Clinical practice guidelines for diagnosis and treatment of colon (C18) and rectosigmoid junction (C19) cancer

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Key words: colon cancer, rectosigmoid junction cancer, guidelines, diagnostics, treatment

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1. Methodological notes

Guidelines developed on the basis of recommendations published between 2012 and 2019 by:
— French Research Group of Rectal Cancer Surgery (GRECCAR);
— French National Society of Coloproctology (SNFCP);
— European Society for Medical Oncology (ESMO);
— National Comprehensive Cancer Network (NCCN);
— European CanCer Organisation (ECCO);
— Association of Coloproctology of Great Britain and Ireland (ACPGBI).

The authors always tried to relate individual recommendations to the published recommendations, taking into account the source publication and (where possible) the grades of recommendations and the levels of evidence, according to the following criteria.

Levels of evidence

I *Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity.*

II *Small randomized trials or large randomized trials with suspicion of bias (lower methodological quality) or meta-analyses of such trials or trials with demonstrated heterogeneity.*

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III Prospective cohort studies.
IV Retrospective cohort studies or case-control studies.
V Studies without a control group, case reports, experts opinions.

Grades of recommendations

A Strong evidence for efficacy with a substantial clinical benefit — strongly recommended.
B Strong or moderate evidence for efficacy but with a limited clinical benefit — generally recommended.
C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs) — optional.
D Moderate evidence against efficacy or for adverse outcome — generally not recommended.
E Strong evidence against efficacy or for adverse outcome — never recommended.

2. Epidemiology

In recent years, malignant neoplasms of the colon and rectosigmoid junction are diagnosed in approximately 12,500 people per year, and the number of deaths is approximately 8,500. Whilst there is continuous increase in morbidity and mortality in the male population, in women the increase in mortality has been halted and has remained stable for over a decade despite the increasing morbidity [1].

3. Diagnostic tests required for diagnosis and staging

— Colonoscopy (up to and including the caecum) with the collection of tumor specimens and/or removal of the polyp/polyps; NCCN [2]; ECCO [3]; ESMO [4]; GRECCAR/SNFCP (III) [5].
— Computed tomography (CT) of the abdomen and pelvis; NCCN; ECCO; ESMO (III, A).
— Chest X-ray (CT of the chest in case of doubtful X-ray findings); NCCN; ECCO; ESMO (III, A).
— Determination of carcinoembryonic antigen (CEA) level; NCCN; ESMO (III, A).
— Basic laboratory panel (complete blood count [CBC], creatinine, bilirubin, protein concentrations, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP] levels) — to assess organ function (III, A).

In individual cases, an abdominal ultrasound (US) could be a valuable addition to the above-mentioned diagnostic workout. It is not recommended to routinely perform positron emission tomography (PET) within the initial diagnosis, as false-positive results may be caused by sigmoid diverticulosis or inflammatory bowel diseases (IBD). However, this examination may be helpful in the diagnosis of distant metastases, when the previously performed imaging tests (CT, magnetic resonance imaging [MRI], US) do not allow to establish the stage of disease. In addition, PET is performed in the diagnosis of cancer relapse in patients with increased CEA level without visible changes in other tests that may correspond to local and/or generalized recurrence.

4. Staging

Staging is based on the 8th edition of the TNM (tumor, node, metastasis) classification (2017). Details are presented in Tables 1 and 2.

5. Therapeutic management

The recommended therapeutic management in colon cancer patients is based on staging (Fig. 1).

5.1. Recommendations for surgical treatment

The surgical treatment guidelines are based on the recommendations of the National Consultant in the field of oncological surgery and the Polish Society of Surgical Oncology.

• **cT1–4 N0–2 M0** — a segmental bowel colon with the tumor and the regional lymphatic system of the relevant bowel segment should be performed.

