In these patients, infections, wound dehiscence and cardiac complications often occur.

In many studies about colorectal cancer, male gender is independently associated with a higher rate of postoperative morbidity and mortality (1,4). This can be partially explained by the higher frequency of bad lifestyle habits and severe comorbidities (heart disease) in men than in women. Some interventions, e.g. total mesorectal excision are technically more difficult to perform in men than in women, which can result in greater intraoperative stress and complications.

Inflammatory markers

Templeton and associates (12) found that inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) may be useful for the prediction of postoperative complications and disease prognosis. A high PLR was identified as an independent factor associated with poor prognosis, that is, survival in patients with colorectal cancer. Data from 47

Tabela 1. Complications after resection of colorectum

Surgical complications	Sistemic complications
Anastomotic dehiscence	Pneumonia
Intra-abdominal infection– apscess	Plumonary embolism
Infection of surgycal wound	Heart attack
Intestinal obstruction	Deep vein thrombosis
Komplikation of stoma	Ileus
Bleeding	Kidney failure
Changes in bowel movements	Urinary infections
Pelvic nerve damage	Other
Other	

Tabela 3. Preoperativni, intraoperativni i postoperativni prediktori postoperativnih komplikacija nakon resekcije kolorektuma

Preoperativni prediktori	Najčešći prediktori
1. Demografske karakteristike	Godine starosti
	Pol
2. Socijalne navike	Pušenje
	Konзумiranje alkohola
3. Kliničke karakteristike	Nutritivni status prema <i>Prognostic nutritional index</i> -PNI
4. ASA klasifikacija	Skor ≥ 3
5. Markeri inflamacije	CRP
	IL-1
	Odnos neutrofila/limfocita (NLR)
	Odnosa trombocita/limfocita (PLR)
6. Komorbiditeti	Dijabetes
	Hipertenzija
Intraoperativni prediktori	
1. Intraoperativni gubitak krvi	>500 ml
2. Dužina trajanja operativnog zahvata	≥ 180 –200 minuta
3. Vrsta hiruške intervencije	Otvorena hirurgija
Postoperativni prediktori	
Postoperativne komplikacije	Infekcije rane
	Respiratorne komplikacije
	Tromboembolijske komplikacije
	Urinarne infekcije
	Dehiscencija rane
	Drugo

jenata sa kolorektalnim karcinomom. Meta analizom sakupljeni su podaci 47 opservacionih studija (14.205 pacijenata sa kolorektalnim karcinomom) i utvrđeno je da su visoke preoperativne vrednosti NLR povezane sa lošijim ukupnim preživljavanjem (17). Takođe, vrednosti NLR ≥ 5 udvostručuje rizik od smrti (17). Visoke vrednosti PLR ukazuju na lošije ukupno preživljavanje pacijenata (17). U drugoj studiji (18) identifikovano je da NLR i PLR predstavljaju značajne nezavisne prognostičke faktore pacijenata sa kolorektalnim karcinomom, tj. da pacijenti u II i III stadijumu bolesti sa vrednostima NLR $\geq 4,98$ i PLR $\geq 246,36$ imaju lošiju stopu petogodišnjeg preživljavanja u poređenju sa pacijentima koji imaju niže vrednosti ovih markera. U prospektivnoj kohortnoj studiji (n=448) sa dužinom praćenja od 5 godina, kod pacijenata

nakon resekcije kolorektalnog karcinoma, preoperativne vrednosti NLR $\geq 2,81$ su bile povezane sa lošijim ukupnim preživljavanjem nakon operacije, dok je PLR imao prognostičku vrednost u nekim podgrupama, ali nije predstavljao nezavisni prediktor lošijeg preživljavanja (19).

