Review paper

Contemporary methods of treatment of colorectal cancer

Współczesne metody leczenia raka odbytnicy

Monika Kozłowska[1], Stanisław Głuszek[2,3]

[1]Department of Normal and Functional Anatomy, Institute of Medical Sciences, Faculty of Medicine and Health Science, Jan Kochanowski University, Kielce, Poland
Head of the Department: Prof. Stanisław Głuszek MD, PhD
[2]Department of Surgery and Surgical Nursing, Institute of Medical Sciences, Faculty of Medicine and Health Science, Jan Kochanowski University, Kielce, Poland
Head of the Department: Prof. Stanisław Głuszek MD, PhD
[3]Department of Surgery and Surgical Nursing with Research Laboratory, Institute of Medical Sciences, Faculty of Medicine and Health Sciences, Jan Kochanowski University, Kielce, Poland
Head of the Department: Prof. Stanisław Głuszek MD, PhD

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Słowa kluczowe: rak odbytnicy, badania przesiewowe, leczenie, przeciwciała monoklonalne.

Abstract

Today, colorectal cancer (CRC) is the third most frequently diagnosed worldwide malignant cancer in males, and the second in females, with more than 1,200,000 new cases and more than 600,000 deaths, annually. Screening tests in oncology allow the detection of cancerous disease at an early, asymptomatic stage. The procedures most frequently performed in the case of colorectal cancer include: low anterior resection by the Dixon method (manual suture or staplers); abdominoperineal resection of the rectum by the Miles method; surgical procedure by the Hartmann method; local resection. Various techniques of preoperative radiotherapy are applied, aimed at tumour mass reduction (scheme I) and/or obtaining local sterilisation (schemes I and II), which results in the reduction of local metastases (by approximately 50%), as well as an improvement with respect to long-term survival (by approximately 10%). At present, the following drugs for treatment of various forms of colorectal cancer have been registered by the Food and Drug Administration (FDA): fluorouracil capecitabine irinotecan, oxaliplatin, cetuximab, and bevacizumab. The combination of complete cytoreductive surgery (CCS), the goal of which is the removal of all visible (macroscopically) cancer foci, with a simultaneous intraperitoneal chemotherapy in hyperthermia – HIPEC, destroying microscopic remains of the disease, allows the curing of some patients with peritoneal cancer. The effect of the action of monoclonal antibodies – cetuximab and panitumumab – is the inhibition of proliferation of cancer cells, intensification of their apoptosis, as well as reduction of synthesis and secretion of pro-angiogenic factors, such as interleukin 8 (IL-8) and vascular endothelial growth factor. In addition, antibodies targeted against EGFR impair the repair of DNA damage caused by chemotherapy and radiotherapy in the cells of the malignant tumour.

Streszczenie

Współcześnie rak jelita grubego jest trzecim najczęściej diagnozowanym nowotworem złośliwym na świecie u mężczyzn, a drugim u kobiet, z ponad 1 200 000 nowymi przypadkami i ponad 600 000 zgonami rocznie. Badania przesiewowe w onkologii pozwalają wykrywać chorobę nowotworową we wczesnej, bezobjawowej fazie. Do najczęściej wykonywanych zabiegów w przypadku raka odbytnicy należą: niska przednia resekcja sposobem Dixona (zespolenie ręczne lub staplery), amputacja brzuszno-kroczowa odbytnicy sposobem Milesa, operacja sposobem Hartmanna i wycięcie miejscowe. Stosuje się różne techniki radioterapii przedoperacyjnej, która ma na celu zmniejszenie masy guza (schemat I) i/lub uzyskanie sterylizacji miejscowej (schemat I, II), co wpływa na zmniejszenie wznów miejscowych (o ok. 50%) oraz poprawę przeżyć odległych (o ok. 10%). Obecnie do leczenia różnych postaci raka jelita grubego, w tym odbytnicy, zostały zarejestrowane przez Agencję ds. Żywności i Leków (FDA) następujące leki: fluorouracyl, kapecytabina, irinotekan, oksaliplatyna, cetuksymab, bewacizumab. Połączenie operacji całkowitej cytoredukcji, mającej na celu usunięcie wszystkich widocznych (makroskopowo) ognisk nowotworu, z jednoczesną chemioterapią dootrzewnową w hipertermii – HIPEC, niszczącą mikroskopowe pozostałości choroby, umożliwia obecnie wyleczenie części chorych ze zrakowacenia otrzewnej. Efektem działania przeciwciał monoklonalnych – cetuksymabu i panitumumabu – jest hamowanie proliferacji komórek nowotworowych, nasilenie ich apoptozy, a także zmniejszenie syntezy i sekrecji czynników proangiogennych, takich jak interleukina 8 (IL-8) i czynnik wzrostu śródbłonka naczyniowego. Ponadto przeciwciała skierowane przeciwko EGFR upośledzają naprawę uszkodzeń DNA wywołanych przez chemioterapię i radioterapię w komórkach guza nowotworowego.

