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SURGICAL SITE INFECTION AFTER ELECTIVE COLORECTAL SURGERY: A REVIEW OF PREVENTION

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Colon cancer is the third leading cause of the disease in the world. In the world, about 1,200,000 people suffer from it every year. The leading cause of morbidity and mortality with about 500,000 deaths per year, SSI (surgical site infections) are most often complications in surgical practice. It is estimated that about 2-5% of patients receive an infection of the operating site after "pure" non-abdominal surgery, and even 20% after interventions in the abdomen. Infections of the operating site are the most common types of hospital infections in the countries of the European Union (19.6%). The reported incidence of these infections in the field of colorectal surgery ranges from 5% to 26%. Knowing the risk factors for the occurrence of surgical infections is a prerequisite for their prevention. Prevention of SSI in the field of colorectal surgery requires the implementation of a variety of preoperative, intraoperative and postoperative measures. More and more performed laparoscopic surgery in elective surgery on the colon against laparotomy with large incisions represents a selection technique that results in a smaller number of SSIs. Studies suggest that delaying resection in urgent conditions by stoma or stent with subsequent resection improves results in terms of a lower rate of complications including SSI, while overall survival time is considerably prolonged.

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Introduction

Annually, around a million people suffer from colon cancer, and half a million die. In 20 to 25% of newly detected patients, already in the diagnosis, there are distant metastases. With the use of multimodal therapy, the average survival of patients with metastases is about 2 years; only 10% of such patients live for five years. In the case of non-metastatic disease, surgery is the main form of treatment for colorectal cancer.

SSIs are the most common complications in surgical practice. It is estimated that about 2-5% of patients acquire an infection of the operative area after "pure" non-abdominal surgery, and even 20% after the procedure in the abdomen. SSIs are the most common and most complicated infections in surgical patients, which contribute to perioperative morbidity, prolonged postoperative hospital stay and increased treatment costs (1, 2, 3). Colorectal surgery is associated with the highest risk of SSI, mainly due to severe bacterial accumulation of the colon (1). Reported incidence of SSI after colorectal surgery ranges from 5% to 26% (4-8).

Surgical site infections and risk factors for their development

Hospital (infantile, intrahospital) infection is an infection that has occurred in patients and staff at the hospital or some other healthcare institution. It occurs as a local or systemic condition (state), which is the result of a reaction of the organism to the presence of an infectious agent (one or more) or its toxins, which was not present in the patient, nor was it incubated in the patient on admission to a hospital or other health institution. This internationally recognized definition was established by experts from the Center for Disease Control (CDC) in Atlanta, 1988. The name "nosocomial" comes from the Greek word nosus meaning "disease" and komeion meaning "to take care of", or Latin words nosocomium meaning

"hospital". Infections of the operating site can be divided into superficial infections, deep infections and organ infections (9).

Superficial infection

The infection occurs within 30 days of surgery and affects only the skin and the subcutaneous tissue of the incision (cut) and the patient has at least one of the following findings:

a) leakage of pus from surface incision;

b) microorganisms isolated from the culture of the secretion or tissue of surface incision (samples taken under aseptic conditions);

c) at least one of the following signs or symptoms of the infection: pain or sensitivity to the palpation, localized swelling, redness, or feeling of heat and deliberately opened wound by a surgeon, unless the culture of incision is negative;

d) the diagnosis of an infection by a surgeon or a treating physician.

Deep infection

Infection occurs within 30 days of surgery if no implant is implanted (a foreign body that is implanted during the operation and remains permanently in the patient's organism, e.g., artificial heart valves, heterologous vascular graft, mechanical heart, or joint prosthesis) or for a year if the implant is implanted and is associated with surgery and involves the deep subcutaneous tissue of the incision, such as facial and muscular lodges, and the patient has at least one of the following findings:

a) leakage pus from deep-tissue incisions;

b) a spontaneous development of wound dehiscence or the wound was intentionally opened by a surgeon because patient has had at least one of the following signs or symptoms: fever (38 °C), localized pain or palpation sensitivity, unless the culture of incision is negative;

c) an abscess or other evidence of an infection determined by a direct insight of the surgeon during a reoperation or a histopathological or radiological examination;

d) diagnosis of a deep infection of the operating site by a surgeon or a treating physician.