Nedavno sprovedena meta analiza je ukazala na vezu između hronične upale, koja je merena cirkulišućim inflamatornim markerima (CRP i IL-6), i povećane incidencije karcinoma, uključujući i kolorektalni karcinom (20). S obzirom da je CRP marker sistemske inflamacije, možemo reći da su njegove povišene vrednosti predisponirajući faktor u nastanku postoperativnih komplikacija. Meta analizom 23 studije, 7141 pacijenta, korišćeni su preoperativni nivoi CRP-a kao prediktora postoperativnih komplikacija, kao što su curenje anastomoze

Tabela 3. Preoperative, intraoperative and postoperative predictors of postoperative complications after colorectal resection

Preoperative predictors	Most common predictors
1. Demographic characteristics	Age
	Gender
2. Social habits	Smoking
	Alcohol consumption
3. Clinical characteristics	Nutritive status
	Prognostic nutritional index -PNI
4. ASA classification	Score ≥ 3
5. Markers of inflammation	CRP
	IL-1
	Neutrophil to lymphocyte ratio (NLR)
	Platelet to lymphocyte ratio (PLR)
6. Comorbidities	Diabetes
	Hypertension
Intraoperative predictors	
1. Intraoperative blood loss	>500 ml
2. The duration of the operation	≥ 180 –200 minutes
3. Type of surgical intervention	Open surgery
Postoperative predictors	
Postoperative predictors	Infection of wound
	Respiratory complications
	Thromboembolic complications
	Urinary infections
	Wound dehiscence
	Other

observational studies were collected with the help of meta-analysis (14,205 patients with colorectal carcinoma) and it was found that high preoperative values of NLR were associated with worse overall survival (13). Also, NLR values ≥ 5 double the risk of death (13). High PLR values indicate worse overall patient survival (13). In another study (14), it was identified that NLR and PLR represent significant independent prognostic factors in patients with colorectal cancer, that is, that patients in stages II and III with NLR values ≥ 4.98 and PLR ≥ 246.36 had a worse five-year survival rate compared to patients who had lower values of these markers. In a prospective cohort study (n=448) with a follow-up of 5 years in patients after colorectal cancer resection, preoperative NLR values ≥ 2.81 were associated with worse overall survival

after surgery, while PLR had a prognostic value in some subgroups, but it was not an independent predictor of worse survival (15).

A recent meta-analysis indicated a relationship between chronic inflammation, which was measured by circulating inflammatory markers (CRP and IL-6) and the increased incidence of cancer, including colorectal cancer (16). Given that CRP is a marker of systemic inflammation, we can say that its elevated levels are a predisposing factor for the occurrence of postoperative complications. A meta-analysis of 23 studies that included 7141 patients used preoperative CRP levels as a predictor of postoperative complications, such as an anastomotic leak and other complications after elective colorectal surgery. CRP levels were elevated in the group that had postoperative

i druge komplikacije nakon elektivne kolorektalne hirurgije. Nivoi CRP su bili povišeni u grupi, koja je imala postoperativne komplikacije u vidu infekcije, dok se nivo CRP nije razlikovao u grupi koja je imala curenje anastomoze nakon operacije, i grupi koja nije imala pomenutu komplikaciju (21).

Nutritivni status

Pored pomenutih markera, u litearturi (22) je opisana i povezanost lošeg nutritivnog statusa pacijenta sa teškim postoperativnim komplikacijama, kao što su pneumonija i ekstrapulmonalne infekcije. Prognostic nutritional index (PNI) je predstavljen kao odnos zasnovan na nivou serumskog albumina, koji predstavlja nutritivni kapacitet i broja limfocita, koji predstavljaju imuni kapacitet organizma. U skladu sa tim, očekivano je da pacijenti sa niskim PNI indeksom imaju oslabljenu sposobnost zarastanja rana i oslabljenu imunološku funkciju (11). Smatra se da PNI indeks predstavlja efikasan biomarker predviđanja postoperativnih komplikacija (intestinalna opstrukcija, abdominalna infekcija, pneumonija, problemi sa anastomozom i infekcija rane) (23), gde niže vrednosti indeksa ukazuju na veću učestalost postoperativnih komplikacija, u odnosu na grupu sa višim indeksom uhranjenosti. Takođe, dobar nutritivni status pacijenta, prikazan ovim indeksom, povezan je sa boljim predviđanjem dugoročnog preživljavanja i manjim rizikom od komplikacija. Kada govorimo o preživljavanju pacijenata sa kolorektalnim karcinomom, pokazano je da pacijenti sa niskim PNI indeksom imaju lošije preživljavanje, u odnosu na pacijente sa dobrim nutritivnim statusom (23).

Životne navike

Kao i u mnogim bolestima, štetne životne navike, kao što su pušenje i konzumiranje alkohola, imaju doprinos i u lošijem postoperativnom ishodu tj. u nastanku postoperativnih komplikacija. Herlo i saradnici (1) su pokazali da su pušenje i konzumiranje alkohola bili češći u grupi pacijenata koji su imali postoperativne komplikacije nakon resekcije kolorektalnog karcinoma.

