Rectal cancer (C20)

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1. Methodological remarks

Guidelines elaborated on the basis of recommendations published in 2012–2019 by:
— The French Research Group of Rectal Cancer Surgery (GRECCAR) [1];
— The French National Society of Coloproctology (SNFCP) [1];
— The European Society for Medical Oncology (ESMO) [2];
— The National Comprehensive Cancer Network (NCCN) [3];
— The European Cancer Organisation (ECCO) [4];
— The Association of Coloproctology of Great Britain and Ireland (ACPGBI) [5];
— The European Society of Gastrointestinal Endoscopy (ESGE) [6, 7];
— The European Society of Digestive Oncology (ESDO) [7];
— The European Association for Endoscopic Surgery (EAES) [8];
— The European Society of Gastrointestinal and Abdominal Radiology (ESGAR) [9];
— The College of American Pathologists (CAP) [10];
— The National Institute for Health and Care Excellence (NICE) [11].

The authors have tried in each case to refer individual recommendations to published recommendations including the source publication and (where it was possible) the class of recommendations, level of reliability of the data according to the criteria listed below.

Level of evidence

I — evidence from properly planned and conducted clinical trials with a random selection of patients or meta-analysis of clinical trials with randomization.
II — evidence from properly planned case-control studies and conducted prospective observational studies.
III — evidence from retrospective or clinical-control analyses.
IV — evidence from experience from clinical practice and/or expert opinions.

Levels of recommendations

A — unequivocally confirmed recommendations unconditionally useful in clinical practice.
B — probable recommendations potentially useful in clinical practice.
C — individually ascertained recommendations.

2. Epidemiology

Rectal cancer (C20) was diagnosed in 5617 persons in Poland in 2017. Almost two-thirds of them were male (3419 persons), and one-third female (2198 persons). 3538 deaths because of this indication were recorded (2161 men and 1377 women). The standardized morbidity coefficient was 10.3/10^5/year in men and 5.1/10^5/year in women, and mortality — 6.1 and 2.6, respectively [12]. The median age of becoming sick was over 70 years. 5-year survival was about 50% and was lower than in Western countries [13].

3. Examinations necessary for diagnosis and evaluation of the degree of progression

3.1. Anatomy

So far there have been several definitions of the agreed boundary separating the rectum from the sigmoid, which caused differences between various centers in determining the site of cancer origin (upper part of the rectum or distal part of the sigmoid). Recently a group of international experts has agreed that this boundary should be determined on the basis of a magnetic resonance (MR) or computer tomography (CT) analysis performed in a sagittal projection [14]. This boundary is at the site of the joining of the mesorectum with the sigmoid mesentery (rectum-sigmoid junction) (Fig. 1). In this place, the intestine running mainly outside the peritoneum along the sacral bone (rectum), turns within the peritoneum at a right angle in the direction of the frontal surface of the stomach forming a sigmoid. The classification based on these anatomical bases distinguishes:
— sigmoid cancers — neoplasms which form above the rectum-sigmoid junction;
— rectum-sigmoid junction cancers — neoplasms which encompass the rectum-sigmoid junction;
— rectal cancers — neoplasms which are formed below the rectum-sigmoid junction.

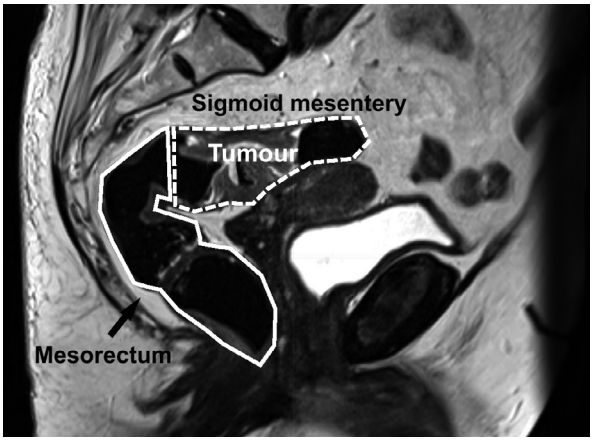

Figure 1. Boundary between the rectum and the sigmoid; after [14]. Rectum is marked by a continuous line; the sigmoid by a dashed line. The boundary between the rectum and sigmoid runs through the rectosigmoid junction, which is at the site where the intestine which runs initially mainly extraperitoneally along the sacral bone (rectum), turns intraperitoneally at a right angle in the direction of the anterior abdomen surface, forming a sigmoid. A tumour is visible which according to endoscopic evaluation starts 14 cm from the edge of the rectum. It is completely behind the rectosigmoid junction, thus should be classified as sigmoid cancer

These guidelines also concern rectal cancer defined according to the above criteria. Guidelines for treating patients with rectum-sigmoid junction cancer and sigmoid cancer were presented earlier in recommendations on colon cancer [15].

The definition of lower rectal cancer has also been made more precise — this is a neoplasm whose lower margin is located at a distance smaller than 6 cm from the edge of the rectum [16]. Anatomically this boundary corresponds to the level of the attachments of levator muscles to the lateral wall of the pelvis.

3.2. Interview

The interview — besides typical principles — is based on an interview directed at rectal cancer symptoms. Among the most common symptoms are the presence of blood in the feces, weight loss and "pseudo diarrhea". The last symptom is due to a obstruction of the intestine by the tumor, which results in frequent deposition of small amounts of liquid feces.

Because of the possibility of occurrence of genetic syndromes — for example, familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) — it is necessary to collect information about the occurrence of neoplasms in the family. In the case of a suspicion of a genetic syndrome, a consultation in a genetic counseling facility is indicated.

3.3. Physical examination

A physical examination encompasses the evaluation of the abdominal cavity in view of the presence of pathological sites of resistance and liver enlargement, groin lymph nodes are examined in view of possible metastases. These nodes are the first site of metastases in cancers present in the lower segment of the rectal canal. Evaluation of the tumor by probing with a finger in the rectum allows a preliminary evaluation of the pathological stage of cancer:

— a small and fully mobile tumour generally indicates stage cT1-2;
— a tumour with a limited mobility and/or a circular tumour in general corresponds to stage cT3;
— an immobile tumour in general indicates stage cT4b or cT3 with a threatened surgical margin.

Description of the *per rectum* examination should contain the following elements:

— approximate distance between the lower edge of the tumour and the edge of the rectum in cm;
— approximate distance between the lower edge of the tumour and the upper edge of the rectal canal in centimeters (evaluation of this distance informs about the necessity of performing an abdomino-sacral amputation or the possibility of performing a an anterior resection);
— approximate distance between the upper edge of the tumour and centimeters in the case of accessibility of the whole tumour during the rectal examination;
— percentage of occupied intestine circumference giving the location (anterior wall, posterior wall, left or right side);
— degree of mobility of the tumour with division into mobile tumours, tumours with limited immobility, and immobile ones;
— approximate size of the tumour in centimeters in the case of the accessibility of the whole tumour during the rectal examination.

3.4. Imaging

MR of the pelvis

MR of the pelvis is necessary to determine the range of the resection and indications for irradiation. For that reason, it is a routine element of preoperative diagnostics in all rectal cancer patients. The CT examination does not provide all necessary information because of insufficient tissue resolution and unreliable evaluation of the mesorectal fascia (MRF) [1–3, 9] (II, A).

A properly performed MR examination must contain the sequences presented in Table 1 and fulfill qualitative criteria. The inclusion of diffusion-weighted imaging (DWI) with a coefficient $B \geq 800$ is also recommended in the routine protocol of the imaging sequence based

Table 1. Qualitative requirements for pelvic examination by magnetic resonance

Sequence	Section plane	Layer thickness/ /GAP	Scope of examination
T2W TSE	Sagittal	3 mm/0.5 mm	Whole pelvis including pelvic wall
T2W TSE whole pelvis	Axial (overview)	5 mm/1 mm	From the iliac ala to the pubic symphysis including the groin
T2W TSE High resolution*	Axial at an angle to rectum in tumour location	3 mm/0.3 mm	Whole tumour and possible tumour deposits outside the wall — section planes perpendicular and parallel to the rectum axis at the site of the tumour
T2W TSE High resolution *	Frontal at an angle to rectum in tumour location + to anal canal (of low location ot the tumour)	3 mm/0.3 mm	In the case of tumours of the lower rectum — frontal sections to anal canal (evaluation of the levator muscle of the anus, sphincters and intersphincter space)

*High resolution — gap between scans visual field and matrix should not exceed pixel size 0.6 × 0.6 mm, or 200 × 200 mm and matrix 384 × 384 or 160 × 160 mm and matrix a 256 × 256; GAP — gap between scans

on diffusion. The intravenous administration of a contrasting agent is not necessary.

The main advantage of an MR examination is an evaluation of whether surgical margin (most often MRF) is involved or threatened. It is accepted that this fascia is threatened (MRF+) if the margin to the tumour is ≤ 1 mm. To determine indications for preoperative radiotherapy version 5 of the TNM classification is useful. It divides grade cT3 into 4 subtypes:
— cT3a: mesorectal infiltrate ≤ 1 mm;
— cT3b: infiltrate > 1 mm, but not larger than 5 mm;
— cT3c: infiltrate > 5 mm, but not larger than 15 mm;
— cT3d: infiltrate > 15 mm.

Diagnosis metastases in lymph nodes in uncertain [17], as small nodes up to 3 mm may contain metastases, and enlarged lymph nodes may be due to inflammation. Therefore the criteria for diagnosis metastases in lymph nodes in the MR examination have been refined. Metastases are diagnosis when the lymph node is at least 9 mm in size. Metastases in smaller lymph nodes are recognized if:
— the outer boundaries are uneven;
— the internal structure is not homogeneous;
— the shape is circular.

Two of the mentioned properties justify the diagnosis of metastasis in a node 5–8 mm in size. Metastases in nodes smaller than 5 mm can be diagnosed if all three properties are present (II, B) [9]. Lymph nodes of the mesorectum and other pelvic lymph nodes are evaluated, including the so-called lateral nodes (internal iliac and obturator).