ESMO; NCCN; ECCO

Recommendations:

— the extent of the colon cancer resection depends on the site of the primary tumor;
— the minimal number of regional lymph nodes that should be retrieved following colon resection is 12;
— minimal resection margins assessed on a fresh specimen before (proximal) and behind (distal) the tumor should be 5 cm;
— in the case of a tumor that infiltrates other organs through the continuity (cT4b), "en bloc" resection should be performed without dissection of the infiltrate;
— laparoscopic resections of colon cancer should now be considered as a standard surgical method, with

Table 1. TNM classification; colorectal cancer

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* — involving lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades visceral peritoneum, and in places without it — pericolorectal tissues
T4	Tumor invades through the visceral peritoneum and continues into adjacent anatomical structures and/or causes perforation of the visceral peritoneum
T4a	Tumor invades through the visceral peritoneum and causes perforation of the visceral peritoneum
T4b	Tumor invades through the visceral peritoneum and continues into adjacent anatomical structures
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumor deposit(s)
N2	Metastasis in 4 or more regional lymph node
N2a	Metastasis in 4–6 regional lymph node
N2b	Metastasis in 7 or more regional lymph node
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis is identified
M1a	Distant metastasis is identified, however, confined to 1 organ or site (e.g. extra-regional lymph node)
M1b	Distant metastasis to two or more sites or organs is identified
M1c	Distant metastasis to the peritoneal surface alone or with other site or organ metastases

Table 2. TNM stages; colorectal cancer

<table>
<tr><th colspan="2"></th><th>Tis</th><th>T1</th><th>T2</th><th>T3</th><th>T4a</th><th>T4b</th></tr>
<tr><td colspan="2">N0 M0</td><td>0</td><td colspan="2">I</td><td>IIA</td><td>IIB</td><td>IIC</td></tr>
<tr><td rowspan="3">N1 M0</td><td>N1a</td><td colspan="3" rowspan="3">IIIA</td><td colspan="2" rowspan="3">IIIB</td><td rowspan="3">IIIC</td></tr>
<tr><td>N1b</td></tr>
<tr><td>N1c</td></tr>
<tr><td rowspan="2">N2 M0</td><td>N2a</td><td colspan="2">IIIA</td><td colspan="2">IIIB</td><td>IIIC</td></tr>
<tr><td>N2b</td><td colspan="3">IIIB</td><td colspan="2">IIIC</td></tr>
<tr><td rowspan="3">M1</td><td>M1a</td><td colspan="6">IVA</td></tr>
<tr><td>M1b</td><td colspan="6">IVB</td></tr>
<tr><td>M1c</td><td colspan="6">IVC</td></tr>
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the oncological outcomes comparable to classic laparotomy. However, laparoscopic resection is allowed only in centers with sufficiently extensive experience.

• **cM1 (pTNM IV)** — surgical treatment of stage IV colon cancer should always be individualized.

Recommendations:

— in liver metastases, the possibility of radical excision (R0) should be considered, usually as sequential treatment with pre- or postoperative chemotherapy; ESMO (III, A); NCCN