Komorbiditeti

Kada govorimo o najčešćim hroničnim komorbiditetima (dijabetes melitus i hipertenzija), oni su takođe značajno češći u grupi pacijenata sa postoperativnim komplikacijama, što prikazuje njihov doprinos u nastanku istih. Iz dostupnih podataka meta analize Tana i saradnika (24),

od 666.886 pacijenata (obrađenih u 55 studija), 93.173 je imalo dijagnostikovan dijabetes melitus. Među pacijentima sa dijabetesom, posle resekcije kolorektalnog karcinoma, curenje anastomoze, infekcija hiruške rane, urinarne komplikacije i ponovna hospitalizacija su bili znatno češći nego kod kontrola. Retrospektivna desetogodišnja kohortna studija, sprovedena u Engleskoj, je pokazala da osobe sa dijabetesom, a koje su bile podvrgnute kolorektalnoj hirurgiji, imaju veći rizik od umiranja i ponovne hospitalizacije u vremenskom periodu 90 dana nakon intervencije, s tim što je korišćenje insulina povećavao ovaj rizik (25). U retrospektivnoj studiji sprovedenoj u Tajvanu (26), koja je obuhvatala pacijente sa II i III stadijumom kolorektalnog kancera a kod kojih je sprovedena kurativna resekcija, postojanje dijabetesa je predstavljalo značajno loš prognostički faktor preživljavanja, a hipertenzija nije značajno uticala na preživljavanje. Međutim, u meta analizi (27), koja je obuhvatila 16 studija, hipertenzija je bila povezana sa boljim kliničkim ishodima, kao što su ukupno preživljavanje i preživljavanje bez progresije bolesti, kod pacijenata sa metastatskim kolorektalnim karcinomom (27). Povezanost hipertenzije sa boljim ishodima (nazvana "hipertenzivni paradoks") često se viđa u onkološkim studijama, posebno u uznapredovaloj bolesti. Može se objasniti na dva načina. Jedan ukazuje da se hipertenzija leči lekovima (npr. ACE inhibitorima, beta-blokatorima) koji mogu imati antitumorski efekat, a drugi da se pacijenti sa hipertenzijom češće prate i leče zbog svog osnovnog stanja, što rezultira boljim onkološkim ishodima.

ASA klasifikacija

ASA klasifikacija predstavlja široko korišćen sistem za ocenjivanje preoperativnog fizičkog stanja hiruških pacijenata, koji može biti koristan i u predviđanju postoperativnih komplikacija tj. samog ishoda nakon hiruške intervencije i preživljavanja pacijenata sa kolorektalnim karcinomom. Kim i saradnici (28) su ukazali da u starijoj populaciji (godine starosti > 80), ASA skor >3 predstavlja značajan nezavisni prediktor povezan sa većim rizikom od 30-o dnevnih postoperativnih komplikacija. To znači da je veći ASA skor povezan sa većom stopom postoperativnih komplikacija, dužim zadržavanjem pacijenata u jedinici intenzivne nege, pa samim tim i povećanim troškovima. U pomenutoj kohortnoj studiji (28), ASA ≥ 3 je takođe značajan nezavisni prediktor većeg umiranja, čak dva

complications in the form of infection, while CRP levels did not differ in the group that had anastomotic leakage after surgery and the group that did not have the mentioned complication (17).

Nutritional status

In addition to the mentioned markers, the association between the poor nutritional status and severe postoperative complications, such as pneumonia and extrapulmonary infections, has been described in the literature (18). Prognostic nutritional index (PNI) has been presented as a ratio based on the level of serum albumin, which represents the nutritional capacity, and the number of lymphocytes, which represent the immune capacity of the organism. Accordingly, patients with a low PNI index are expected to have impaired wound healing ability and weakened immune function (11). The PNI index is considered to be an effective biomarker for predicting postoperative complications (intestinal obstruction, abdominal infection, pneumonia, problems with anastomosis and wound infections) (19), where lower index values indicate a higher frequency of postoperative complications compared to the group with a higher nutritional index. In addition, a good nutritional status of the patient, shown by this index, is associated with a better prediction of long-term survival and a lower risk of complications. When it comes to the survival of patients with colorectal carcinoma, it has been shown that patients with a low PNI index have worse survival in comparison to patients with a good nutritional status (19).