Occupation of the mesorectal veins seen in an MR examination, the so-called EMVI+ (extramural venous invasion), is an important unfavorable prognostic factor both for local and for distant recurrence (II, A) [9]. In the case of cancers of the lower part of the rectum, rectal MR answers threatened the question of whether the intersphinteric space is threatened. Its occupation excludes the possibility of making an anterior resection [16].

CT analysis

CT of the chest and the abdominal cavity is necessary in order to exclude or detect the presence of distant metastases (II, A) [2–4]. Both these examinations are performed after a single administration of contrast. A conventional chest X-ray (RTG) can replace CT if this examination was not performed together with a CT of the abdominal cavity. Pelvic CT is performed if an MR examination is not possible.

Transrectal ultrasound

Transrectal ultrasound analysis can be performed as a supplementary examination in the case of small lesions. This examination better than MR makes it possible to distinguish between stage cT1 and cT2 but is worse than MR in evaluating the infiltration of the mesorectum (II, B) [8].

Positron emission tomography linked to CT (PET-CT)

PET-CT examination is not indicated during routine diagnostics before treatment. It is only performed to solve a particular clinical problem. An example is an increase in the concentration of the carcinoembryonic antigen (CEA) after treatment, whose cause was not elucidated after CT of the chest, abdominal cavity, and pelvis. Another example is the occurrence of synchronous or metachronous distant metastases potentially suitable for radical surgery or radical stereotactic radiotherapy. In such cases, the aim of the PET-CT examination is to determine whether the existence of other metastatic foci makes radical surgery impossible.

3.5. Endoscopic examination

A full colonoscopy (up to the caecum) is indicated by taking biopses from the tumour and/or removal of the polyp/polyps (II, A) [1–4]. If a full colonoscopy is not

possible because of the obstruction of the intestine by the tumour, then this examination must be performed soon after surgery.

3.6. Pathomorphological evaluation

Microscopic examination of the sections or whole lesions taken from the rectum is the basis for diagnosing preinvasive lesions and rectal cancer. The tissue material is relatively easily available and — besides pathomorphological diagnosis — may be also used to determine the character of the genetic changes in tumour cells, which together with the standard pathomorphological report makes it possible to choose the most appropriate method for treating the patient.

Microscopic examination is used for small tissue sections (biopsies of the lesion), endoscopically removed whole lesions and material derived from surgeries. Each time the pathomorphologist should have the full set of clinical information, the result of the endoscopic analysis together with a description, information concerning the neoadjuvant treatment, and other information from the interview and examination, which could affect the course of the disease and the diagnosis.

Precursor changes

According to the classification of the World Health Organization (WHO) of 2019, among precursor chances of colon and rectal cancer are above all epithelial polyps. A characteristic property of their development is the limitation to the lamina propria of the intestinal mucus membrane, and morphologically they are divided into dentate polyps and conventional adenomas. The morphological division also reflects with some simplification the two main pathways of carcinogenesis of colon cancer, which is the alternative pathway of so-called dentate neoplasia/microsatellite instability (about 20% of cases) and the classical pathway of chromosomal instability. Dentate lesions include hyperplastic polyps (with the subtype microsigmoidular hyperplastic polyp, MVHP) and goblet cell-rich hyperplastic polyp, (GCH), sessile dentate lesions (encompassing previously used descriptions: sessile dentate polyps and sessile dental adenoma), and traditional dentate adenoma. Among conventional adenomas, depending on the architecture of the lesion, the following are distinguished:
— tubular adenomas;
— tubulovillous adenomas;
— villous adenomas.

In all lesions with dysplasia, the pathologist is obliged to define its extent (small or large degree dysplasia) taking into consideration architectonic and cytological changes. On the basis of clinical and pathological data in the group of conventional adenomas the so-called advanced adenomas are distinguished, i.e. lesions characterized by at least one or more of the properties below:
— high degree dysplasia;
— diameter over 1cm;
— villous component.

This is particularly important for the evaluation of the risk of development of colon cancer and is the basis for supervision recommendations in screening programmes.

The condition for diagnosing colon cancer is an invasion of the submucosa. Terms previously used for lesions limited to the epithelium and mucous membrane such as carcinoma *in situ* or carcinoma intramucosum should not be used. Currently, these lesions are classified as high-level dysplasia.

However, particular attention should be paid to differentiating true invasion from the so-called pseudoinvasion, in which dysplastic epithelium invades the head, peduncle or deeper layers of the intestinal wall due to mechanical lesions. The translocated epithelium is generally accompanied by extracellular mucus pools, erythrorragia, hemosiderophages or fragments of the lamina propria without desmoplasia, which indicates the benign character of the lesion.

Endoscopically removed early cancers (malignant polyps)

This group includes cancers limited to the submucosa which are removed by polypectomy, endoscopic submucosal dissection (ESD), and — less frequently — by endoscopic mucosal resection (EMR). In the tissue material the degree of histological differentiation of adenocarcinoma is evaluated (grade, G) G1, G2 or G3, the presence of angioinvasion (in lymphatic and blood vessels), the free margin of the submucosa within the removed lesion (a margin of less than 1 mm is generally taken as a negative prognostic factor). Depending on the formation of the lesion (polypoid lesions in respect to sessile ones) a scale of evaluating the depth of submucosa infiltration according to Haggitt (Table 2) and Kikuchi (Table 3), relating the depth of infiltration to the structures of the polyp (head, neck, stalk) or the level of infiltration of the submucosa — dividing the width of the submucous membrane into three equal parts (sm1, sm2 and sm3). Because of difficulties with interpretation recently as the most conclusive the absolute measurement of the depth of infiltration of the submucous membrane is accepted, and a depth of less than 1 mm is accepted as a positive prognostic factor. Optionally evaluation of the front of cancer infiltration is accepted as a prognostic factor — evaluation of budding and the presence of poorly differentiated clusters and the breadth of cancer infiltration in the submucous membrane. Optimally these factors are evaluated in the lesions removed en bloc.

Table 2. Haggitt scale of cancer classification in peduncled polyps

Level 1	Cancer infiltrates submucosa of the polyp head
Level 2	Cancer infiltrates the polyp neck
Level 3	Cancer infiltrates the polyp peduncle
Level 4	Cancer infiltrates submucosa below the stalk but above myenteron proper

Table 3. Kikuchi scale of cancer classification in sessile polyps

Sm1	Cancer infiltrates up to 1/3 of the upper thickness of the submucosa
Sm2	Cancer infiltrates up to 2/3 of the upper thickness of the submucosa
Sm3	Cancer infiltrates up to 1/3 of the lower thickness of the submucosa

Surgical material

Macroscopic examination

In surgical material after surgery of rectal cancer the evaluation of the quality of the surgery is of fundamental importance, the completeness of the removal of the mesorectal tissues (surgical removal of the rectum in the range of 2/3 of the lower part of the organ) should be evaluated deficits. The scale used (Table 4) encompasses macroscopic evaluation of the surface of the mesorectum and eventual deficits together with their depth. In each case of colon cancer, the macroscopic depth of the infiltration in respect to the intestinal wall layers should be determined, the material should be analyzed to find regional lymph nodes, samples should be taken from the margins of resection and the site of the deepest infiltration of cancer in respect to the margin in the mesorectum or the serosa — the radial margin is defined as the distance of the tumour tissue or the metastatic lymph node to the surface of the mesorectum. In the case of neoadjuvant treatment additional attention should be paid to the presence of neoplastic cells or any other changes within the area previously described as the tumour and the presence of fibrosis and regressive changes in the intestinal wall. Material is taken from the tumour or the area previously considered as the tumour — the sections should be numerous and in the case of complete tumour regression after treatment, the suspected area should be taken as a whole in several steps.

Microscopic examination

In a histopathological report concerning rectal cancer the following elements of microscopic evaluation should be included (II, A):

- The histological type of cancer
  Most colon cancers (90%) have the structure of the type adenocarcinoma not otherwise specified (NOS), however, the WHO classification of 2019 distinguishes several subtypes, some of which are characterized by specific clinical properties, prognostic factors or genetic changes. They include serrated adenocarcinoma, adenoma-like adenocarcinoma, micropapillary adenocarcinoma, mucinous adenocarcinoma, poorly cohesive carcinoma, signet-ring cell carcinoma, medullary adenocarcinoma, adenosquamous carcinoma, undifferentiated carcinoma, and carcinoma with sarcomatoid component.
- Degree of histological differentiation of cancer — low-grade type lesions (highly and moderately differentiated cancers G1 and G2) and high-grade (poorly differentiated cancers G3).
  The focus/component with the lowest differentiation is taken as the grade of cancer differentiation.
- Depth of infiltration of the intestinal wall
  Evaluation of the T characteristic in the pTNM classification concerns the deepest layer of the rectum wall, in which live cancer cells are present. Cell-free mucus pool masses are not treated as remains of the tumour in patients undergoing neoadjuvant therapy. The number of evaluated lymph nodes and the number of nodes with metastases; evaluation of the N characteristic should be based on the pTNM classification. Cell-free mucus pool masses are not treated as remains of the tumour in patients undergoing neoadjuvant therapy; at least 12 lymph nodes should be evaluated, though some elaborations allow

Table 4. The scale of evaluation of surgical treatment performed macroscopically on the basis of the appearance of the external surface of the postoperative specimen

1. Surface of the muscularis propia of the muscularis propia	Small volume of mesorectum with a very irregular surface; profound deficits reach the muscularis propia. Quality of surgical treatment insufficient.
2. Surface within the mesorectum	Average volume of mesorectum with irregular surface and deficits; none of them reaches the myenteron. Slight conical constriction of the preparation in the distal segment. Quality of surgical treatment intermediate.
3. Surface of mesorectum	Mesorectum intact with a smooth surface; small deficits ≤ 5 mm possible. No conical constriction of the preparation in the distal segment. Quality of surgical treatment good.

10 in persons treated before the surgery. According to the 8th edition of the American Joint Cancer Committee (AJCC) [18], in cases, when the whole size of the metastasis is < 0.2 mm or when isolated cancer cells are present (in an IHC examination), such a case should be classified as pN0.