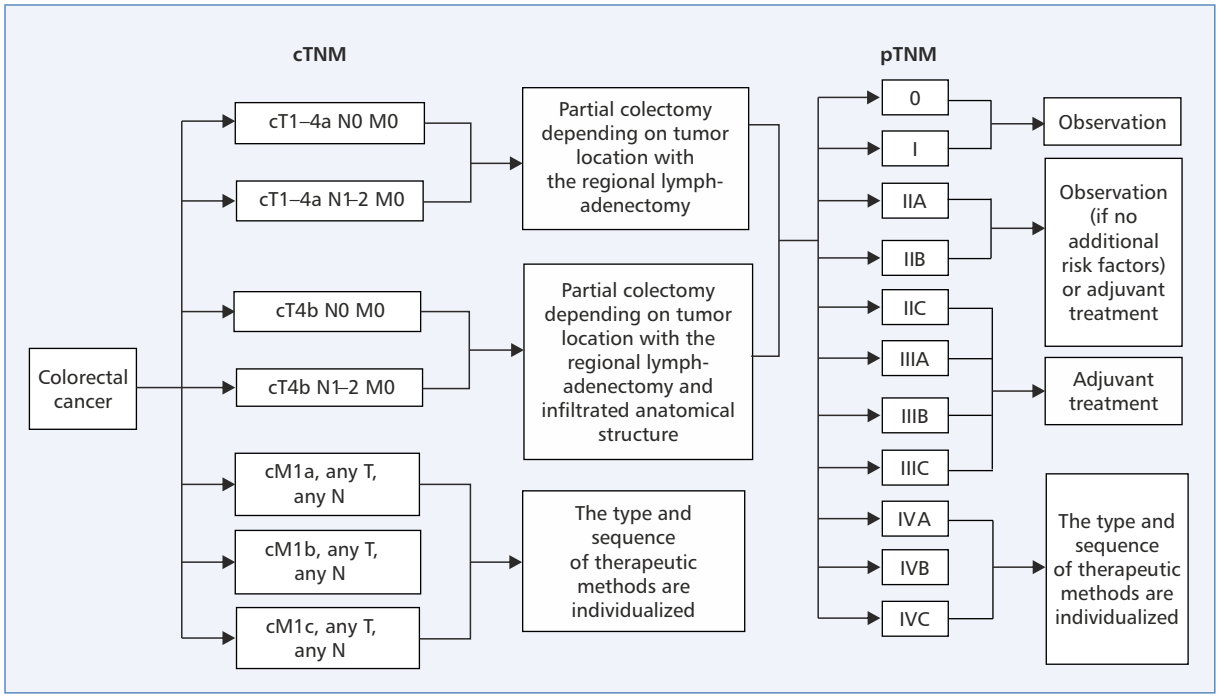

Figure 1. Therapeutic management depending on the clinical (cTNM) and pathomorphological stage (pTNM)

— ablation of liver metastases can be performed in patients ineligible for resection. Current ineligibility criteria for metastasectomy are defined on the basis of post-resection liver parenchyma volume (30% and less) and the number of lesions (5 and more) as well as the coexistence of metastases in other organs [6];
— complex treatment of liver metastases is possible, including anatomic and non-anatomic liver resections and ablative methods (e.g. segment II and III resection and ablation of segment VII lesions);
— resections or ablation of single metastatic lesions in other organs (e.g. in the lung) may be considered, provided that the primary colon tumor and any secondary lesions (e.g. in the liver) can be completely resected or successfully ablated;
— in patients with carcinomatosis peritonei, the so-called Peritoneal Cancer Index (PCI) is used to assess the advancement of changes (Table 3). Each region of the peritoneal cavity can be scored between 0 and 3 points. Total PCI score is obtained by adding up points from all regions (Table 3). If the PCI score is < 20 points, qualification for cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) may be considered — ESMO (IV, B); NCCN. However, a randomized clinical trial (RCT) showed that in systemically treated patients underwent effective cytoreduction HIPEC did not affect the prognosis compared to surgery alone (II, E) [7].

The 5-year survival rate in patients after radical resection of both the primary tumor and metastatic lesions in the liver ranges from 25–55%, while in patients in whom radical resection is not possible, it does not exceed 5%.The aim of surgical treatment of patients with disseminated colon cancer with the presence of unresectable distant metastases is to prolong the survival time. The management and its sequence (symptomatic treatment, chemotherapy-surgery, surgery-chemotherapy, chemotherapy alone) should be individualized depending on patient performance status (PS) and possible therapeutic benefits — ESMO; NCCN.

Final remarks

— In unresectable lesions, creating a stoma (ileostomy or colostomy) or bypass surgery should be considered.
— In case of an obstruction, resection (with anastomosis and/or stoma) or decompression-only surgery is possible. In the latter case, radical resection should always be considered after stabilization of the patient's general status.
— Radical tumor resection must include not only the cancerous colon segment with appropriate margins but also the entire area of regional lymphatic drainage. A detailed description of the topographic resection extent depending on tumor location is presented in oncological surgery textbooks („Chirurgia onkologiczna", Vol. 3: PZWL 2019).

Table 3. Peritoneal Cancer Index

Region of the peritoneal cavity	Lesion size score (LS)			
	LS = 0 (no tumor seen)	LS = 1 (tumor up to 0.5 cm)	LS = 2 (tumor up to 5 cm)	LS = 3 (tumor > 5 cm or confluence)
Central				
Right upper				
Epigastrium				
Left upper				
Left flank				
Left lower				
Pelvis				
Right lower				
Right flank				
Upper jejunum				
Lower jejunum				
Upper ileum				
Lower ileum				
PCI	**Total LS from all regions =**			

— In the case of colon tumor resection, the decision to perform a simultaneous anastomosis depends on many factors related to cancer stage and patient general condition, the intraoperative assessment of the conditions necessary for the healing of anastomosis and surgeon's experience. Tumor resection and stoma creation do not exclude the technical possibility of restoring the continuity of the gastrointestinal tract in the second stage of surgical treatment.
— The decision regarding appropriate management depends on patient's general condition and tumor stage.

5.2. Recommendations for radiation therapy

Both pre- and postoperative irradiation is not routinely used in colon cancer patients. A randomized study that compared postoperative irradiation combined with postoperative chemotherapy *versus* postoperative chemotherapy alone, showed no improvement in post-irradiation survival with greater toxicity. This is probably due to rare local recurrences as the only site of progressive disease; relapse is usually associated with distant metastases. In addition, a significant toxicity is caused by a large volume of small bowel to be irradiated.