Infection of the organ/space of the operative site

Infection of the organs/space of the operative site includes any part of the body, except for incisions of the skin, fasciae or muscle boxes, which have been opened or manipulated with during the operation.

As far as the time of its occurrence is concerned, it must meet the previously mentioned criteria:

a) leakage of pus from the drain placed in the body/space of the operating site;

b) microorganisms isolated from the culture of the secretion or tissue of the operating site taken under aseptic conditions;

c) an abscess or other evidence of an infection of the organs/space of the operating site determined by the direct insight of the surgeon during a reoperation or histopathological or radiological examination;

d) the diagnosis of an organ/space infection by a surgeon or a treating physician.

The incidence of hospital infections varies in developed and developing countries, but it is also different in individual hospitals and in individual departments. Their incidence is 5-10%, prevalence in developed countries is on average 7.6% (between 3.5% and 12%), while in developing countries it is on average 10.2% (from 5.7% to 19.1%). Infections of the operating site are the most common types of hospital infections in the countries of the European Union (19.6%) (10-13).

Knowing the risk factors for the development of surgical infections is a prerequisite for their prevention. Risk factors for the development of surgical infections include factors related to the patient (age, sex, obesity, diabetes, compromised immune system, comorbidity, etc.), factors related to therapeutic approach (invasive procedures that damage normal host defense mechanisms such as urinary and vascular catheters, mechanical ventilation, irrational antibiotic therapy, etc.) and factors related to the work methods of health workers (application of measures to control infection) (14-17). Risk factors for the development of surgical infections vary depending on the type of hospital and the department where the patient is hospitalized. Patients in intensive care units are particularly exposed to many risk factors. Although we cannot influence most of the risk factors, which concern the patient itself, their knowledge is necessary, as health professionals will treat patients with risk with special care. Studies conducted in countries with high economic standards have shown that the most common risk factors for the development of SSI: age over 65 years, admission as an emergency in the intensive care unit, hospitalization longer than seven days, use of the central venous catheter, urinary catheter or endotracheal tube, surgical intervention, trauma-induced immunosuppression, neutropenia, rapid or extreme fatal disease (according to McCabe-Jackson classification) and reduced functional status or coma (7, 16). In medium-developed and underdeveloped countries, other risk factors have been identified for the development of surgical infections such as malnutrition, parenteral nutrition, and the existence of two or more comorbidities. The significant risk factors in these countries are the lack of financial support, the insufficient number of trained staff involved in controlling the infection, the lack of health workers in hospital departments and the insufficient capacity of equipment and tools (17).

Prevention of SSI in colorectal surgery

Preventing SSI in colorectal surgery requires the implementation of a variety of preoperative, intraoperative and postoperative measures to control risk factors. Patients undergoing colon and rectum surgery have potentially numerous risk factors for infection, apropos, the infection can develop as a result of many specific events during the surgical intervention itself. Choosing surgical technique,

strategy and preparation of patients as well as postoperative monitoring can lead to an improvement in the outcome of surgical treatment in these patients (17). For didactic reasons, preventive measures will be divided into preoperative, intraoperative and postoperative.

Preoperative preventive measures

Pre-hospital cleaning of the surgical field or site. Significant roles in preoperative preparation for planned interventions are played by preoperative bathing, showering and/or cleaning of the proposed surgical site with antiseptic soap and/or antiseptic. Despite a series of clinical studies, meta-analysis did not demonstrate a decrease in SSI rates in pure surgery or in any group of operations (18). One recent study indicates the need for repetition of showering or peeling of the antiseptic area, in order to achieve adequate efficacy in preventing SSI (19). The main source of microbiological contamination in colon surgery is actually the lumen itself, and not the skin, and it is unlikely that SSI will be prevented by aggressive prehospital cleansing.

Prolonged preoperative treatment. Classic of Cruse and Foord's study (18) and recent Vogel's et al. studies (19) showed that prolonged preopera-tive hospitalization, 3-4 days before surgery, incre-ases SSI rates and the incidence of other hospital infections. Prolonged preoperative hospitalization is likely to be related in connection with the case itself, namely other factors requiring a more rigorous pretreatment. Prolonged hospitalization also represents a permanent exposure to pathogens of the hospital environment that negatively affects the skin's resistance, and even the microflora of the colon.