- Evaluation of the proximal and distal intestinal margin and the circumferential resection margin (CRM). The margin is treated as positive when the distance of the tumour tissue from it is ≤ 1 mm. This margin is established from the infiltration of the tumour mass itself or the metastatically altered lymph node.
- The presence of angioinvasion in blood and/or lymph vessels.
- The presence of invasion of nerve trunks.
- The presence of cancer deposits, i.e. irregular foci of cancer infiltrate in pericentric adipose tissue outside the main tumour mass, not containing even remnants of lymph node structure.
- Optionally information concerning the presence of budding and poorly differentiated clusters — see subchapter on early lesions.
- Evaluation of the response to neoadjuvant treatment.

It should be stressed that the basis of placing such an evaluation in the histopathological report is clinical information concerning the used treatment which must be considered in the referral for histopathological analysis. As a minimum, the pathomorphological report should contain information whether in the microscopic picture there are characteristics which could be the result of the used treatment (fibrosis and hyalinization; cell-free mucus pools, degeneration of cancer cells, necrosis, etc.). However, it is recommended to use numerical systems that are based on a quantitative evaluation of the described lesions in the area previously taken up by the cancer. The system should be understandable for collaborating clinicians; one of the more commonly used systems is the scale recommended by the AJCC Cancer Staging Manual (8th edition) [18] and the College of American Pathologists (CAP) [10] (Table 5).

It should, however, be stressed that all classifications of the degree of response to preoperative treatment are based on qualitative regression of the tumor volume in the analyzed tissues and require, as was mentioned earlier, the correct taking of a sufficient number of sections, and in the case of a suspicion of a complete response — an analysis of a series encompassing the area of the putative presence of the tumour.

Table 5. Classification of cancer response to irradiation

0	Complete response: in a series of sections there is no living tumour tissue
1	Considerable response: only a few cancer foci present in the material.
2	Small response: cancer cells and fibrosis are present
3	Poor response: minimal or lack of response to treatment

Genetic analysis

Analysis of mutations based on the analysis of the tumour tissue can be performed on fixed material derived from the primary tumour and distant metastases. Such an analysis is always performed in a paraffin block which contains a sufficient percentage of the live tumour tissue which is confirmed by the pathomorphologist in microscopic analysis. Analyses with established clinical significance include analysis of mutations in the *KRAS, NRAS,* and *BRA*F genes and analysis of microsatellite instability (MSI). Such analyses can be performed using the polymerase chain reaction (PCR) or within a next-generation sequencing (NGS) panel, and additionally, in an immunohistochemical analysis the expression of the protein products of DNA repair genes (*MLH1, MSH2, MSH6, PMS*2) can be analyzed. The presence of expression of all proteins is an indication of the correct activity of the genes and the absence of expression can be a preliminary result in general requiring confirmation of MSI by molecular analysis.

Broad panels of genetic profiling of rectal cancer contain the signatures of numerous genes which can take part in the development of a neoplasm (e.g. *APC, PIK3CA, SMAD, MUTYH, POLD, POLE, GREM1, PTEN, TP53, NTRK, c-MET, DCC*). On the basis of these analyses, molecular profiles have been created which divide rectal cancer into 4 subtypes (the so-called Consensus Molecular Subtypes, CMS). Cancers qualified to particular groups besides the set of genetic changes may also be characterized by special morphological properties, as well as develop from specific precursor lesions. The molecular classification plays an important role in clinical trials but currently has no practical significance. It is also worth mentioning that some rectal cancer cases can respond to immunotherapy which will require the evaluation of the MSI degree or perturbations in the functions of DNA repair genes.

All molecular analyses should be performed in certified laboratories, which are regularly subjected to quality control, including international audits.

3.7. Laboratory analyses

It is necessary to determine the CEA concentration in serum, blood morphology with a smear, indices of the clotting system, and biochemical analyses (glucose concentration in serum, creatinine, urea, electrolytes, bilirubin, and the activity of transaminases, alkaline phosphatase and lactate dehydrogenase (LDH) (II, A) [2, 3]. Other analyses are performed depending on individual indications.

4. Evaluation of disease stage

Evaluation of the disease stage is based on the TNM classification (edition 8 of 2017) [18]. The details are presented in Tables 6 and 7.

5. Therapeutic procedures

The recommended mode of treatment of patients with rectal cancer depends on the disease stage, localization of the tumour and the clinical evaluation of its

Table 6. TNM classification — colon cancer

Primary tumour	
TX	Impossible to evaluate primary tumour
T0	Primary tumour absent
Tis	„In situ" cancer — infiltrating the lamina muscularis of the mucosa
T1	Cancer infiltrates the submucosa
T2	Cancer infiltrates the myenteron proper of the intestinal wall
T3	Cancer infiltrates the serous membrane and in sites where it is absent — infiltrates the pericolic tissue
T4	Neoplastic infiltrate goes through the serous membrane and passes through continuity to neighboring anatomical structures and/or causes perforation of the visceral peritoneum
T4a	Neoplastic infiltrate causes perforation of the visceral peritoneum
T4b	Neoplastic infiltrate passes through the serous membrane and passes through continuity to neighboring anatomical struct
Regional lymph nodes	
NX	Impossible to evaluate regional lymph nodes
N0	No metastases in regional lymph nodes
N1	Metastases in 1–3 regional lymph nodes
N1a	Metastases in 1 regional lymph node
N1b	Metastases in 2–3 regional lymph nodes
N1c	Neoplasm deposits
N2	Metastases in ≥ 4 regional lymph nodes
N2a	Metastases in 4–6 regional lymph nodes
N2b	Metastases in ≥ 7 regional lymph nodes
Distant metastases	
M0	Without distant metastases
M1	Distant metastases present
M1a	Metastases present but limited to one organ or localization (eg. Nonregional lymph node)
M1b	Metastases present in more than one organ
M1c	Metastases to the peritoneum, with or without metastases to other organs

Table 7. Classification according to TNM — colon 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="5">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>
</table>

resectability (on the basis of mobility evaluated in a *per rectum* examination) and the possibility of obtaining a negative circular margin evaluated in a pelvic MR examination) (Fig. 2).

Very early cT1N0 cancer with the possibility of endoscopic treatment

Local excision of the lesions in the rectum is performed by four main endoscopic techniques [6, 7, 19] (Fig. 3), which are:

— standard endoscopic polypectomy using an endoscopic diathermic loop — mild lesions, stalked, up to 4 cm in size or „sessile" up to 2 cm;
— mucosectomy — loop polypectomy after the previous injection of physiological salt under the lesion (EMR) where it is possible to excise "bit by bit" only for mild lesions of an "en-block" technique for lesions suspected of infiltration where the diameter does not exceed 2 cm;
— endoscopic submucosal dissection (ESD) — details are given below;
— trans-anal endoscopic microsurgery (TEM) with the TAMIS (trans anal minimally invasive surgery) modification which allows transmural excision of the lesion using a stiff surgical rectoscope and appropriate tools and is indicated for lesion up to 3 cm, localized up to 8 cm from the anal canal.

The greatest achievement in recent years has been the introduction of the ESD technique. It gives the possibility of removing extensive pre-neoplastic lesions and early cancers with a large diameter (even greater than 3cm) using special knives with the intention of complete removal of the lesion in one fragment ("en-block"). This method allows complete control of resection margins and precise histological evaluation of the removed lesion, being an oncologically safe alternative for a surgical operation in the case of lesions limited to the mucous membrane and shallow layers of the submucosal membrane and fulfilling strictly defined histopathological criteria. The use of this technique is also possible in situations in which treatment using other endoscopic techniques is very difficult or impossible (recurrences after earlier attempts at endoscopic or surgical treatment, lesions localized in areas with strong fibrosis in the submucosal membrane i.e. nonspecific inflammatory intestinal diseases, prior a radiotherapy, the vicinity of surgical anastomoses).

Before excisions lesions in the rectum are evaluated macroscopically using appropriate classifications (Paris, Kudo, NICE, JNET), which make it possible to evaluate the risk of the existence of invasive early cancer in a T1 lesion and the depth of cancer infiltration in the submucosal membrane (surface or deep) [5]. A detailed discussion of the mentioned classifications is beyond the scope of the present paper. The possibility of using the above-mentioned classification is given by modern advanced imaging techniques available in endoscopes of the latest generations.

Decisions concerning further procedures in patients with early rectal cancer are taken after endoscopic removal of the lesion. At this point the patients are divided into two groups:

— high risk of metastases in neighboring lymph nodes — additional treatment is necessary;
— low risk (the risk of local and distant recurrence below 1%) — no additional procedures are recommended and only observation is indicated.

The high-risk group is indicated when one or more of the criteria below are fulfilled. A low-risk group is indicated when NONE of the criteria below are fulfilled.

The risk criteria are:

— low degree of differentiation (G3);
— deep infiltration of the submucous membrane (≥ 1000 μm below the level of the lamina muscularis of the mucusa, or sm2–3 for unpeduncled polyps, Haggitt 4 class for peduncled polyps);
— infiltration of blood or lymphatic vessels (LVI);
— presence of intensive tumour budding;
— positive resection margins (R1), defined as lines of occurring ≤ 1 mm from cancer tissue when they cannot be defined (when the excision was NOT "en-block").