Life habits

As in many diseases, harmful life habits, such as smoking and alcohol consumption, contribute to a worse postoperative outcome, that is, the occurrence of postoperative complications. Herlo et al. (1) showed that smoking and alcohol consumption were more common in the group of patients who had postoperative complications after resection of colorectal carcinoma.

Comorbidities

As far as the most common chronic comorbidities are concerned (diabetes mellitus and hypertension), they are also significantly more common in the group of patients with postoperative

complications, which shows their contribution to their occurrence. The available data from the meta-analysis conducted by Tan and associates (20) showed that of 666,886 patients (analyzed in 57 studies), 93,173 were diagnosed with diabetes mellitus. An anastomotic leak, surgical wound infection, urinary complications, and hospital readmission after resection of colorectal carcinoma were more frequent in patients with diabetes than in controls. A retrospective 10-year cohort study conducted in England showed that people with diabetes who underwent colorectal surgery had a higher risk of death and hospital readmission within 90 days after the intervention, as well as that insulin use increased the risk (21). In a retrospective study conducted in Taiwan (22), which included patients with stage II and III colorectal cancer who underwent curative resection, the presence of diabetes was a significantly poor prognostic factor for survival, while hypertension did not significantly affect survival. However, in a meta-analysis (23), which included 16 studies, hypertension was associated with better clinical outcomes, such as the overall survival and disease-free survival in patients with metastatic colorectal cancer (23). The association between hypertension and better outcomes (called the "hypertensive paradox") is often seen in oncological studies, especially in advanced stages of disease. It can be explained in two ways. One indicates that hypertension is treated with drugs (e.g. ACE inhibitors, beta-blockers) that can have an antitumor effect, and the other indicates that patients with hypertension are more often monitored and treated because of their underlying condition, which results in better oncological outcomes.

ASA classification

The ASA classification is a widely used system for assessing the preoperative physical condition of surgical patients, which can be useful for predicting postoperative complications, that is, the outcome after surgical intervention and survival of patients with colorectal cancer. Kim et al. (24) indicated that in the elderly population (age > 80), the ASA score > 3 was a significant independent predictor associated with a higher risk of 30-day postoperative complications. This means that a higher ASA score is associated with a higher rate of postoperative complications, longer stay of

puta je veći rizik od smrtnog ishoda nakon jedne godine, kao i smanjenog dugoročnog preživljavanja posebno u kombinaciji sa drugim faktorima kao što su TNM stadijum i postoperativne komplikacije (29). Kada je reč o odabiru hiruškog pristupa kod pacijenata sa kolorektalnim karcinomom, pokazalo se da laparaskopska hirurgija, kod pacijenata sa ASA ≥ 3 , značajno smanjuje postoperativne komplikacije, u odnosu na otvorenu hirurgiju (30,31). Mnogi autori navode da bi bilo dobro da se ASA skor i odabir hiruškog pristupa u skladu sa njim inkorporira u preoperativnu pripremu pacijenta i procenu rizika od pojave postoperativnih komplikacija i boljeg preživljavanja.

Intraoperativni prediktori komplikacija i lošijeg preživljavanja nakon kolorektalne hirurgije

Od svih intraoperativnih prediktora komplikacija najčešće se spominju intraoperativni gubitak krvi, dužina trajanja operativnog zahvata i vrsta hirurške intervencije (tabela 2)(32-34).

Intraoperativni gubitak krvi

U studiji gde su analizirani podaci nakon 700 kolorektalnih operacija (1), intraoperativni gubitak krvi >500 ml i produženo operativno vreme bili su značajni nezavisni prediktori postoperativnih komplikacija (28,5%) i 30-dnevnog mortaliteta (5,2%). Takođe, u meta analizi (32), koja je obuhvatila 43 studije (≈ 60.000 pacijenata), prikazano je da gubitak krvi $>150-350$ ml povećava mortalitet, anastomotsko curenje, postoperativni ileus i dužinu boravka u bolnici, a gubitak krvi $>200-500$ ml rizik od postoperativne infekcije hiruške rane i lošijeg ukupnog preživljavanja. Multicentrična, retrospektivna studija (2000-2019. godine) (33) koja je obuhvatila oko 1600 pacijenata je pokazala da je veći intraoperativni gubitak krvi (više od 200 ml krvi) značajno nezavisno povezan sa lošijim ukupnim preživljavanjem.