Preoperative irradiation should be considered rarely, only in advanced cases. It could be justified by CT or MRI examination indicating extensive tumor infiltration, which limits the possibility of keeping surgical margins free or even makes complete resection impossible. An example is a sigmoid cancer, which extensively infiltrates the bladder or the sidewall of the pelvis near large vessels. Pre-operative irradiation results in tumor shrinkage, which in turn may enable R0 surgery. The irradiation area covers only visible neoplastic lesions with an appropriate margin but does not include the elective area of regional lymph nodes. Radio(chemo)therapy regimens are the same as in patients with rectal cancer. However, another possible option is the induction of chemotherapy (II, A) [8, 9].

There are rare indications for postoperative radio(chemo)therapy — only in the case of R2 resection with a small residual tumor or R1 surgery or a very close free surgical margin (less than 1 mm). In addition to classic irradiation regimens, stereotactic body radiotherapy (SBRT) is also used.

5.3. Recommendations for systemic therapy

Adjuvant chemotherapy

Stage I

Due to the very good prognosis, adjuvant therapy should not be used, and observation is the standard of care (IV, E).

Stage II

The RCTs did not show any unquestionable effect of adjuvant chemotherapy on the improvement of prognosis. They usually included patients with a higher risk of recurrence and only a slight increase in 5-year disease-free survival rate (< 5 percentage points) was observed. Except for the QUASAR trial, which also

enrolled patients with rectal cancer (increase in overall 5-year survival rate < 4 pp), there was no effect of adjuvant treatment on overall survival [10].

Therefore, adjuvant therapy should not be used in most patients, and observation remains the standard of care (II, D). Adjuvant chemotherapy using fluoropyrimidine for six months can be used in patients with high-risk factors for recurrence (presence of at least one of the following features: pT4 [pT4b category is generally considered sufficient to qualify for adjuvant treatment], the number of removed lymph nodes less than 12, high histological grade, perineural infiltration, intratumor vessels emboli, perforation or obstruction), however, factors related to the patient's contraindication (e.g. concomitant diseases or life expectancy) are equally important and should be also considered (II, B). The addition of oxaliplatin does not significantly increase the efficacy of adjuvant chemotherapy in stage II (II, D).

Stage III

Adjuvant treatment should be used in all patients without contraindications to chemotherapy because it prolongs disease-free survival and overall survival (I, A). Adjuvant treatment should be initiated as soon as possible after surgery, preferably within 4–6 weeks, because the greater the delay, the less the impact on prognosis improvement (IV, A). The only justification for delaying the initiation of adjuvant chemotherapy could be medical reasons (e.g. postoperative complications) (IV, B).

The 6-month chemotherapy with fluorouracil and calcium folinate or capecitabine significantly reduces the risk of relapse and increases overall survival rate (even by a dozen or so pp after 5 years) (I, A). Capecitabine was not shown to be more effective than fluorouracil and only a non-significant trend in favor of capecitabine was observed in phase III clinical trial [11].

The addition of oxaliplatin to a fluoropyrimidine (usually the FOLFOX or CAPOX regimen; the FLOX regimen is less frequently used due to toxicity) leads to significant (usually by a few pp) increase in long-term overall survival and such treatment should be the standard of care (I, A) [12, 13]. Another factor that may reduce the benefit of adding oxaliplatin is age over 65–70 years (II, C).

It has not been proven that a 3-month adjuvant therapy with oxaliplatin is non-inferior to standard 6-month therapy (I, D) [14]. The analysis of post hoc created subgroups of the IDEA study indicates that in patients with better prognosis (pT1–3, pN1) 3-month chemotherapy with the CAPOX regimen (instead of 6-month) can be used (II, B). In other patients, 6-month chemotherapy should be the standard treatment, and modifications of chemotherapy (including dose reduction or discontinuation of oxaliplatin) should be based on its toxicity (I, A).

Irinotecan regimens have no advantage over fluoropyrimidine monotherapy, and anti-EGFR drugs and bevacizumab added to chemotherapy are ineffective in adjuvant postoperative treatment (I, E).

In patients receiving fluorouracil in prolonged infusions, the use of portable infusers allows shortening hospital stay (IV, A). However, access to a large vessel (the so-called vascular port) should be ensured beforehand to avoid local complications (peripheral phlebitis) associated with high levels of cytotoxic drug.