Recommendations:

1. For endoscopic treatment patients are qualified who have lesions in the rectum, which evaluated using advanced imaging methods and appropriate classifications show at most a surface infiltration of the submucus membrane and — for technical reasons — it is possible to remove them completely with an appropriate margin and in one block using the EMR, ESD or TEM technique. The greatest possibility of excision as far as size is concerned is given by ESD (II, B).
2. Endoscopic excision as the only treatment is an acceptable procedure for cancers of T1N0 grade, which were removed by an adequate endoscopic technique, giving the possibility of an R0 resection in one block and when the accepted criteria of low risk of local and distal recurrence are fulfilled (II, A).
3. Criteria of low risk of recurrence after endoscopic treatment encompass not fulfilling ANY of the conditions below:
   a. Low grade of differentiation (G3);
   b. Deep infiltration of the submucosa (≥ 1000 μm below the level of the lamina muscularis of the mucusa, or sm2–3 for unstalked polyps, Haggitt 4 class for stalked polyps);

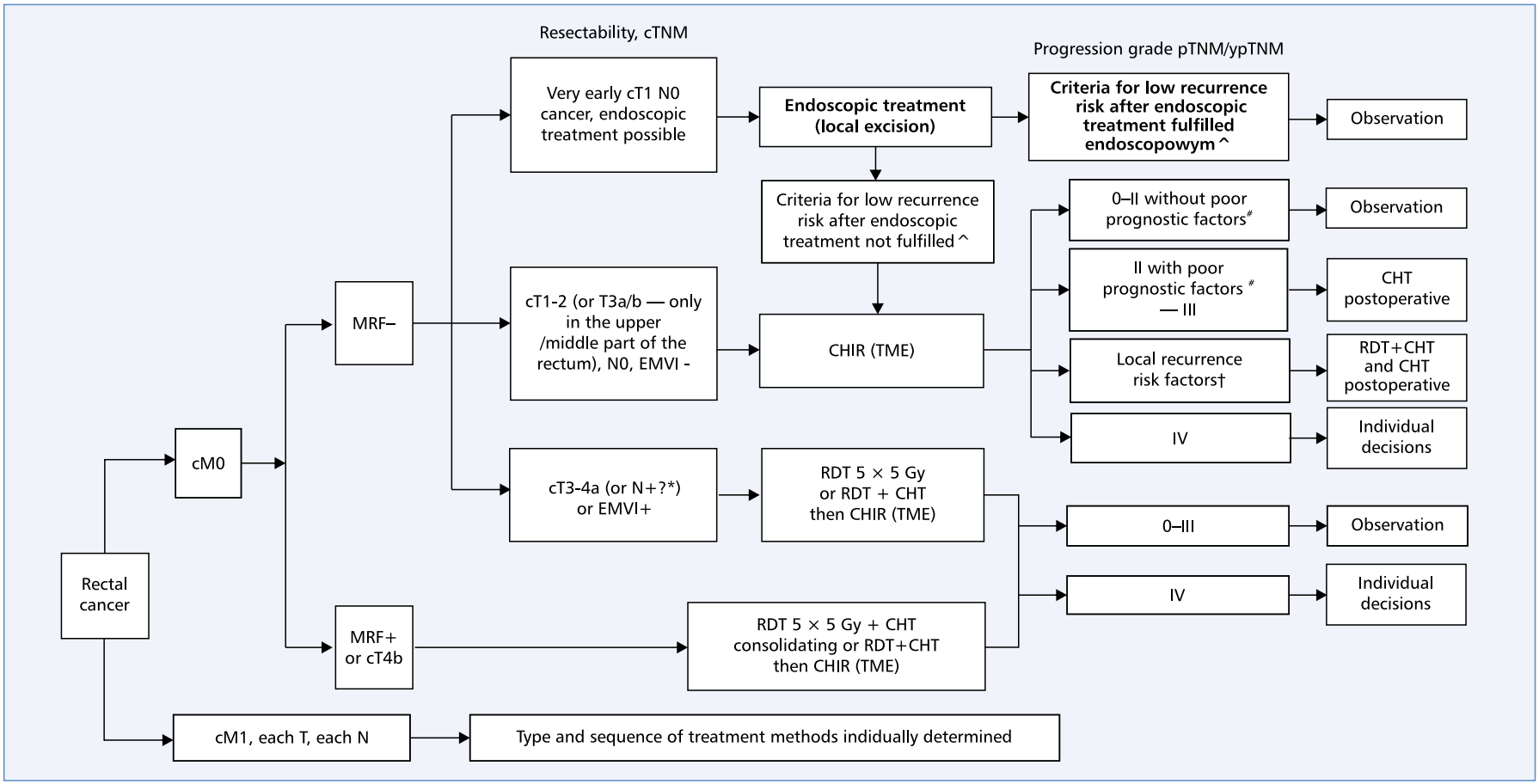

Figure 2. Scheme of therapeutic procedure in patient with rectal cancer depending on the evaluation of tumour resectabillity and the clinical stage evaluated by (cTNM) and pathomorphologically (pTNM or ypTNM). *Characteristic cN+ as an indication for preoperative radiotherapy is the subject of controversy — see chapter about MR examination and about radiotherapy; ^ — see chapter about endoscopic treatment; # — see chapter about chemotherapy; † — see chapter about radiotherapy; CHIR — surgical treatment; CHT — chemotherapy; EMVI — cancer infiltrate extramural venous invasion; MRF — mesorectal fascia; RDT — preoperative radiotherapy; RDT+CHT — long preoperative radiotherapy; TME — total mesorectal excision

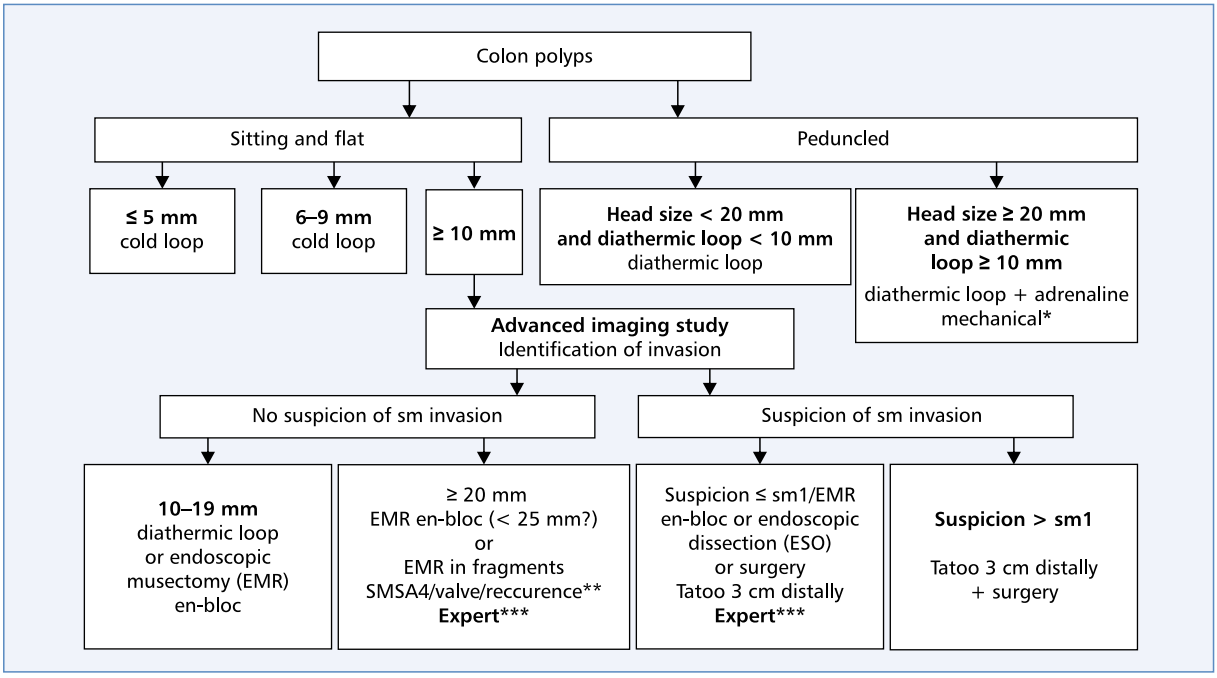

Figure 3. Scheme of selection of the technique of treating colon polyps depending on the size, shape, suspicion of submucosal invasion (sm) according to ESGE guidelines [6] (Ferlitsch et al., Endoscopy 2017). *As the head of the polyp is large and the peduncle thick — it is recommended prophylactically BEFORE polypectomy to inject adrenalin at a dilution of 1:10 000 prophylactically into the base of the polyp or to place a mechanical clip; **SMSA is a special system to evaluate the difficulty of polypectomy (from 1 to 4 points), taking into consideration the size, shape, localization and endoscopic access (Size, Morphology, Site, Access); SMSA4 is a foreseen very difficult polypectomy. A very difficult polypectomy is also foreseen when the lesion is on the Bauhin valve or the lesion is a recurrence after earlier endoscopic treatment; ***Expert — this indicates that patients in the described situation should be treated in expert centers, defined as experienced in complex endoscopic treatment

c. infiltration of blood or lymphatic vessels (LVI);
d. presence of intensive tumour budding;
e. positive resection margins (R1), defined as lines of occurring ≤ 1 mm from cancer tissue when they cannot be defined (when the excision was NOT "en-block") (II, A).

4. In the case of qualification into a high-risk group after endoscopic treatment, additional treatment is necessary. The standard is conversion to total mesorectal excision (TME) (II, B) [2, 3]. The effectiveness of radio(chemo)therapy in lowering local recurrence risk is lower. For this reason, this treatment is only used in patients with a high risk at the surgery or in the case of lack of agreement of the patient to the surgery (II, B) [2, 3]. Then a dose of 50 Gy is given in fractions of 2 Gy with additional radiation on the scar left after the excised tumour up to 60 Gy, if possible with simultaneous chemotherapy (II, B).

Early cancer without indication for local resection (cT1 with unfavourable prognostic factors — cT2, cT3a/b — only localized in the middle and upper parts of the rectum) with MRF- and cN0 and no EMVI

Standard treatment is complete excision of the mesorectum in cancers of the lower and middle rectum or partial excision of the mesorectum (at least 5 cm below the tumour) in cancers of the upper part. If the surgery is performed correctly, the risk of local recurrence does not exceed 5%, which does not justify the use of preoperative radiotherapy (I, A) [2]. However, if the surgery is to be performed in a center that does not have sufficient experience in treating rectal cancer patients, then preoperative radiotherapy should be considered in all patients with cancer with grade cT3.

Preoperative chemoradiotherapy should be considered if the progression of cancer evaluated by microscopic analysis of a post-surgical sample is greater than

was indicated by the MR before the surgery — see the chapter on radiotherapy.