Dužina operativnog zahvata

Studija koja je obuhvatila 6224 pacijenta nakon radikalne kolektomije (2011-2016.)(34) je pokazala da duže operativno vreme predstavlja značajan nezavisni prediktor kratkoročnih ishoda kao što su postoperativne komplikacije, duži boravak u jedinici intenzivnog lečenja i duža hospitalizacija uopšte. To znači da produženo vreme operacije utiče na lošije ukupno preživljavanja pacijenata nakon radikalne kolektomije (34). Takođe, operativno vreme

$\geq 180-200$ minuta predstavlja značajan nezavisni faktor koji utiče na postoperativni nastanak komplikacija nakon desne laparaskopske kolektomije (35). U navedenoj studiji uočeno je i da dijabetes i konverzija laparoskopije u otvoren pristup doprinose većem riziku od nastanka infekcije opeartivne rane. U studiji Gabriele i saradnika (2005-2012.), koja je obuhvatila 113.615 pacijenata nakon operacije kolorektalnog karcinoma (36), pacijenti su bili podeljeni u tri grupe prema dužini trajanja intervencije (kratke, prosečne i duge). Pacijenti sa dugim trajanjem intervencije (12%) imali su za 34% više postoperativnih infekcija rane, za 36% dužu hospitalizaciju, za 40% više reintervencija, za 44% više tromboembolijskih komplikacija, kao i za 69% više abdominalne dehiscencije (36).

Vrsta hirurške intervencije

Iako je laparaskopska hirurgija tehnički zahtevnija i potencijalno duže traje, rezultati brojnih studija pokazuju da minimalno invazivni pristup nudi bolje kratkoročne ishode nego klasična (otvorena hirurgija) (37).

Postoperativni prediktori komplikacija i lošijeg preživljavanja nakon kolorektalne hirurgije

Law i saradnici (38) su pokazali da postoperativne komplikacije, koje nastaju nakon resekcije kolorektalnog karcinoma predstavljaju značajan nezavisni faktor rizika, koji loše utiče na dugoročno preživljavanje pacijenata. Radi njihove lakše interpretacije i procene njihove težine napravljena je standardizovana Clavien-Dindo klasifikacija (CDC), koja se sastoji od 5 različitih stepena (20). Step 1 CDC podrazumeva svako odstupanje od normalnog postoperativnog toka, koje ne zahteva farmakološku terapiju ili hirušku intervenciju. Komplikacije II stepena CDC zahtevaju farmakološki tretman, parenteralnu ishranu i transfuzije krvi. Komplikacije III stepena zahtevaju hirušku, endoskopsku ili radiološku intervenciju (IIIa- nije u opštoj anesteziji, IIIb- u opštoj anesteziji). Komplikacije IV stepena CDC su opsane po život i zahtevaju intenzivnu negu (IVa- disfunkcija jednog organa, IVb- disfunkcija više organa), a V stepena predstavljaju postoperativnu smrt pacijenta (20). Utvrđeno je da kod pacijenata sa postoperativnim komplikacijama, posebno sa visokim stepenom CDC, postoji lošija dugoročna prognoza ishoda bolesti (39). Pacijenti sa III stepenom CDC imali su veći rizik od pojave lokoregionalnih recid-

patients in the intensive care unit, and therefore, higher costs. In the above mentioned cohort study (24), ASA ≥ 3 was also a significant independent predictor of higher mortality, with the risk of deathly outcome after one year being two times greater, as well as a predictor of reduced long-term survival, especially in combination with other factors such as TNM stage and postoperative complications (25). When it comes to the choice of surgical approach in patients with colorectal carcinoma, it shown that laparoscopic surgery in patients with the ASA score ≥ 3 , significantly reduced postoperative complications in comparison to open surgery (26,27). Many authors state that it would be good to incorporate the ASA score and the selection of surgical approach in accordance with it into the preoperative preparation of patients and the assessment of risks related to postoperative complications and better survival.

Intraoperative predictors of complications and worse survival after colorectal surgery

Intraoperative blood loss, duration of surgical procedure and the type of surgical intervention are the most frequently mentioned of all intraoperative predictors of complications (28-30).