Introduction

At present, colorectal cancer (CRC) is the third most frequently diagnosed worldwide malignant cancer in males, and the second in females, with more than 1,200,000 new cases and more than 600,000 deaths, annually. The incidence of colorectal cancer rapidly increases in geographical regions with historically low risk, such as Eastern Asia and Eastern and Central Europe. In the United States, death rates have decreased due to improved management strategies and early detection; however, in countries with limited financial resources and worse infrastructure of health care – in Central Europe, Eastern Europe, South America – mortality is still increasing. In Poland, colorectal cancer occupies third position among cancerous diseases in males, following lung and prostate cancer, and the second position among females – following breast cancer. With respect to morbidity, colorectal cancer holds the sixth position in males, and ninth among females [1]. In Poland, only 25% of patients survive 5 years after diagnosis of colorectal cancer, which mainly results from the fact that diagnosis of the disease takes place at a stage when the symptoms have already occurred. Hence, it is necessary and justified to carry out screening tests in order to detect the disease when the symptoms are not present [1, 2].

Colorectal cancer screening tests

Screening tests in oncology allow the detection of cancerous diseases at an early, asymptomatic stage. The basic indicator of the effectiveness of screening tests in colorectal cancer is a decrease in mortality due to colorectal cancer, and even a decrease in its incidence due to the detection and removal of precancerous states – polyps that are adenomas. The development of polyps lasts for 7–12 years. Most frequently polyps do not cause any significant symptoms. During colonoscopy performed in patients aged over 50 years, polyps are found in every fourth case – the majority of them being adenomas in a precancerous state. It has been documented that the removal of all polyps from the intestine decreases the incidence of colorectal cancer by 95%. Typical screening tests are performed in groups at mediocre colorectal cancer risk. The major risk factor is age, because it is known that at the age of over 50 years the incidence of colorectal cancer rapidly increases. In screening tests for colorectal cancer, two basic methods are applied: the single-stage method consisting of the performance of colonoscopy once in 10 years, and the two-stage method, which covers the performance of the Faecal Occult Blood Test (FOBT), and performance of colonoscopy in patients with a positive result of this test. For these purposes three subsequent stools specimens are collected, two samples each, and obtaining a positive result is an indication for colonoscopy [2, 3].

Scheme of performance of examinations according to the risk of colorectal cancer

– Negative family history – examinations from the age of 50 years every 10 years.
– Positive family history of colorectal cancer:
  • One first-degree relative with diagnosis of colorectal cancer at the age of over 60 years – examinations from the age of 40 years;
  • Two or more first-degree relatives with colorectal cancer diagnosed at the age of over 60 years, or one first-degree relative with the diagnosis of CRC at the age under 60 years – examinations at the age of under 40 years;
  • Examinations from the age of 40 years or 10 years earlier than the age of the youngest relative with the diagnosis of CRC.
– Positive history of HNPCC – from the age 20–25 years – complete colonoscopy (with the removal of potential changes) every 1–2 years from the age of 30 years – additionally gastroscopy every 2 years, from the age of 25–35 years – annual screening tests for endometrial cancer (endometrial aspiration biopsy, transvaginal USG).
– Positive history of FAP – genetic examination, from the age 12–15 years – colonoscopy every 12 months.
– Inflammatory bowel diseases (ulcerative colitis – UC, Crohn's disease – CD) – after 8 years of the disease – colonoscopy (with the collection of specimens from suspicious changes, and randomly selected sites) every 1–2 years (Figure 1) [4].