In older patients with progression cT1N0 or cancer cT2 larger than 3 cm and with a high surgery risk, preoperative radiotherapy or chemoradiotherapy can be considered and transmural local excision (II, B) [8] or observation without surgery in the case of complete regression of the tumour (III, C) [20]. In cases of poor tumour response to irradiation observed in a microscopic evaluation of a sample after local excision (positive or narrow ie. 1–2 mm surgical margin, cancer infiltration in lymphatic vessels or ypT2-3) conversion to a radical resection with abdominal access is indicated.

Cancer with intermediate risk — cT3 located in lower rectum or >cT3a/b in central and upper rectum (or cN+?), or EMVI+ and MRF–

There are controversies whether the cN+ characteristic should be an indication for preoperative radiotherapy — see the chapter about MR and radiotherapy. In the remaining patients from this group, the local recurrence risk is higher than 10%, which justifies preoperative irradiation (I, A) [2, 3]. In all patients with cancer localized in the lower rectum with the cT3 characteristic, the recurrence risk is high [16, 21]. This is due to a high risk of metastases into internal iliac lymph nodes and the thin layer of the mesorectum, which leads to the occupation of the surgical radial margin when the postoperative samples are subjected to pathological analysis.

In this group of patients, it is not necessary that the tumour shrinks after irradiation in order to obtain a negative surgical margin. Therefore, it is possible to both use irradiation according to the 5 × 5 Gy scheme directly before the surgery as well as 5 × 5 Gy with the surgery delayed by about 4–8 weeks or conventionally fractionated chemoradiotherapy (I, A) [2, 3].

Cancer with threatened surgical margin ("non-resectable"): MRF+ or cT4b

Preopertivz irradiation combined with chemotherapy — simultaneous conventionally fractionated chemoradiotherapy (I, A) or 5 × 5 Gy combined with consolidating chemotherapy (I, B) should be unconditionally used [2, 3, 22, 23]. A decrease in tumour size after irradiation enables its resection with cancer-free margins. Irradiation 5 × 5 Gy with immediate resection should not be used as the time between irradiation and surgery is too short for the size of the tumour to decrease (I, A). Patients with contraindications for chemotherapy should receive irradiation 5 × 5 Gy alone with resection delayed by about 2 months (III, B) [24]. The characteristic cT4a by itself is not an indication for preoperative irradiation if the surgical margin is not compromised.

The evaluation of irradiation effectiveness on the basis of imaging studies (MR or CT) performed before the surgery is uncertain as the remaining tumour may contain only or to a large extent fibrous tissue of the stroma without cancer cells. On the other hand, macroscopic disappearance of cancer infiltration in the neighboring organ or structure may be accompanied by microscopic cancer infiltration. Therefore in principle an attempt at tumour resection should be made regardless of its response to irradiation, and the scope of the resection should encompass tissues occupied by the cancer before irradiation in an MR examination [25].

5.1. Recommendations for surgical treatment

Recommendations of the National Consultant in the field of oncological surgery and the Polish Society of Oncological Surgery

- The gap between finishing chemoradiotherapy and the surgery should be about 6–8 weeks. After a short irradiation 5 × 5 Gy the surgery should be performed directly after radiotherapy (preferably at the beginning of the following week) or about 8–12 weeks after it ends. If after 5 × 5 Gy chemotherapy is given, the surgery should be performed not earlier than 4 weeks after the last cycle of chemotherapy.
- In the case of a tumour in the lower rectum complete resection of the mesorectum should be performed during an anterior resection, abdomino-perineal amputation or the Hartmann procedure (I, A).
- In the case of tumours with a higher localization, a partial excision of the mesorectum can be performed, the distal margin of mesorectum excision should in this case be 5 cm.
- For tumours with a lower localization the margin of unaffected intestine should be not less than 1 cm (II, A) [1–3].
- The removal of suspected enlarged lymph nodes is recommended localized outside the area of the main upper rectal artery, but routine extended pelvical/extraperitoneal lymphadenectomy is not recommended (II, B) [2].
- The aim should be to restore the continuity of the alimentary tract with the assumption of minimizing the risk of occurrence of the "anterior resection" syndrome.
- In the cases of low anastomoses or the presence of other factors of increased risk a protective ileostomy should be considered.

Moreover:

— In non-resectable lesions a decompressing stoma (ileostomy or ileocolostomy) should be considered.
— In lack of patency the surgery can have the character of a resection (with the stomy e.g. by the Hartmann method) or exclusively decompressing.
— The decision about a defined procedure depends on the patient's general state and the degree of oncological progression.

Final remarks

If it is possible, the aim should be to perform a microscopically radical resection of rectal cancer with the maintenance of the sphincters and recreation (in one or two operations) of the continuity of the digestive tract. With total mesorectal excision (TME) the quality (completeness) of its removal should be evaluated (II, B) [2]. A laparoscopic resection procedure is allowed only in centers with appropriately extensive experience in preforming low-invasive surgery.

5.2. Recommendations concerning the use of radiotherapy

Preoperative radio(chemo)therapy is the procedure of choice in patients treated by the combined method (I, A) [2, 3]. It has replaced the previously used postoperative chemoradiotherapy, as in trials with a random selection of patients it was shown that preoperative irradiation is more effective in decreasing the risk of local recurrence and causes fewer early and late post-irradiation complications [26, 27].

The percentage of local recurrences has decreased considerably after the application of complete mesorectum excision in comparison with the previous surgery technique. Trials with randomization in patients with complete mesorectum excision did indicate a decrease of recurrence percentage by about 60% in patients who received preoperative irradiation — from about 10–11% to 4–6% — but without an improvement in overall survival [28, 29].

It should be stated that radiotherapy causes late post-irradiation complications, of which the most common is the exacerbation of the anterior resection syndrome (fecal and gas incontinence, frequent defecation and urgency) (I, A) [26, 30, 31]. This exacerbated syndrome occurs after surgery alone in about 30% of patients, whereas after preoperative irradiation its frequency increases almost two-fold. Currently, obstruction of the small intestine caused by a post-irradiation damage is very rarely observed. Among other late complications are: in women an arrest of ovarian function, dryness of the vagina causing painful sex, in men perturbations of erection (I, A) [32–34]. Data about an increased risk of post-irradiation neoplasms were not confirmed in newer investigations [35]. Taking into consideration these post-irradiation complications and lack of improvement of survival after irradiation of "resectable" cancers, currently, the indications for irradiation have been limited to advanced cancers. Limited indications for irradiation can be used in highly specialized centers, in which high TME quality does not give rise to doubts and the percentage of local recurrences does not exceed 8–10%.

Indications for preoperative irradiation are the subject of controversy. According to NCCN recommendations, irradiation is indicated in all patients with cT3 cancer [3], whereas ESMO recommendations [2] in the case of cancers of the middle or upper part of the rectum limit recommendations to cT3 cancer deeply infiltrating the mesorectum. It is also not clear whether the cN+ characteristic should be taken into consideration as an indication for irradiation. NCCN [3] and NICE [36] guidelines recommend preoperative irradiation in all patients with the cN1–2 characteristic, however, according to ESMO guidelines, routine use of radiotherapy is controversial in this case [2, 37]. The cause are observations indicating that the enlarged lymph nodes visualized in MR to which the cN1–2 category was attributed often do not contain metastases. On the other hand, unvisualized nodes, smaller than 2–3 mm, can contain these metastases. Therefore, the accuracy of clinical diagnosis of metastases is small, close to tossing a coin [17]. EMVI visualized in MR is not in doubt as an indication for irradiation, as this characteristic is an indication of a high local recurrence risk (II, A) [38].

The lower a tumour is located the higher the risk of a local recurrence and thus indications for preoperative irradiation increase. If the lower edge of the tumour is above the peritoneal reflection fold and the surgical margin is not compromised then preoperative irradiation is not indicated (I, A) [2].

It is not necessary to perform a stoma before initiating irradiation, even in the case of a partial lack of patency. Generally, these symptoms become less pronounced after initiating irradiation because of tumour regression.

Selection of the type of preoperative irradiation

There are four schemes of preoperative irradiation which may be used routinely:

— Chemoradiotherapy, or long irradiation with a dose of 50 Gy in fractions of 1.8 or 2 Gy with simultaneous administration of capecitabine or fluorouracil in a continuous infusion or fluorouracil as an injection with calcium folinate (I, A). This scheme is used in the following cancers:

- "non-resectable" where the surgical margin is compromised, which necessitates decreasing the tumour size before the surgery (I, A) [2, 3]

  And
- "resectable", where the surgical margin is not threatened (I, A) [2, 3].

This scheme should not be used in elderly patients. In patients with contraindications for chemotherapy, it is more effective to administer 5 × 5 Gy than long irradiation without simultaneous chemotherapy [39].

— Short irradiation (5 × 5 Gy) with surgery performed within 10 days after using the first irradiation fraction (I, A). This scheme is used in "resectable" cancers where there is no need to decrease the size of the tumour before the surgery [2, 3]. The

effectiveness in decreasing the local recurrence risk, percentages of postoperative complications, and later post-irradiation complications are similar to those observed after chemoradiotherapy. However, acute post-irradiation complications are smaller after short irradiation than after chemoradiotherapy [40, 41]. Moreover, irradiation 5 × 5 Gy in comparison with chemoradiotherapy is easier to use (only 5 fractions of irradiation) and cheaper.

— Short irradiation (5 × 5 Gy) with surgery performed 4 do 8 weeks after finishing irradiation. This scheme is used in cancers which are:

- "resectable" (I, A) [2]. The effectiveness in diminishing local recurrence risk is similar to short radiotherapy with immediate surgery [39]. Acute post-irradiation complications are more pronounced in patients with delayed surgery whereas post-surgical complications are more common in patients with immediate surgery [39];
- "non-resectable" in patients with contraindications for chemotherapy (III, B) [2]. The treatment of choice is the administration of 5 × 5 Gy with surgery delayed by 6–8 weeks [24, 42, 43]. The long gap until the surgery allows the decrease in the size of the tumour and increases the chance for an R0 surgery. Treatment is less toxic than other schemes as chemotherapy is not administered, and there is a gap between radiotherapy and surgery, which allows convalescence after irradiation.