Palliative treatment

General remarks

In patients with metastatic colon cancer, it is essential to determine whether radical local treatment is possible, both in the primary lesion and with regard to metastases. Therefore, in many patients for whom local treatment is possible, it is necessary to obtain the opinion of a surgeon experienced in liver surgery or a thoracic surgeon, depending on metastases location. In such situations, local treatment is usually combined with systemic treatment and in some patients, it is possible to achieve long-term survival (IV, A).

Before starting systemic treatment, in addition to information on organ capacity (e.g. CBC, biochemical tests to assess the liver and kidney function), in patients for whom at least doublet chemotherapy is planned, it is necessary to perform molecular diagnostics (exons 2–4 of *KRAS* and *NRAS* genes, *BRAF* V600 mutations), which is a prerequisite for the addition of a biological drug and also provides prognostic information (unfavorable prognosis in patients with the *BRAF* V600 mutation) (I, A).

In disseminated disease, when radical surgery (including metastasectomy) is not possible, systemic therapy prolongs overall survival (I, A).

The median survival time in patients enrolled in RCTs assessing first-line systemic treatment over the last few decades has gradually improved, accounting for about 12 months for fluoropyrimidine monotherapy, several months for multi-drug chemotherapy, and up to over 2 years (multi-drug chemotherapy with a biological drug). The improvement of prognosis is significantly influenced by the possibility of using several lines of treatment, not only the type of first-line therapy (I, A) [15].

First-line treatment

In addition to the availability of individual drugs, the choice of 1st line treatment depends primarily on:

— patients performance status, comorbidities, biological age (IV, A);
— cancer dynamics, cancer-related symptoms, laboratory abnormalities and the degree of critical organs involvement (IV, A);

— tumor molecular characteristics (I, A);
— prior adjuvant treatment (II, B);
— patient preferences regarding the expected toxicity (V, A).

In patients without contraindications to more intensive treatment, at least two-drug chemotherapy with the addition of a biological drug is used as a rule (I, A). The choice of the drug added to fluoropyrimidine in first-line palliative therapy must take into account the type of prior adjuvant treatment (the preferred use of irinotecan in patients receiving oxaliplatin in adjuvant treatment) (I, B).

For some combinations of anti-EGFR drugs with chemotherapy, e.g. cetuximab combined with FOLFIRI or FOLFOX chemotherapy and panitumumab combined with FOLFOX chemotherapy, improved overall survival (median difference usually several months) was directly proven in phase III clinical trials [16, 17]. The prerequisite for the successful anti-EGFR treatment is the normal state of exons 2–4 in *KRAS* and *NRAS* genes in tumor cells., i.e. wild-type *RAS* genes (I, A). It is also important to confirm the absence of the *BRAF* V600 mutation (II, B). Anti-EGFR drugs should not be combined with regimens containing capecitabine (II, E).

Data on the value of anti-angiogenic drugs are inconclusive, although bevacizumab combined with IFL has been shown to prolong survival. The practical value of this observation is small due to the fact that the IFL regimen is currently considered suboptimal and should not be used (I, C). A meta-analysis of 7 RCTs shows that adding bevacizumab to chemotherapy containing irinotecan or oxaliplatin and fluorouracil used in prolonged infusions significantly prolongs progression-free survival, but not overall survival (I, B) [18].

Direct comparisons of anti-EGFR drugs and bevacizumab combined with chemotherapy give conflicting results. In the FIRE-3 study, a significantly improved overall survival was observed (median difference of about 4 months) in patients receiving cetuximab instead of bevacizumab with FOLFIRI chemotherapy, but there were no differences in progression-free survival and objective response rate (II, B) [19, 20]. In the CALGB/SWOG 80405 study, in which the majority of patients received mFOLFOX6 regimen, the advantage of cetuximab was not shown and the survival time was similar regardless of the type of antibody used. Retrospective analyzes taking into account the primary tumor location (left or right) may indicate a greater benefit from the use of anti-EGFR drugs than bevacizumab in patients with left-sided tumors, but this observation alone should not determine the choice of management strategy, as well as suggestions about a possible predictive value of some molecular factors (e.g. microsatellite instability, tumor mutational burden [TMB], molecular subtype) (IV, C).