Surgical treatment

The procedures most frequently performed in the case of colorectal cancer are:
– abdominoperineal resection of the rectum by the Miles method in the case of tumours located in the lower part of the rectum, when there is no possibility of obtaining a distal margin (1–2 cm below the tumour on the non-stretched intestine), or when there is concern about the possibility of damage to the anal sphincters, or when the sphincters are infiltrated by carcinoma;
– low anterior resection by the Dixon method (manual suture or staplers) – in the case of tumours located in the middle and upper rectum, and in the lower rectum, when it is possible to perform a radical procedure (with an appropriate margin) using staplers;
– surgical procedure by the Hartmann method – in the case of tumours located in the upper rectum in the situation when there is a concern that the suture of the distal part of the rectum with the proximal section of the colon may not be sealed (e.g. faecal peritonitis in the case of perforation of the malignant tumour);
– local resection – the procedure performed only in specialised centres with great experience in colorec-

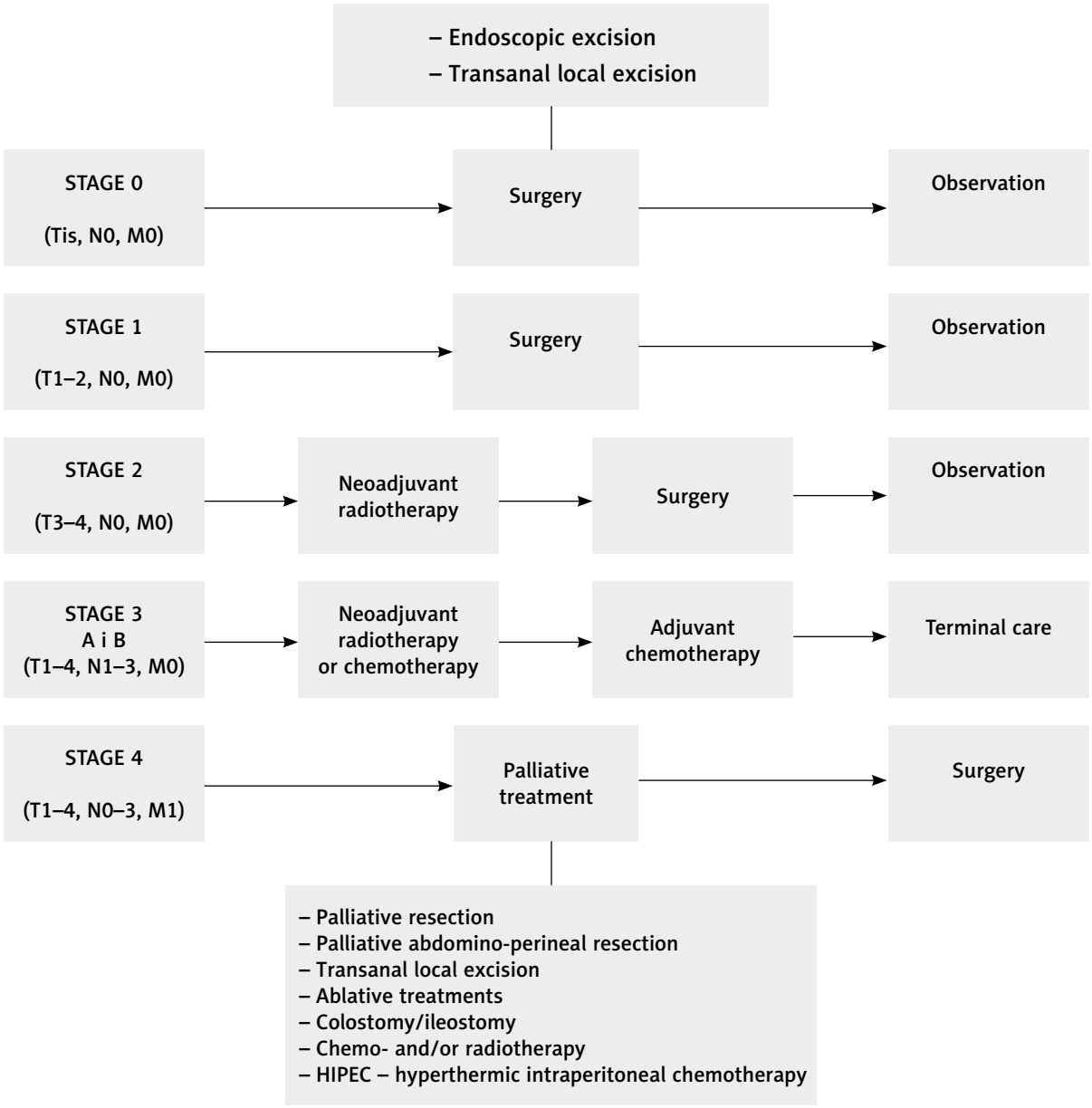

Figure 1. Scheme of treatment of colorectal cancer according to the degree of clinical advancement according to Dziki and Wallner in own modification [5]

tal cancer surgery, according to strictly specified indications:

- adenomas of various degree of dysplasia,
- cancer of polyp type, diameter below 3 cm, located in the retroperitoneal part of the rectum, on the posterior or lateral wall,
- poor general status and/or advanced age of patients, which excludes safe performance of the classic procedure,
- informed consent of the patient for performance of local resection.

Mesorectal excision – in each case efforts should be undertaken to perform possibly the widest excision of the perirectal tissue, containing lymph nodes and cancer infiltrations. This procedure decreases the risk of local recurrence and increases chances for recovery [3–6].

The upper ligation of inferior mesenteric artery does not improve the therapeutic outcome, but may increase the risk of ischaemia of the suture or colostomy. Usually the ligation of inferior mesenteric artery is performed beneath the origin of the left colic artery. In the case of infiltration of the serous membrane by cancer, removal of the greater omentum is recommended [3–5].

In menopausal women with infiltration of the serous layer by cancer, the presence of massive metastases to the regional lymph nodes, with macroscopically changed ovaries, family history of ovarian cancer, and the presence of adhesions between the primary cancer and the ovaries, some researchers postulate the performance of prophylactic ovariectomy (removal of the ovaries). This is not a standard procedure and requires randomised clinical studies [4].

Although no surgical method of anastomosis protection has been undoubtedly confirmed as effective, it seems that the formation of preventive stoma remains the most justified method. This procedure should be seriously considered in the case of concomitance of additional risk factors of unsealed anastomosis, such as: older age of the patient, male gender, low anastomosis in the retroperitoneal part of the rectum, past preoperative radiotherapy, lack of correct bowel preparation, greater perioperative bleeding, necessity for transfusion of blood products, and burden of serious concomitant diseases [5–7].

It is considered that routine blood transfusion is a factor unfavourable from the aspect of prognosis, because in the case of the necessity for administration of blood during surgery there is an increased risk of later occurrence of local metastasis, and the prognosis deteriorates. Blood should be administered either during the period prior to surgery or 72 h after the surgery [4, 6].

Radiotherapy in colorectal cancer

Various techniques of preoperative radiotherapy are applied, aimed at tumour mass reduction (scheme I) and/or obtaining local sterilisation (schemes I and II), which exerts an effect on both reduction of local metastases (by approximately 50%) and improvement with respect to long-term survival (by approximately 10%). An indication for its application may be the infiltration of the whole rectal wall (T3) or infiltration of adjacent structures (T4). Magnetic resonance is the standard procedure in perioperative diagnostics. It is considered that perioperative radiation increases the chance of performing a sphincter-saving procedure [8, 9].

Treatment schemes

I. 5000 cGy in fractions of 200 cGy for a period of 5 weeks. The procedure is performed 4–6 weeks after completion of radiotherapy. When applied in borderline cases it increases the chances of performing a sphincter-saving procedure.
II. 1000–2500 cGy in fractions of 200–500 cGy for a period of 5 days. The procedure is performed 3–7 days after the completion of radiation, prior to the development of acute post-radiation reaction. In this case, it is possible to apply supplementary postoperative radiotherapy.

Postoperative radiotherapy

Postoperative radiotherapy is the standard procedure in the case of factors that are unfavourable with respect to prognosis, which include:
– infiltration of perirectal adipose tissue;
– metastases in perirectal lymph nodes, especially with the presence of infiltration of the lymph node capsule;
– cancer infiltration along the nerve structures;
– presence of tumour cell emboli in lymph and blood vessels;
– high degree of malignancy of the tumour;
– perforation of the tumour, spontaneous or iatrogenic, during surgical procedure [8].