Intraoperative blood loss

In a study, in which data after 700 colorectal surgeries were analyzed (1), intraoperative blood loss > 500 ml and longer duration of the operation were significant independent predictors of postoperative complications (28.5%) and 30-day mortality (5.2%). Also, in a meta-analysis (28), which included 43 studies ($\approx 60,000$ patients), it was shown that blood loss $> 150-350$ ml increased mortality, anastomotic leak, postoperative ileus and length of hospital stay, and blood loss $> 200-500$ ml increased the risk of postoperative surgical wound infection and worse overall survival. A multicentre, retrospective study (2000-2019) (29), which included about 1600 patients, showed that greater intraoperative blood loss (more than 200 ml of blood) was significantly independently associated with worse overall survival.

Duration of surgical procedure

The study, which included 6224 patients after radical colectomy (2011-2016) (30), showed that longer operation time was a significant independent predictor of short-term outcomes

such as postoperative complications, longer stay in the intensive care unit and longer hospitalization in general. This means that prolonged operative time affects worse overall survival of patients after radical colectomy (30). Also, operative time $\geq 180-200$ minutes was a significant independent factor affecting postoperative complications after right laparoscopic colectomy (31). In the above mentioned study, it was observed that diabetes and the conversion of laparoscopy to an open approach contribute to a higher risk of surgical wound infection. In a study by Gabriel and associates (2005-2012), which included 113,615 patients after colorectal cancer surgery (32), patients were divided into three groups according to the duration of the intervention (short, medium and long). Patients with long operative procedures (12%) had 34% more post operative wound infections, 36% more prolonged length of stay, 40% more reinterventions, 44% more thrombotic complications, and 69% more abdominal dehiscence (32).

Type of surgical intervention

Although laparoscopic surgery is technically more demanding and potentially lasts longer, the results of numerous studies show that the minimally invasive approach offers better short-term results than classical (open surgery) (1).

Postoperative predictors of complications and worse survival after colorectal surgery

Law and associates (33) showed that postoperative complications, which occur after the resection of colorectal carcinoma, represent a significant independent risk factor, which adversely affects the long-term patient survival. In order to interpret and assess their severity more easily, the standardized Clavien-Dindo classification (CDC), which consists of five different grades, was created (16). CDC grade I implies any deviation from the normal postoperative course, which does not require pharmacological therapy or surgical intervention. CDC grade II complications require pharmacological treatment, parenteral nutrition and blood transfusion. Grade III complications require surgical, endoscopic or radiological intervention (IIIa – not under general anesthesia, IIIb – under general anesthesia). CDC grade IV complications are life-threatening and require intensive care (IVa / dysfunction of one organ,

iva i udaljenih metastaza, što se poklapa sa rezultatima drugih istraživača. Primer III stepena CDC jeste curenje anastomoze, što se pokazalo da je u vezi sa povećanom stopom lokalnih recidiva i lošijim ukupnim preživljavanjem (40). Pacijenti sa IV stepenom CDC pokazali su najlošije stope preživljavanja bez bolesti i ukupne stope preživljavanja, u poređenju sa drugim pacijentima studije (39). Posle hiruške resekcije kolorektalnog karcinoma, nekim pacijentima može biti indikovana i adjuvantna terapija. Prema Nemačkim smernicama za kolorektalni karcinom, koje su zasnovane na dokazima, pacijenti oboleli od raka debelog creva treba da započnu adjuvantnu hemioterapiju u roku od 8 nedelja, pod uslovom normalnog postoperativnog toka bez komplikacija (41). Pacijenti sa postoperativnim komplikacijama imaju povećan rizik ako ne počnu na vreme sa adjuvantnom terapijom, što može dovesti do povećanja stope metastaziranja, samim tim i smanjene stope preživljavanja (39). Biagi i saradnici (42) koji su obuhvatili podatke za 10 studija (15. 410 pacijenata) su pokazali da je produžavanje vremena za 4 nedelje, od predviđenog vremena za adjuvantnu terapiju nakon resekcije karcinoma, povezano sa značajnim smanjenjem ukupnog preživljavanja i preživljavanja bez bolesti (42). Studija Bayarkara (43) i saradnika je došla do istog zaključka. Odlaganje adjuvantne terapije za više od 60 dana nakon operacije, kod pacijenata sa kolorektalnim karcinomom sa II i III stadijumom bolesti, dovodi do lošije prognoze tj. lošeg ukupnog preživljavanja. Kanadska studija, koja je obuhvatila 1053 pacijenta sa III stadijumom kolorektalnog karcinoma, nije pokazala značajnu razliku u preživljavanju pacijenata koji su primali adjuvantnu terapiju nakon 8 nedelja i između 8 i 12 nedelje nakon hiruškog lečenja (44). Međutim, lošije preživljavanje je zabeleženo kod pacijenata koji su adjuvantnu terapiju primili između 12 i 16 nedelje nakon intervencije i posle više od 16 nedelja nakon operacije su imali dvostruko veći rizik od mortaliteta, u odnosu na pacijente koji su terapiju dobili do 8 nedelja nakon intervencije.