The intensification of chemotherapy involving the administration of three drugs, instead of two, with or without the addition of a biological drug, does not have a clear effect on prognosis improvement (II, C), and is associated with increased toxicity. However, in some patients in very good performance status, but at risk of developing an organ crisis or with unfavorable prognosis (e.g. *BRAF* V600 mutation), such management (e.g. FOLFOXIRI ± bevacizumab) may be the preferred option (II, B).

When used without a biological drug, irinotecan- or oxaliplatin-based regimens have similar efficacy (I, A) [21, 22], and the decision to select the type of chemotherapy should take into account the expected toxicity.

In patients preferring less intensive treatment, with poorer performance status, elderly, or with significant comorbidity a monotherapy with fluoropyrimidine (fluorouracil with folinic acid, capecitabine) (I, A). The addition of bevacizumab to fluoropyrimidine prolongs progression-free survival and overall survival (I, B) [18].

First-line treatment is continued until progression or unacceptable toxicity occurs (I, A). The value of de-escalation systemic treatment strategies has not been proven in well-designed RCTs (II, D). In particular, it has not been proven that pre-scheduled discontinuation of all oxaliplatin-based chemotherapy and its re-administration after progression is non-inferior to continuous treatment in terms of progression-free survival or disease control duration (II, D). However, the occurrence of oxaliplatin-specific toxicity (e.g. polyneuropathy) very often forces the discontinuation of this drug and the continuation of therapy with fluoropyrimidine alone (IV, A). However, it has been shown that treatment with the FOLFIRI regimen for 2 months, followed each time by 2-month interval is non-inferior to continuous treatment in terms of overall survival (an increase in the relative risk of death by 36% or more was excluded) (II, C) [23]. Data from studies with biological drugs also indicate that pre-planned discontinuation of chemotherapy and continuation of therapy with a biological agent alone may have an adverse effect on progression-free survival compared to continuous treatment or withdrawal of only one cytotoxic agent (II, D).

Second- and subsequent lines treatment

The decision to use the second-line treatment depends to the greatest extent on the patient's PS and the values of vital organs function indexes (IV, A).

The treatment regimen depends on what drugs were used in first-line therapy (I, A) [24]. The rule is to change the cytotoxic drug, i.e. oxaliplatin to irinotecan or vice versa, and administer it together with a fluoropyrimidine (if FOLFOX or XELOX was used in the first-line, then in the second-line FOLFIRI should be administered and vice versa).

For some combinations of anti-angiogenic drugs and chemotherapy (bevacizumab with FOLFOX, aflibercept with FOLFIRI and ramucirumab with FOLFIRI) a small effect on the increase in overall survival (median difference of approximately 1.5–2.0 months) was shown in phase III clinical trials (I, A) [25–27]. If bevacizumab was used in first-line treatment, continued administration of this drug along with switching of chemotherapy also slightly prolongs survival compared to switching chemotherapy alone (I, B).

In phase III clinical trials the addition of anti-EGFR drug to irinotecan-based second-line chemotherapy did not show an increase in survival time — only a slight increase in progression-free survival was observed (difference in medians of 2 months in the study evaluating panitumumab added to FOLFIRI and 1.4 months in the study evaluating cetuximab added to irinotecan) and an increase in objective response rates (25 and 12 percentage points, respectively) (I, C) [28].

In patients previously treated with fluoropyrimidine, irinotecan and oxaliplatin, the phase III EPIC study showed that cetuximab monotherapy prolonged overall survival compared to best supportive care (BSC) (difference in medians of 4.7 months) and improved quality of life (QoL) (I, A) [29]. The phase III ASPECCT study demonstrated that panitumumab was non-inferior to cetuximab and retained 82–130% of the overall survival benefit of cetuximab demonstrated in the EPIC study (I, A) [30].

In patients who previously received all available standard drugs, trifluridine/tipiracil and regorafenib slightly increase overall survival compared to placebo (difference in medians < 2 months) (I, A) [31, 32].

In uncontrolled phase II clinical trials in previously systemically treated patients with tumors showing the evidence of microsatellite instability or with impaired function of DNA repair genes, it was shown that immunotherapy with pembrolizumab or nivolumab, as well as nivolumab with ipilimumab, allows for 20–50% objective responses, the 1-year progression-free survival rate of approx. 70%, and overall survival rate of approx. 80% (III, A) [33].

In phase III study in systemically treated patients (approximately half of whom received irinotecan) with *BRAF* V600 mutation, the combination of encorafenib, binimetinib and cetuximab, as well as doublet therapy with encorafenib and cetuximab, prolonged overall survival (differences in medians 3.6 and 3.0 months respectively) compared to cetuximab in combination with irinotecan-containing chemotherapy (II, A) [34].