— Short irradiation (5 × 5 Gy) followed by short (six weeks) consolidating chemotherapy according to the FOLFOX4 or CAPOX scheme, or according to DeGramont and surgery performed about 4 weeks after finishing chemotherapy [2, 23, 44, 45] (I, B). In a Polish trial with randomization [23] comparing conventionally fractionated chemoradiotherapy with short irradiation 5 × 5 Gy and 3 courses of FOLFOX4 or according to the DeGramont scheme administered 10 days after finishing radiotherapy, acute complications were smaller in patients receiving short irradiation. Postoperative complications, the percentage of R0 surgeries, distant oncological results and late complications were similar. The results of this trial were negative as the hypothesis of the trial about the superiority of the experimental scheme to chemoradiotherapy was not confirmed. In spite of that, irradiation 5 × 5 Gy with short term consolidating chemotherapy may be a valuable method in "non-resectable" cancers: it can be used instead of conventionally fractionated chemoradiotherapy, because of the previously mentioned advantages of short-term irradiation (I, B).

In the summary of the RAPIDO trial published so far, comparing conventionally fractionated chemoradiotherapy with short irradiation 5 × 5 Gy with long-term preoperative chemotherapy (6 cycles according to the CAPOX scheme or 9 cycles according to the FOLFOX4 scheme) better early oncological results were obtained after using the latter scheme [44]. Acute toxicity of grade ≥ 3 occurred two times more frequently after this treatment in comparison with long chemoradiotherapy [46]. The intensity of toxicity is related to the length of consolidation chemotherapy — in a Polish trial where 6 weeks of chemotherapy were used, toxicity of grade ≥ 3 occurred in 23% patients, whereas in the RAPIDO trial, where 18 weeks of chemotherapy were administered, in 48%. At the moment of writing these guidelines, there is no basis for routine use of long-term preoperative chemotherapy, because of high toxicity and lack of evidence for improvement of overall survival.

Determining the clinical target volume for irradiation

Of key importance is the irradiation of as small a volume as possible of the small intestine and the anal canal. The volume of the anal canal irradiated with a high dose was shown to correlate with an intensification of the anterior resection syndrome. The clinical target volume (CTV) should always encompass the primary tumour (determined on the basis of CT fusion with an MR examination), mesorectum, lymph nodes along the course of upper rectal vessels and — in tumours localized below the peritoneal reflection — internal iliac lymph nodes. It is not justified to perform irradiation of obturator or external iliac lymph nodes, even in patients with cT4b cancer, as they are not sites of failure [47, 48]. The groin is irradiated electively if the anal canal below the dentate line is involved. In the case of cancers of the upper and lower segment of the rectum the lower CTV boundary should be 4 cm below the lower margin of the primary tumour (range of spreading of microscopic cancer infiltrates in the mesorectum by continuity or the lymphatic system). In the case of cancers localized in the lower rectum, the lower CTV boundary should be up to 1.5 cm below the lower margin of the primary tumour (range of spreading of microscopic cancer infiltrates in the intestinal wall in the distal direction). Irradiation of rectal fossae is not justified if they are not occupied by the tumour — a margin of 1 cm around the gross tumour volume (GTV) is sufficient. The upper CTV boundary should be at the level between S2 and S3 — above this level local recurrence is very rare [49, 50]. Higher CTV contouring is justified when this is required by the location of the primary tumour or because of the high localization of lymph nodes suspected of metastases.

Postoperative chemoradiotherapy

Postoperative chemoradiotherapy is currently rarely used as it has been replaced by preoperative radio(chemo)therapy. Most frequently postoperative chemoradiotherapy should be considered if preoperative irradiation

was not applied and the progress of cancer turned out to be greater than was indicated by an MR examination before the surgery (i.e. there is a high risk of local recurrence). The indications encompass (I, A) [2, 3]:

— If the TME technique is used:
- close (< 2 mm) or positive surgical margin;
- numerous metastases to lymph nodes particularly with the infiltration of the lymph node capsule (the presence of metastases to lymph nodes by itself is not an absolute indication for postoperative irradiation);
- massive occupation of the vessels or numerous perineural infiltrates;

— if the TME technique was not used or excision of the mesorectum was of poor quality:
- pT3 characteristic with deep infiltration of the mesorectum ;
- pT4b;
- metastases to regional lymph nodes;

— if the tumour was perforated during the surgery.

The scheme of fractionated radiotherapy and simultaneous chemotherapy is the same as with preoperative chemoradiotherapy. The IMRT technique is indicated in order to increase the protection of the small intestine which generally fills the bed after the excised tumour. In patients after a perineo-abdominal amputation, the area of irradiation should encompass the perineal scar. The volume of the small intestine (taking the whole peritoneal cavity as its localization) irradiated with a dose of 45 Gy or higher should not exceed 195 cm^3. After this treatment patients additionally receive adjuvant chemotherapy for four months.

If in a patient irradiated before the surgery the pathomorphological examination indicates cancer in the surgical margin, this does not justify increasing the dose after the surgery as the site of lack of radicalness of the procedure is difficult to determine, and the toxicity of such treatment would be high.

Radical irradiation

Radical irradiation is used in older patients with comorbidity when there are contraindications for complete excision of the mesorectum (III, B). Combined with simultaneous chemotherapy fractionation of 2 Gy is used; the elective dose on the area of regional lymph nodes is 44–50 Gy. If the decision is taken not to use chemotherapy because of fear of its toxicity it is possible to use a fractionated dose of 2.5 Gy and a total dose of up to 40 Gy or a fractionated dose of 3 Gy and a total dose of up to 39 Gy. In patients with cancer of grade cT2 the area of elective irradiation should be smaller than used in advanced cancers [51, 52]. Then on the area of only GTV plus the margin, the dose is increased to 60–68 Gy, depending on the location of the tumour in relation to the small intestine. Local cure is possible in only about 20% of patients [53, 54]. A higher percentage of cures (about 70%) can be obtained by combining irradiation with external beams with brachytherapy. This treatment is possible if the tumour is not larger than 3–4 cm and occupies not more than 50% of the intestinal circumference (III, C) [55].

5.3. Observation without surgery in patients with clinical complete regression of the tumour after radio(chemo)therapy

Patients who have complete regression of the primary tumour after preoperative radio(chemo)therapy are increasingly proposed to be observed without surgery (watch-and-wait) as an alternative to complete excision of the mesorectum (III, C) [56]. The advantages are avoidance of a stoma, better functionality of the rectum than after frontal resection, lack of mortality and surgical complications. However, there is no evidence on the safety of this method shown by randomised trials. Good results were shown in several meta-analyses of observational studies and one international database [20, 57, 58]. The percentage of local recurrences after 3 years is high and is about 25%. However, the effectiveness of salvage surgery is also high. Meta-analyses have shown that the salvage surgery was performed in 89% of patients, of these 98% were R0 surgeries. The main reasons for disqualifying for surgery were distant metastases or a history of internal diseases; very rarely (less than 1%) overly advanced local progression [20, 57, 58]. Among all patients observed without surgery the percentage of distant metastases is small (8%) and 5-year overall survivals are high (85%) [20]. This high percentage of survivals can be explained by the lower aggressiveness (including a lower tendency to the formation of distant metastases) of a radiation-sensitive than radiation-resistant cancer [59, 60]. In other words, irradiation is not only a treatment but also a prognostic test, which separates cancers with a good prognosis (the ones which underwent complete regression) from aggressive ones (remaining after irradiation).

There is a risk that in patients undergoing observation without surgery in the time between the irradiation and the detection of a local recurrence distant metastases will form. In the whole population of patients subjected to observation without surgery the additional risk of metastases is about 3% [61]. The additional risk of metastases is thus similar to the 90-day postoperative mortality in younger patients and lower than the postoperative mortality in older patients [62].

Observation without surgery is a controversial method. None of the guidelines recommend its routine use. Some of the guidelines (GRECCAR/SNFCP [1], ESMO [2], NICE [11]) allow it exclusively during trials in patients with high surgical risk, other guidelines (NCCN [3]) — only in centers having a multidisciplinary

group with considerable experience with this method. This is mainly due to the fear of committing errors, both in recognizing complete clinical regression and early recurrence. These errors may lead to a decreased chance of a cure.

The authors of these recommendations believe that the results of analyses warrant consideration of observation without surgery (III, C) as an alternative option to total excision of the mesorectum in patients accepting the risk associated with such a procedure. Observation may be used only in centers that have a multidisciplinary diagnostic-therapeutic group experienced in this method. Patients must have access to control endoscopic examinations and to pelvic MR.

5.4. Recommendations concerning the systemic treatment

Preoperative chemotherapy

In the Polish II multicenter trial no superiority of 3 courses of FOLFOX given after short-term radiotherapy over classical chemoradiotherapy was shown in respect to the frequency of microscopically radical resections, disease-free survival (DFS) and overall survival (OS) [23, 63].

At the ASCO conference in 2020 early results of two trials with randomization, RAPIDO and PRODIGE 23, were presented in which the effectiveness of preoperative chemotherapy was evaluated lasting 4.5 or 3 months, respectively, combined with preoperative short radiotherapy or chemoradiotherapy, in comparison with preoperative chemoradiotherapy alone [44, 64]. In both trials, a decrease in the risk of distant metastases was observed after preoperative chemotherapy. So far, no extension of OS was observed.

So far thus there is no sufficient proof for introducing long-term preoperative chemotherapy to routine practice (I, C).

Postoperative chemotherapy

— Patients, who did not receive preoperative radiotherapy should receive adjuvant chemotherapy according to the principles and indications previously described in guidelines for treating colon cancer [15] (grade III and II with high-risk factors) (I, A) [2, 3].
— Patients, who received preoperative radio(chemo) therapy, routinely should not receive adjuvant chemotherapy, as meta-analyses of trials with randomization showed a lack of improvement in OS (I, B) [65, 66].