Depilation. Follicules at the site of surgery are always considered to be at risk of accumulating bacteria. However, there is no evidence to support hair removal and with a reduced rate of SSI (20). Study of Alexandra et al. (21) has shown that any removal of the hair, the night before surgery increases the risk of SSI. Mechanical hair removal with a shaver results in cutting and damaging the skin. These injuries on the surface of the skin on the night before the surgery are likely to become sites for microbial growth of the skin microflora (e.g. Staphylococcus aureus) and increase the probability of developing infection at the site of the incision. These studies also identified that the removal of hair in the patient's room was also associated with an increased rate of SSI. If hair removal is considered necessary, it should be done immediately before surgery, in the patient preparation room, immediately prior to the application of the antiseptic.

Preparing the site of the incision. The three main antiseptic solutions used to prepare the site of the incision are chlorhexidine, povidone iodine and isopropyl alcohol. Isopropyl alcohol has the best antibacterial efficacy but is highly inflammable and there is a risk of fire in the operating room when used in combination with an electrocautery. Fires in the operating rooms occur more than 500 times a year in the United States and consistently identified were flammable antiseptics, oxygen and flammable foils (23) as the main causative agents. Chlorhexidine is associated with a better antiseptic effect than povidone iodine and it is more effective in the prevention of infections (22-24). One review and one meta-analysis conclude that better preparation of the field in the prevention of SSI is with using chlorhexidine (22, 25, 26).

Plastic foils/wound dressings. Plastic foils are placed on the skin at the site of the incision and used for a certain period of time to prevent colonization of the microbes on the skin. Initial cases reported unexpectedly higher rates of infection with these plastic films, which was probably due to the effect of "greenhouse", sweat and microbiological proliferation under plastic (27). Recent versions of these plastic films now use an antiseptic (e.g. povidone iodine) on the surface of the adhesive and have better adhesion to the surface of the skin. However, recent meta-analysis has not shown any reduction in SSI rates with the use of newer generation foils (28). It is proposed to cleanse the surgical site with antiseptic, completely dry the antiseptic and press the plastic film before the incision. Another variation on the topic of plastic film is a ring structure that is inserted into the abdomen, which with a simple twist, completely separates the wound from the site of surgical work. This makes sense for temporary protection when the contamination that occurs in the colorectal operations is concerned. Meta-analysis has identified benefits for this type of film (29), but additional clinical trials are necessary.

Preventive use of antibiotics. Preventive use of antibiotics in elective colon surgery is generally seen as an important method that has positive effects in the prevention of SSI. With the introduction of antibiotics in clinical practice during the Second World War, a wide use of antibiotics in operative procedures begins, especially in the digestive tract. A positive effect should be no especially in colorectal surgery where the rate of contamination is high. The initial enthusiasm, especially in patients treated with colorectal disease, has very quickly whittled away due to the low rate of reduction of surgical wound infections. The question was: when is the right time to give antibiotics? At that time, antibiotics were given after surgery, and in cases with high rates of infection (e.g., colon surgery), as well as in cases of low-infection surgery (e.g. inguinal hernia reparation). The impact of the period of administration of antibiotic prophylaxis in surgery was identified in experimental studies by Miles et al. (30), and in clinically relevant experimental models, Burke (31). The key characteristics of the preventive use of antibiotics in these experimental studies were that a tissue antibiotic was needed at the time of bacterial contamination of soft tissues and that in this way the applied antibiotic prevents the spread of infection in the tissues. The antibiotic that was given more than two hours after contamination had no effect on the onset of infection. Polk and Lopez made the first clinical study on the importance of prophylactic administration of antibiotics before surgery, which showed a statistically significant reduction in the rate of SSI using antibiotic (cephaloridine) before the surgical incision (32). Patients received the second and third dose 5 and 12 hours after the initial dose, and then all antibiotics were