Induction therapy in patients with potentially resectable liver metastases

Good direct response to systemic treatment makes metastasectomy possible to perform. The optimal chemotherapy regimen has not been established, however, due to the desire to obtain a direct response, at least two-drug protocols are used. As phase III studies have shown that adding an anti-EGFR drug to chemotherapy increases the response rate, this treatment is also a good option in patients with liver-limited metastases (II, B) [35, 36].

Due to the possibility of harmful effect of long-term chemotherapy on healthy liver parenchyma, which may make it difficult to perform extensive resections, the operability assessment should be carried out quite early, after 2–3 months of treatment (IV, B).

Perioperative treatment of patients with resectable liver metastases

RCTs did not provide clear evidence that perioperative treatment improves the prognosis in patients with resectable liver metastases. Borderline effect of FOLFOX chemotherapy on PFS improvement was observed, but not on overall survival (II, C) [37]. The addition of an anti-EGFR drug to FOLFOX chemotherapy had an adverse effect on progression-free survival (II, E) [38].

However, the decision to use perioperative treatment may result from the need to postpone the second surgery (usually the primary tumor is removed first, followed by metastasectomy) (V, A).

After metastasectomy, adjuvant chemotherapy is usually used, as in stage III (preferably regimens with oxaliplatin) (II, B). The only exception are patients with metastases occurring relatively soon after post-operative adjuvant chemotherapy (V, D).

6. Post-treatment follow-up

The main goal of active observation of patients after completed oncological treatment is early detection of disease recurrence (local and/or generalized) and introduction of appropriate treatment. However, the current meta-analysis did not show that regular follow-up examinations prolong overall survival compared to less strict monitoring or no monitoring (II, C) [39].

There are numerous ongoing discussions regarding optimal patient monitoring regimen taking into account two basic requirements:

— the ability to detect an early and potentially curable relapse;
— the frequency of follow-ups according to the risk of recurrence.

The incidence of relapses in patients with stage I colon cancer and without other poor prognostic factors is so low that the dates and scope of follow-up examinations can be scheduled individually. On the other hand, in primary advanced cases, with no treatment options, or in patients whose clinical condition

Table 4. Long-term follow-up

Year	1							2				3			4		5
Time since treatment completion (months)	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CEA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Imaging of the abdominal cavity/pelvis[1]				X				X				X		X		X	
Imaging of the chest[2]				X				X				X		X		X	
Colonoscopy	X[3]			X										X[4]			

[1]CT preferred, US acceptable. In the case of CEA elevation, always CT with contrast *i.v.*

[2]CT preferred, X-ray acceptable. In the case of CEA elevation, always CT with contrast *i.v.*

[3]Only if a full colonoscopy before surgery not possible

[4]If the result is correct, the next examination in 5 years

is contraindication to any causal treatment (surgery, radiotherapy, chemotherapy), routine follow-ups to detect cancer recurrence are pointless. The general protocol of the proposed oncological surveillance is presented in Table 4 (V, B). It should be noted, however, that this is an intensive surveillance regimen which, if used, should also apply to patients at high recurrence risk (e.g. stage III).

Due to the possibility of synchronic diseases, a colonoscopy should be performed in every patient, regardless of stage, unless it was performed prior to surgery (IV, A).

7. Diagnostic and therapeutic management in special cases

7.1. Familial adenomatous polyposis (FAP)

This is a disease associated with germinal mutations in the *APC* gene, inherited in an autosomal, dominant manner. In about 25% of families, the disease appears without prior history of the genetic burden as "*de novo* mutation". Penetration of the *APC* gene is almost 100% in both genders.

- **Diagnostic panel necessary to diagnose and stage the disease**
  - as in point 3;
  - pedigree interview;
  - genetic testing for mutations in the APC gene.
- **Staging in case of cancer diagnosis**
  - as in point 4.
- **Therapeutic management**
  - surgery: diagnosis of FAP is an indication for elective proctocolectomy, regardless of the presence or absence of concomitantly diagnosed cancer.
- **Scheme of long-term observations**
  - in the case of confirmed colon cancer coexisting with FAP, the follow-up scheme is as in point 6 except performing a colonoscopy.