Meta-analysis of trials with randomization performed a long time ago when preoperative radio(chemo) therapy was not used showed a slight lengthening of DFS and OS after post-operative chemotherapy in comparison with observation without postoperative treatment [67]. This justifies the use of postoperative chemotherapy in patients who were not irradiated before the surgery (I, A).

The use of postoperative chemotherapy in patients, who received preoperative radio(chemo)therapy is controversial. Two meta-analyses of trials with randomization did not show statistically significant differences in disease-free survival and overall survival between the group of patients receiving postoperative chemotherapy and the group of patients who were just observed [65, 66]. However, a meta-analysis of the trials was performed separately in which random assignment to postoperative chemotherapy was performed not before starting treatment but after the surgery (thus at the moment when the decision to use chemotherapy is made in routine clinical practice) a small improvement in DFS was shown which did not translate into an improval of OS (66). A limitation affecting the interpretation of these meta-analyses is the design of some trials in which adjuvant chemotherapy was suboptimal (time of duration, drug doses).

In a phase II trial with randomization ADORE a prolongation of DFS without an effect on OS was observed after using adjuvant chemotherapy with oxaliplatin combined with fluoropyrimidine in comparison with fluoropyrimidine alone in patients after preoperative chemoradiotherapy in stage II or III determined in histopathological examination of post-operative material [68]. These data also indicate the low effectiveness of postoperative chemotherapy in decreasing the recurrence risk.

The data presented above are, however, interpreted differently in available procedural guidelines. In patients after preoperative radio(chemo)therapy ESMO [2] guidelines do not generally recommend postoperative chemotherapy, but they recommend considering such treatment in patients with stage III cancer and stage II with high recurrence risk. In turn, NCCN guidelines [3] recommend postoperative chemotherapy in all patients irradiated before the surgery regardless of the cancer stage determined after the surgery. ESMO [2] and NCCN [3] guidelines justify their procedures by transferring to rectal cancer indubitable proof on the effectiveness of postoperative chemotherapy in patients with colon cancer, assuming a considerable similarity of these two diseases. In turn, guidelines which base their recommendations only on the results of trials concerning rectal cancer (e.g. Dutch recommendations), do not recommend routine postoperative chemotherapy in patients subjected to preoperative irradiation. The authors of the present recommendations have a similar position. In our opinion, the harm from the use of adjuvant chemotherapy (toxicity, effect on the quality of life and costs) outweigh the potential and uncertain benefits (in the best case prevention or delay of recurrence in a few patients, without proven improvement in OS). This

concerns above all patients subjected to preoperative chemoradiotherapy. In patients after short-term preoperative radiotherapy with immediate surgery, adjuvant chemotherapy may, however, be a rational procedure, similarly as in non-irradiated patients (IV, B).

5.5. Treating patients with local recurrence

Radical surgical treatment

Radical surgical treatment in patients with a local recurrence often is not possible because of the high degree of local progression and/or the coexistence of distant metastases. Resection of a recurrence is technically difficult because of the loss of natural anatomical planes due to the previous surgery. Therefore, such surgeries should be performed in specialized centers.

Even a small local recurrence (e.g. in intestinal anastomoses) indicates a high aggressiveness of cancer and the risk of yet another local recurrence after resection, therefore in each case preoperative radiotherapy (III, B) [2, 3] should be used. In patients who did not receive previous irradiation for the pelvic area the scheme of the applied radiotherapy is the same as that described previously in patients with primary cancer with a compromised surgical margin. In patients after previous irradiation (5 × 5 Gy or after chemoradiotherapy) 30.6 Gy is given in doses of 1.8 Gy on a limited area simultaneously with chemotherapy (III, B) [69–71].

In a few cases for patients with a small recurrence and disqualified for surgery radical irradiation (e.g. by the stereotactic technique) can be considered (IV, C).

Palliative treatment

Generally, local recurrence is accompanied by pronounced symptoms. This indicates that palliative systemic treatment, radiotherapy and/or forming a stoma should be considered. In patients who have not been irradiated previously administration of 5 × 5 Gy may ensure a long-term palliative effect and prevent the necessity of forming a stoma [72]. In patients after previous irradiation (5 × 5 Gy or after chemoradiotherapy) 30.6 Gy may be given in doses 1.8 Gy on a limited area simultaneously with chemotherapy (III, B).

5.6. Treatment of patients with synchronous distant metastases

In patients with rectal cancer and synchronous distant metastases, three categories of metastases are distinguished, on which the method of treatment depends: resectable, potentially resectable, and non-resectable. These methods of treatment have been described in detail in the guidelines for colon cancer treatment [15]. If resectable distant metastases are present the primary tumour should be resected. Resection of the primary tumour should also be considered when the metastases are potentially resectable. There are no indications to perform resection of the primary tumour when the metastases are non-resectable.

However, in rectal cancer much more frequently than in colon cancer the surgical margin of tumour excision is a compromised surgical margin. Also, more commonly the primary tumour causes subjective, burdensome clinical symptoms. For these reasons in rectal cancer in general preoperative radiotherapy of the pelvic area is necessary. Irradiation according to the 5 × 5 Gy scheme is recommended, generally as the first treatment (II, B) [2, 3]. This treatment scheme has the advantage over conventional fractionated long-term chemoradiotherapy, as then multidrug chemotherapy with complete doses is only slightly delayed, toxicity is smaller, and the palliative effect is faster [72, 73]. Irradiation according to the 5 × 5 Gy scheme is used not only with radical intention in borderline resectable tumours in patients with resectable or potentially resectable metastases [73] but also in patients with non-resectable metastases. In the latter case, about 80% patients can avoid a stoma, even if the tumour considerably restricts the intestine (does not allow insertion of an endoscope) [72].

6. Principles of observation after treatment

The main aim of active observation after completed oncological treatment is early detection of a recurrence (local and/or general) and initiation of appropriate treatment. Numerous discussions which are in progress about elaborating the optimal scheme of monitoring the patient take two fundamental requirements into consideration:

— the possibility of detecting an early and potentially treatable recurrence;
— the frequency of the control examinations is suited to the recurrence risk.

The frequency of recurrence in patients with stage I and without unfavourable prognostic factors is so small that the date and extent of control examinations can be determined individually. In turn in primarily advanced cases, which cannot be treated, or in patients whose clinical status would prevent the use of any causal treatment. (surgery, radiotherapy, chemotherapy), the performance of routine control examinations, which would be aimed at detecting a recurrence of the neoplastic process is not worthwhile. The general scheme of the proposed oncological supervision is presented in Table 8.

It should be stressed that this is an intensive supervision scheme, which should pertain to patients with a high recurrence risk (e.g. stage III of clinical progression).

Table 8. Scheme of distant observation

Time from finishing treatment	Year	1				2				3				4		5	
	Month	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 antygen determination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging examination of abdominal cavity/pelvis[a]					X				X				X		X		X
Imaging examination of chest[b]					X				X				X		X		X
Colonoscopy		X[c]			X										X[d]		

[a]Computer tomography (CT) preferred, (USG) admissible. In the case of an increase in the concentration of carcinoembryonic antigen (CEA), always CT with intravenous contrast (*i.v.*); [b]Computer tomography (CT) preferred × ray examination (RTG) admissible. In the case of an increase in the concentration of carcinoembryonic antigen (CEA), always CT with *i.v.* contrast; [c]Only if a complete colonoscopy before the surgery was not possible; [d]If the result is normal, the next examination in 5 years

Conflict of interest

The authors declare no conflict of interest.