Zaključak

Na osnovu opsežne analize, jasno je da na ishod i preživljavanje nakon kolorektalne hirurgije utiče niz međusobno povezanih preoperativnih,

intraoperativnih i postoperativnih faktora. U cilju smanjivanja rizika od komplikacija i obezbeđivanja boljeg preživljavanja nakon resekcije kolorektalnog karcinoma neophodna je optimizacija preoperativnog statusa pacijenta (poboljšanje ishrane, kontrola komorbiditeta i loših socijalnih navika, dobra klinička procena statusa pacijenta), kao i minimizacija intraoperativnog stresa, gubitka krvi, obezbeđivanje adekvatnog monitoringa i hiruškog pristupa. U slučaju pojave postoperativnih komplikacija, neophodna je njihova blagovremena dijagnostika i sanacija u adekvatnim vremenskim okvirima, potrebnim za početak adjuvantne terapije.

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IVb – dysfunction of multiple organs), and grade V complications represent the postoperative death of the patient (16). It was found that in patients with postoperative complications, especially with a high grade of CDC, there was a worse long-term prognosis of disease outcome (34). Patients with CDC grade III had a higher risk of occurrence of locoregional recurrence and distant metastases, which is consistent with other researchers' results. An example of CDC grade III is anastomotic leakage, which was shown to be associated with an increased rate of local recurrence and worse overall survival (35). Patients with CDC grade IV showed the worst rates of disease-free survival and overall survival compared to other patients in the study (34). After the surgical resection of colorectal cancer, adjuvant therapy may be indicated for some patients. According to the German guidelines for colorectal cancer, which are based on evidence, patients with colon cancer should start adjuvant chemotherapy within 8 weeks, when the postoperative course is normal with no complications (36). Patients with postoperative complications have an increased risk if they do not start on time with adjuvant therapy, which can lead to an increase in the rate of metastases, and therefore, a reduced survival rate (34). Biagi and associates (37) who included data from 10 studies (15,410 patients) showed that a 4-week delay to adjuvant therapy after resection of carcinoma was associated with the significant decrease in overall survival and disease-free survival (37). A study by Bayarktar et al. (38) came to the same conclusion. Postponing adjuvant therapy for more than 60 days after surgery in patients with stage II and III colorectal cancer leads to a worse prognosis, that is, poor overall survival. A Canadian study, which included 1053 patients with stage III colorectal cancer, did not show a significant difference in the survival of patients who received adjuvant therapy 8 weeks after surgical treatment and between 8 and 12 weeks after surgical treatment (39). However, worse survival was observed in patients who received adjuvant therapy between 12 and 16 weeks after the intervention and more than 16 weeks after the intervention. Also, patients who received adjuvant therapy more than 16 weeks after surgery had twice the risk of mortality compared to patients who received therapy up to 8 weeks after the intervention.

Conclusion

Based on extensive analysis, it is clear that mutually interrelated preoperative, intraoperative and postoperative factors influence the outcome and survival after colorectal surgery. In order to reduce the risk of complications and ensure better survival after resection of colorectal cancer, it is necessary to optimize the preoperative status of the patient (improving nutrition, controlling comorbidities and bad social habits, good clinical assessment of patient's status), as well as to minimize the intraoperative stress, blood loss, and ensure adequate monitoring and surgical approach. If postoperative complications occur, timely diagnosis and treatment are needed in adequate time frames for the start of adjuvant chemotherapy.

Competing interests

The authors declared no competing interests.

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