7.2. Hereditary non-polyposis colon cancer (HNPCC)

This is the most common hereditary form of colon cancer, characterized by mutations in the *MLH1*, *MSH2*, *MSH6*, *PMS1*, and *PMS2* genes. This form of hereditary colon cancer is clinically known as Lynch I or Lynch II syndrome. Lynch I syndrome is characterized by the presence of familial cancer located exclusively in the colon. In Lynch II syndrome, malignant tumors occur not only in colon but also in the uterus, stomach, kidneys, pancreas and ureters, bile ducts and small intestine.

- **Diagnostic panel necessary to diagnose and stage the disease**
  - as in point 3;
  - pedigree interview based on Amsterdam criteria and Bethesda guidelines;
  - immunohistochemical tests of postoperative material for microsatellite instability and defects in DNA mismatch repair proteins.
- **Staging in case of cancer diagnosis**
  - as in point 4.
- **Therapeutic management**
  - surgery: there is no scientific evidence for the advisability of removing the entire colon, neither in healthy mutation carriers nor in patients with HNPCC. The resection extent depends on tumor location and stage.
- **Scheme of long-term observations**
  - colonoscopy every 1–2 years;
  - gastroscopy every 1–2 years;
  - abdominal ultrasound every 1–2 years;
  - in women, gynecological examination with transvaginal ultrasound every 1–2 years and determination of CA-125 level every year;
  - others, as in point 6.

7.3. Cancer in a colon polyp

The margin of polypectomy resection is an important prognostic factor, although it can be difficult to assess

when the polyp has been fragmented. There is no uniform definition of a positive (infiltrated) polypectomy margin. The current European guidelines recommend that a margin of < 1 mm be considered infiltrated, as the presence of a tumor near the polyp resection margin is associated with a significant risk of residual tumor in the draining lymph nodes or the intestinal wall. If the resection margin is considered positive, surgical resection of the appropriate intestine segment is recommended, provided that the patient is fit enough to undergo such surgery — ACPGBI (B).

In the presence of cancer in the removed polyp, microinvasion of lymphatic vessels is associated with an increased risk of lymph node metastases. It most often occurs together with other unfavorable prognostic factors. If it occurs alone (without other poor prognostic factors), surgical treatment should be individually discussed with the patient — ACPGBI (C).

Low-grade cancer in a polyp is rare but is associated with a high risk of residual disease in the lymph nodes. It is usually associated with other risk factors for residual disease. If there is low-grade invasive cancer in a polyp, surgical resection of the appropriate intestine segment should be considered, provided that the patient is fit enough to undergo such surgery — ACPGBI (B).

- **Diagnostic panel necessary to diagnose and stage the disease**

— as in point 3.

- **Staging in case of cancer diagnosis**

— as in point 4.

- **Therapeutic management**

— surgery: before commencing surgical treatment, it is necessary to mark the site of a previously performed polypectomy by performing endoscopic tattooing. Moreover, the operation should be performed in a center capable of performing the intraoperative colonoscopy.

- **Scheme of long-term observations**

— in the case of confirmed colon cancer coexisting with FAP, the follow-up scheme is as in point 6.

7.4. Colon cancer and synchronous, unresectable distant metastases

- **Diagnostic panel necessary to diagnose and stage the disease**

— as in point 3.

- **Staging in case of cancer diagnosis**

— as in point 4.

- **Therapeutic management**

The optimal surgical management of primary colon tumor with coexisted persistently unresectable distant metastases raises a number of controversies, especially when the primary tumor does not show clinical symptoms. The most common complication in patients who did not undergo colon tumor resection before starting chemotherapy is gastrointestinal obstruction (8–29%). There are presumptions based on the results of numerous meta-analyzes and systematic literature reviews that resection of intestinal lesion in patients undergoing palliative systemic treatment improves the prognosis, but these analyzes are burdened with apparent selection bias (IV, B) [40]. Although surgery extends the time to start palliative chemotherapy, most patients can start systemic therapy, and primary tumor resection prevents some local complications (obstruction, bleeding). Therefore, the main challenge for the surgeon is to minimize the risk of severe postoperative complications, which could significantly extend the time to start palliative systemic treatment. Unfortunately, there are no reliable results of RTCs so far, which does not allow for a clear definition of the role of asymptomatic primary tumor resection in the treatment of patients with generalized colon cancer. The interim analysis of one study [41], including, however, twice as few patients as originally planned, presented at the beginning of 2020, indicates that resection of the primary tumor in the case of synchronous, unresectable metastatic lesions may not improve the prognosis (II, C).

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