abolished. Subsequent studies by Stone et al. about pure and contaminated surgeries, including colon resections, have shown the antibiotic given prior to surgery was effective in reducing SSI, and further receiving antibiotics after closing the wound has no effect on the SSI rate (33, 34, 35). After these pioneering clinical trials, there were a number of reported studies that further confirmed the benefits of preoperative use with antibiotics. Baum et al. showed the striking results of numerous placebo-controlled studies that showed the benefit of preoperatively prophylactically-applied antibiotics in colon and rectal surgery and concluded that there was no use for further placebo-controlled studies (35). It is important to consider why the antibiotic given after the wound closure does not improve the SSI rate. Bacterial contamination of the environment occurs after tissue injury, bacteria are instantly incorporated into fibrin as part of the inflammatory response to tissue injury. During surgery, contamination of the surgical wound continues from several potential sources. In the act of closing the wound, subcutaneous tissue and skin, the enclosed space is also filled with fibrin that leaves a dense protein matrix with twisted microbes. The fibrin matrix is impermeable to systemic antibiotics from the circulation. The presence of the drug is required at a time when fibrin is produced from the protein serum to act on bacterial strains. Antibiotics administered after contamination of fibrin do not make contact with the surgical site. In addition, edema as well as the activated inflammatory response continues after closing the wound which results in increased hydrostatic pressure in the tissues around the closed incision (36).

The selection of antibiotic for elective surgery on the colon is detailed in Table 1.

Table 1. The most commonly used antibiotics for elective colon surgery

Drug choice (dose)	Advantages	Disadvantages
Cefoxitin (1 g)	Low toxicity cephalosporin with many years of use for prophylaxis, aerobic and anaerobic coverage.	Short biological elimination half-life (45 min); concerns about gram negative resistance.
Cefotetan (1 g)	Low toxicity cephalosporin with many years of use for prophylaxis, aerobic and anaerobic coverage. Long biological elimination half-life (4 hr).	Concerns about gram negative resistance.
Ampicilin/Salbactam (1.5 g-3.0 g)	Extensively used penicillin with a beta-lactamase inhibitor; good anaerobic coverage.	Short biological elimination half-life (1 hr); emerging E. coli resistance in up to 40% of isolates.
Ertapenem (1 g)	Extended gram negative coverage (not Pseudomonas spp.); long biological elimination half-life (3.5 h).	Expense

The selection of antibiotics should have an effect against potential pathogens for contamination of the surgical site. It is expected that this selection will cover staphylococci as the main contaminant of the skin then E. coli of the main enteral gram negative strain in the colon, and Bacteroidesfragilis, which is the primary colonic anaerobic pathogen. This coverage profile was identified in the second generation of cephalosporin antibiotics cefoxitin or cefotetan. This is also seen in semisynthetic penicillins with a β-lactamase inhibitor. Combined antibiotics such as the first generation cephalosporins (e.g., cefazolin) with anaerobic coverage and metronidazole or clindamycin are a choice of antibiotics for prophylaxis, while fluoroquinolone with metronidazole or clindamycin is another option. Another consideration in the use of preventive antibiotics is the biological half-life of the antibiotic elimination. Because of the half-life, i.e., the effects of antibiotics, application immediately before surgery for β-lactam antibiotics (i.e., penicillins or cephalosporins) is recommended. The next generation of antibiotics (cefotetane or ertapenem) are desirable due to the longer period of coverage compared with the second group of antibiotics, for which there is an insufficiently solid evidence of efficacy in elective colon surgery (36, 38).

The second question that is commonly referred to is antibiotic dosing. The traditional dosage was to use the same dose for all patients. A general increase in body mass index (BMI) of patients has raised concerns that the volume of drug distribution in larger patients (37) has been expanded. For bariatric and other operations in patients with BMI > 30, the dose of antibiotic for prophylaxis should be considered. The occurrence of methicillin-resistant Staphylococcus aureus acquired under non-hospitable conditions (CA-MRSA) has caused concern and

led many to advocate the examination of nasopharyngeal and perioperative decontamination as well as the liberal use of vancomycin as a preventive antibiotic (38). The role of this type of prophylaxis is most often performed in large-scale pure surgeries such as coronary bypass or complete joint replacement in orthopedics.