Chemotherapy of colorectal cancer

At present, the following drugs for the treatment of various forms of colorectal cancer have been registered by the Food and Drug Administration (FDA): fluorouracil capecitabine irinotecan, and oxaliplatin cetuximab bevacizumab [10–12]. Additionally, the following drug kits have been registered:
– IFL (irinotecan, bolus fluorouracil + leucovorin) – first-line treatment of advanced colorectal cancer with distant metastases;
– FOLFOX (oxaliplatin fluorouracil infused + leucovorin) – first- or second-line treatment of advanced colorectal cancer with distant metastases;
– fluorouracil + bevacizumab – first-line treatment of advanced colorectal cancer with distant metastases;
– cetuximab + irinotecan – second-line treatment of advanced colorectal cancer with distant metastases after detection of the presence of receptor for the epidermal growth factor (EGF).

Postoperative chemotherapy

Postoperative chemotherapy is a standard procedure in the case of advancement in stages B2, C1, and C2, as well as infiltration of adjacent structures and organs (stage of advancement D) [8, 13–15].

Hyperthermic intra-peritoneal chemotherapy (HIPEC)

Patients with distant metastases produced through the blood vessels are usually subjected to systemic

treatment. Metastasis limited to the peritoneal surface is qualified for regional treatment. The main goals of HIPEC are:

1) provision of a proper dose in order to overcome relative resistance to drugs.
2) provision of optimum conditions for uniform distribution of drugs in the peritoneal cavity.
3) possibility of treatment on hyperthermic conditions, which in a selective way increases the effectiveness of chemotherapeutics.

At present, the combination of complete cytoreductive surgery (CCS), the goal of which is the removal of all visible (macroscopically) cancer foci, with a simultaneous intraperitoneal chemotherapy in hyperthermia – HIPEC, destroying microscopic remains of the disease, allows the curing of some patients with peritoneal cancer [4].

Monoclonal antibodies

In 1983, John Mendelsohn *et al*. synthesised mouse antibody, which in cell cultures showed an activity in the inhibition of proliferation of tumour cells both *in vitro* and in animal models [16]. Cetuximab is a chimeric immunoglobulin G1 and a monoclonal antibody. It has been registered for the treatment of colorectal cancer at the stage of metastasis, after failure of chemotherapy based on irinotecan [17, 18]. Indications for the application of cetuximab are based on the assumptions that EGFR expression in immunohistochemical examination is both a qualitative and quantitative predictive factor of response to cetuximab [17]. Panitumumab is a fully human (immunoglobulin G2) monoclonal antibody with a strong affinity to the EGFR receptor.

In studies, panitumumab showed effectiveness similar to cetuximab in patients with metastatic colorectal cancer, in whom the response to standard treatment with cytostatics ended. A human antibody is related with lower intensity of allergic reactions than a chimeric antibody, which is cetuximab [19]. Panitumumab is characterised by high affinity to the EGFR, approximately five-times higher than cetuximab [13]. The mechanism of action of monoclonal antibodies targeted against EGFR is complex. Cetuximab and panitumumab specifically bind to the extracellular domain of the EGFR, making the binding of EGF and tumor growth factor-α to the receptor impossible, consequently preventing its activation. These antibodies block dimerisation of EGFR, phosphorylation of tyrosine kinase, and receptor autophosphorylation, and therefore inhibit the transmission of intracellular signals [18]. The effect of action of cetuximab and panitumumab is the inhibition of proliferation of cancer cells, intensification of their apoptosis, as well as reduction of synthesis and secretion of pro-angiogenic factors, such as interleukin 8 (IL-8) and vascular endothelial growth factor. In addition, antibodies targeted against the EGFR impair the repair of DNA damage caused by chemotherapy and radiotherapy in the cells of the malignant tumour [18, 20–22].

Conclusions

The problem of cancers, especially malignant ones, still remains one of the most vital problems that remains unsolved. Despite tremendous material and intellectual outlays devoted to this goal, morbidity due to the majority of cancerous diseases – including colorectal cancer – is constantly increasing. The cause and conditioning of the cancerous process and possibilities of defence and/or cancer control is an issue of common interest, both scientific and social. In spite of the achievements of the basic sciences explaining the importance of the changes that take place in the genome of cancer cells, this knowledge is still insufficient to develop fully effective methods of treatment.

Conflict of interest

The authors declare no conflict of interest.

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Address for correspondence:

Monika Kozłowska
Department of Normal and Functional Anatomy
Institute of Medical Sciences
Jan Kochanowski University
ul. IX Wieków Kielc 19, 25-317 Kielce, Poland
Phone: +48 602 390 428
E-mail: monikachir@gmail.com