Preparation of the colon. Mechanical preparation of the intestine with the reduction of the intestinal flora in elective surgery of the colon and rectum was soon considered as a standard protocol of preoperative preparation. Mechanical cleansing of the intestine before colorectal surgery depends on the localization of tumor, stenosis, planned surgery (type of procedure) (39). Different techniques and the use of drugs used for the purpose of preparing the intestine depend on the practice of a doctor who leads the preoperative preparation. The use of oral laxatives and skis is combined, as well as local application of chilled 10% solution of Mannitol and skis. However, the application of mechanical cleansing of the intestine with preoperative hunger leads to a disturbance of the balance of volume and electrolytic status, which disrupted the homeostasis of the organism. During mechanical cleaning of the intestine, the patient should be sufficiently hydrated (40). Most recent clinical studies state that there is no statistically significant difference in the incidence of postoperative complications in patients in whom mechanical preparation of the bowel was performed in relation to patients in whom mechanical preparation of the bowel was not performed (41).

Intraoperative preventive measures

Postincision measures. Surgical technique during surgery is a critical issue for preventing SSI in operative treatment. According to Altemire in 1958, "evidence clearly indicates that antibiotic therapy cannot prevent the development of a local infection, unless surgical principles are established or technical details are ignored during the procedure (42)." A poor surgical technique can override the benefits that preventive administration of antibiotics can provide.

Minimizing tissue injury in incision by layers is important to prevent SSI. Rough handling often causes a greater tissue injury further resulting in local inflammation and increasing the risk of leakage and the dehiscence of anastomosis and the development of SSI. Prevention of hematoma formation requires effective hemostasis. Rolled scarves such as silk should be avoided in surgical procedures. Excessive use of electrocautery leaves the necrotic beaches inside the wound and leads to an increased infection rate. Bipolar devices are useful in achieving correct haemostasis, without excessive tissue injury. The electrocautery can be used as an alternative to a surgical knife without increasing the infection rate (42), but should be used with appropriate programs to avoid damaging the tissue. Electrocautery is not recommended for cutting hoses that will be anastomosed due to necrosis of the tissue and loss of perfusion. Placing the drains is done through a newly formed opening, never through the surgical incision itself.

Air handling systems. Bacteria that are transmitted by air as a source of contamination of the wound are long-standing concerns of the surgeon. Lister allegedly aerosolizes carbolic acid into an operating room that prevents the spread of bacteria. Fifty years ago, there has been interest in the use of ultraviolet light in the operating space for the elimination of microbes in the air. Large multicentric studies have been conducted that have proved the unsuitable use of ultraviolet light in this way (43). The use of the Laminar Air Flow System is justified in pure opera-tions (44). Restricting traffic to and from operation reduces the generation of air currents that can significantly reduce bacteria from the floor in the air (45). Given the large number of bacteria from the colon, the dominant operative wound infection in colorectal surgeries will almost always be from the bowel's contents, and in these operations, no major accent is given to the aforementioned procedures, which, however, should not be abandoned.

Antibacterial sewing material. Over the past 15 years, antibacterial sewing material has been developed for closing fascia, subcutaneous tissue, and anastomosis of the organs. The material is coated with antiseptic triclosan. Triclosan is commonly used as an antiseptic in cosmetics and other products and is safe for human use (46). Through *in vivo* experiments, it has been proven that this sewing material reduces the growth of bacteria, but also numerous studies from different countries constitute conflicting evidence of the development of SSI despite the use of sewing material with antibacterial protection (47-51).

Rinse the surgical field. Rinse the surgical area is part of the surgical technique, and is necessary especially for "dirty surgeries" such as surgery of the colon. Depending on the technique, various antimicrobial or antiseptic agents are used.

Core Body Temperature Control. Hypothermia during the operative procedure is associated with haemostasis problems and experimentally proven in the laboratory results in damage to the phagocytic function. Kurz et al. (52) in a randomized study with 200 surgical patients with colorectal disease, intraoperatively examined the body temperature maintained in normotermia (36.6 degrees) compared to patients who were allowed to have a temperature drop (34.7C). SSI was developed by 19% of patients with hypothermia, but only 6% in the group of patients with normothermia. Until recently, there was little evidence to support or reject the merits of maintaining normotermia in colon surgery, but was nevertheless adopted by the US Surgical Care Improvement Project (SCIP) as a process to improve treatment outcomes.

Glycemic control. Complications in surgical patients with diabetes are associated with a risk of developing infections and poor wound healing. Better control of diabetes is closely linked to a better outcome in the treatment. This observation led to the primary research carried out by Furnari et al. (53) for controlling blood sugar < 200mgs/100mL in patients with diabetes by using intraoperative and postoperative insulin infusion. This program included over 2500 patients with diabetes which resulted in a decrease in SSI versus the same rate as

patients who did not suffer from diabetes. Hyperglycaemia has multiple immunosuppressive effects on the host. Accordingly, perioperative hyperglycaemia is practically related to surgical infections including colon resection (54). Generally operated patients with hyperglycemia have a higher risk of postoperative infection including SSI (55).

Delayed primary closure. Delayed primary closure stands as a strategy for the prevention of SSI for possible encounter with an active infection or serious contamination during surgery. Introduced in 1940 (56), this method implies the closure of the abdominal fascia after laparotomy, as well as leaving the skin and subcutaneous tissue open for daily dressing of the wound. In the case of planned surgeries, this method should be considered only in rare cases of contamination of the abdominal cavity with colon contents in an unprepared patient or due to an unplanned occurrence of abscess during surgery.

Postoperative preventive measures

It is known that every operation carries a certain risk of developing a series of complications, some of which may even be life-threatening. The post surgical treatment of surgical site - the type of post surgical care of the surgical wound is determined by the time of closing the incision; any operative site, regardless of the type of closure, must be dressed with the use of sterile gloves, sterile instruments and with respect to the aseptic techniques during the working. Drains placed in the surgical wound could increase the risk of developing an infection because they act as a foreign body and reduce local immunological reaction, i.e. natural mechanisms of tissue defense. In order to prevent and repress intra-hospital infections at all surgical departments, the basic measures of prevention of hospital infections should be consciously and continuously implemented: hand washing, cleaning, washing and ventilation of rooms, cleaning and washing of the related equipment, air quality assurance, early detection and isolation of patients with a hospital infection.

Conclusion

SSI are the most common complications in surgical practice, which contribute to perioperative morbidity, prolonged postoperative stay in the hospital and increased treatment costs. Colorectal surgery is associated with the highest risk of SSI, mainly due to severe bacterial loading of the colon. It is necessary to continuously use all accepted prevention techniques in order to reduce SSI. New methods have to be implemented to reduce SSI in colorectal surgery. There is a great progress in systemic antibiotics in prevention as well as in achieving optimal physiological conditions - intraoperative supplemental oxygen, normothermia, and proper glycemic control. However, despite extensive research in this field and significant progress, SSI will remain a long-standing challenge in surgery.

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INFEKCIJE MESTA HIRURŠKOG RADA NAKON ELEKTIVNIH KOLOREKTALNIH OPERACIJA – PREGLED PREVENCIJE

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Rak debelog creva treći je vodeći uzrok oboljevanja u svetu. U svetu godišnje oboli oko 1.200.000 ljudi. Rak debelog creva vodeći je uzrok morbiditeta i mortaliteta sa oko 500.000 smrtnih slučajeva godišnje. SSI (eng. surgical site infections – infekcije na mestu hirurškog rada) najčešće su komplikacije u hirurškoj praksi. Procenjuje se da oko 2% - 5% bolesnika dobije infekciju operativnog mesta nakon "čistih" neabdominalnih operacija, a čak 20% nakon intervencija u abdomenu. Infekcije operativnog mesta su, u zemljama Evropske unije, najučestaliji tipovi bolničkih infekcija (19,6%). Prijavljena incidencija ovih infekcija, u oblasti kolorektalne hirurgije, iznosi od 5% do 26%. Poznavanje faktora rizika za nastanak hirurških infekcija predstavlja preduslov za njihovu prevenciju. Sprečavanje SSI u oblasti kolorektalne hirurgije zahteva implementaciju mnoštva preoperativnih, intraoperativnih i postoperativnih mera. Sve više izvođena, laparoskopska hirurgija, kod elektivnih operacija na debelom crevu, u odnosu na laparotomije sa velikim incizijama, predstavlja tehniku izbora koja rezultira manjim brojem SSI. Istraživanja pokazuju da odlaganje resekcije kod urgentnih stanja, bilo stomom ili stentom, uz kasniju resekciju, poboljšava rezultate, u smislu manje stope komplikacija među kojima je i SSI, dok je ukupno vreme preživljavanja znatno produženo.

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Ključne reči: *kolorektalni karcinom, hirurške infekcije, antibiotska profilaksa*