References

1. Lakkis Z, Manceau G, Bridoux V, et al. French Research Group of Rectal Cancer Surgery (GRECCAR) and the French National Society of Coloproctology (SNFCP). Management of rectal cancer: the 2016 French guidelines. Colorectal Dis. 2017; 19(2): 115–122, doi: 10.1111/codi.13550, indexed in Pubmed: 27801543.
2. Glynne-Jones R, Wyrwicz L, Tiret E, et al. ESMO Guidelines Committee, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 28 Suppl 4(suppl_4): iv22–iv40, doi: 10.1093/annonc/mdx224, indexed in Pubmed: 32369883.
3. National Comprehensive Cancer Network, Rectal Cancer, Version 6.2020; https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (dostęp z dnia 29.06.2020r).
4. Beets G, Sebag-Montefiore D, Andritsch E, et al. ECCO Essential Requirements for Quality Cancer Care: Colorectal Cancer. A critical review. Crit Rev Oncol Hematol. 2017; 110: 81–93, doi: 10.1016/j.critrevonc.2016.12.001, indexed in Pubmed: 28109408.
5. Williams JG, Pullan RD, Hill J, et al. Association of Coloproctology of Great Britain and Ireland. Management of the malignant colorectal polyp: ACPGBI position statement. Colorectal Dis. 2013; 15 Suppl 2: 1–38, doi: 10.1111/codi.12262, indexed in Pubmed: 23848492.
6. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2017; 49(3): 270–297, doi: 10.1055/s-0043-102569, indexed in Pubmed: 28212588.
7. Hassan C, Wysocki PT, Fuccio L, et al. Endoscopic surveillance after surgical or endoscopic resection for colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Digestive Oncology (ESDO) Guideline. Endoscopy. 2019; 51(3): 266–277, doi: 10.1055/a-0831-2522, indexed in Pubmed: 30722071.
8. Morino M, Risio M, Bach S, et al. European Association for Endoscopic Surgery, European Society of Coloproctology. Early rectal cancer: the European Association for Endoscopic Surgery (EAES) clinical consensus conference. Surg Endosc. 2015; 29(4): 755–773, doi: 10.1007/s00464-015-4067-3, indexed in Pubmed: 25609317.
9. Beets-Tan RGH, Lambregts DMJ, Maas M, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol. 2018; 28(4): 1465–1475, doi: 10.1007/s00330-017-5026-2, indexed in Pubmed: 29043428.
10. https://documents.cap.org/protocols (dostęp z dnia 17.08.2020r).
11. NICE. Colorectal cancer (update). (C4) Deferral of surgery in people having neoadjuvant therapy for rectal cancer. NICE guideline NG151 evidence reviews. January, 2020. https://www.nice.org.uk/guidance/ng151/evidence/evidence-reviews-january-2020-7029391213?tab=evidence (dostęp z dnia 29.06.2020r).
12. Wojciechowska U, Didkowska J. Zachorowania i zgony na nowotwory złośliwe w Polsce. Krajowy Rejestr Nowotworów, Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie — Państwowy Instytut Badawczy. Dostępne na stronie http://onkologia.org.pl/raporty (dostęp z dnia 05.08.2020r).
13. Holleczek B, Rossi S, Domenic A, et al. EUROCARE-5 Working Group: On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999–2007 — Results from the EUROCARE-5 study. Eur J Cancer. 2015; 51(15): 2158–2168, doi: 10.1016/j.ejca.2015.07.024, indexed in Pubmed: 26421819.
14. D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, et al. Definition of the Rectum: An International, Expert-based Delphi Consensus. Ann Surg. 2019; 270(6): 955–959, doi: 10.1097/SLA.0000000000003251, indexed in Pubmed: 30973385.
15. Potemski P, Bujko K, Rutkowski A, Krzakowski M. Wytyczne postępowania diagnostyczno-terapeutycznego u chorych na raka okrężnicy (C18) i zagięcia esiczo-odbytniczego (C19). Dostępne na stronie https://journals.viamedica.pl/onkologia_w_praktyce_klin_edu/article/view/70008; Opublikowany online: 16.07.2020r.
16. Battersby NJ, How P, Moran B, et al. MERCURY II Study Group. Prospective Validation of a Low Rectal Cancer Magnetic Resonance Imaging Staging System and Development of a Local Recurrence Risk Stratification Model: The MERCURY II Study. Ann Surg. 2016; 263(4): 751–760, doi: 10.1097/SLA.0000000000001193, indexed in Pubmed: 25822672.
17. Brouwer NPM, Stijns RCH, Lemmens VE, et al. Clinical lymph node staging in colorectal cancer; a flip of the coin? Eur J Surg Oncol. 2018; 44(8): 1241–1246, doi: 10.1016/j.ejso.2018.04.008, indexed in Pubmed: 29739638.
18. Amin BA, Edge SB. AJCC cancer staging manual. 8th ed. Springer, New York 2017.
19. Spychalski M, Kamiński MF. Endoskopowa dyssekcja podśluzówkowa — evidence based medicine. Gastroenterologia Kliniczna. 2019; 11: 16–20.
20. van der Valk MJM, Hilling DE, Bastiaannet E, et al. IWWD Consortium. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet. 2018; 391(10139): 2537–2545, doi: 10.1016/S0140-6736(18)31078-X, indexed in Pubmed: 29976470.
21. Kusters M, Slater A, Betts M, et al. The treatment of all MRI-defined low rectal cancers in a single expert centre over a 5-year period: is there room for improvement? Colorectal Dis. 2016; 18(11): O397–O404, doi: 10.1111/codi.13409, indexed in Pubmed: 27313145.
22. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. 2008; 26(22): 3687–3694, doi: 10.1200/JCO.2007.15.3858, indexed in Pubmed: 18669453.
23. Ciseł B, Pietrzak L, Michalski W, et al. Polish Colorectal Study Group. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal

cancer: long-term results of the randomized Polish II study. Ann Oncol. 2019; 30(8): 1298–1303, doi: 10.1093/annonc/mdz186, indexed in Pubmed: 31192355.
24. Radu C, Berglund A, Påhlman L, et al. Short-course preoperative radiotherapy with delayed surgery in rectal cancer — a retrospective study. Radiother Oncol. 2008; 87(3): 343–349, doi: 10.1016/j.radonc.2007.11.025, indexed in Pubmed: 18093674.
25. Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. Br J Surg. 2013; 100(8): 1009–1014, doi: 10.1002/bjs.9192, indexed in Pubmed: 23754654.
26. Frykholm GJ, Isacsson U, Nygård K, et al. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. Dis Colon Rectum. 1993; 36(6): 564–572, doi: 10.1007/BF02049863, indexed in Pubmed: 8500374.
27. Sauer R, Becker H, Hohenberger W, et al. German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004; 351(17): 1731–1740, doi: 10.1056/NEJMoa040694, indexed in Pubmed: 15496622.
28. Peeters KC, Marijnen CAM, Nagtegaal ID, et al. Dutch Colorectal Cancer Group. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg. 2007; 246(5): 693–701, doi: 10.1097/01.sla.0000257358.56863.ce, indexed in Pubmed: 17968156.
29. Sebag-Montefiore D, Stephens R, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. 2009; 373(9666): 811–820, doi: 10.1016/s0140-6736(09)60484-0.
30. Birgisson H, Påhlman L, Gunnarsson U, et al. Swedish Rectal Cancer Trial Group. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. J Clin Oncol. 2005; 23(34): 8697–8705, doi: 10.1200/JCO.2005.02.9017, indexed in Pubmed: 16314629.
31. Peeters KC, van de Velde CJH, Leer JWH, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients — a Dutch colorectal cancer group study. J Clin Oncol. 2005; 23(25): 6199–6206, doi: 10.1200/JCO.2005.14.779, indexed in Pubmed: 16135487.
32. Holm T, Singnomklao T, Rutqvist LE, et al. Adjuvant preoperative radiotherapy in patients with rectal carcinoma. Adverse effects during long term follow-up of two randomized trials. Cancer. 1996; 78(5): 968–976, doi: 10.1002/(SICI)1097-0142(19960901)78:5<968::AID-CNCR5>3.0.CO;2-8, indexed in Pubmed: 8780533.
33. Marijnen CAM, van de Velde CJH, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol. 2005; 23(9): 1847–1858, doi: 10.1200/JCO.2005.05.256, indexed in Pubmed: 15774778.
34. Jørgensen JB, Bondeven P, Iversen LH, et al. Pelvic insufficiency fractures frequently occur following preoperative chemo-radiotherapy for rectal cancer - a nationwide MRI study. Colorectal Dis. 2018; 20(10): 873–880, doi: 10.1111/codi.14224, indexed in Pubmed: 29673038.
35. Wiltink LM, Nout RA, Fiocco M, et al. No Increased Risk of Second Cancer After Radiotherapy in Patients Treated for Rectal or Endometrial Cancer in the Randomized TME, PORTEC-1, and PORTEC-2 Trials. J Clin Oncol. 2015; 33(15): 1640–1646, doi: 10.1200/JCO.2014.58.6693, indexed in Pubmed: 25534376.
36. NICE. Colorectal cancer (update). (C2) Preoperative radiotherapy and chemoradiotherapy for rectal cancer. NICE guideline NG151 evidence reviews. January, 2020. https://www.nice.org.uk/guidance/ng151/evidence/evidence-reviews-january-2020-7029391213?tab=evidence (dostęp z dnia 29.06.2020r).
37. Glynne-Jones R, Harrison M, Cheetham D. NICE guideline for rectal cancer: already out of date. Lancet. 2020; 395(10240): e105–e106, doi: 10.1016/S0140-6736(20)30855-2, indexed in Pubmed: 32534652.
38. Chand M, Siddiqui MRS, Swift I, et al. Systematic review of prognostic importance of extramural venous invasion in rectal cancer. World J Gastroenterol. 2016; 22(4): 1721–1726, doi: 10.3748/wjg.v22.i4.1721, indexed in Pubmed: 26819536.
39. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol. 2017; 18(3): 336–346, doi: 10.1016/S1470-2045(17)30086-4, indexed in Pubmed: 28190762.
40. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006; 93(10): 1215–1223, doi: 10.1002/bjs.5506, indexed in Pubmed: 16983741.
41. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol. 2012; 30(31): 3827–3833, doi: 10.1200/JCO.2012.42.9597, indexed in Pubmed: 23008301.
42. Pettersson D, Holm T, Iversen H, et al. Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg. 2012; 99(4): 577–583, doi: 10.1002/bjs.7796, indexed in Pubmed: 22241246.
43. Hatfield P, Hingorani M, Radhakrishna G, et al. Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. Radiother Oncol. 2009; 92(2): 210–214, doi: 10.1016/j.radonc.2009.04.007, indexed in Pubmed: 19409638.
44. Hospers G, Bahadoer R, Dijkstra E, et al. Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: The randomized RAPIDO trial. Journal of Clinical Oncology. 2020; 38(15_suppl): 4006, doi: 10.1200/jco.2020.38.15_suppl.4006.
45. Wiśniowska K, Nasierowska-Guttmejer A, Polkowski W, et al. Polish Colorectal Study Group. Does the addition of oxaliplatin to preoperative chemoradiation benefit cT4 or fixed cT3 rectal cancer treatment? A subgroup analysis from a prospective study. Eur J Surg Oncol. 2016; 42(12): 1859–1865, doi: 10.1016/j.ejso.2016.08.001, indexed in Pubmed: 27546011.
46. van der Valk MJM, Marijnen CAM, van Etten B, et al. Collaborative investigators, Collaborative investigators. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. Radiother Oncol. 2020; 147: 75–83, doi: 10.1016/j.radonc.2020.03.011, indexed in Pubmed: 32240909.
47. Ogura A, Konishi T, Beets G, et al. Lateral nodal features on restaging magnetic resonance imaging associated with lateral local recurrence in low rectal cancer after neoadjuvant chemoradiotherapy or radiotherapy. JAMA Surg. 2019; 154(9): e192172, doi: 10.1001/jamasurg.2019.2172.
48. Sanfilippo NJ, Crane CH, Skibber J, et al. T4 rectal cancer treated with preoperative chemoradiation to the posterior pelvis followed by multivisceral resection: patterns of failure and limitations of treatment. Int J Radiat Oncol Biol Phys. 2001; 51(1): 176–183, doi: 10.1016/s0360-3016(01)01610-8, indexed in Pubmed: 11516868.
49. Syk E, Torkzad MR, Blomqvist L, et al. Local recurrence in rectal cancer: anatomic localization and effect on radiation target. Int J Radiat Oncol Biol Phys. 2008; 72(3): 658–664, doi: 10.1016/j.ijrobp.2008.01.063, indexed in Pubmed: 18495376.
50. Nijkamp J, Kusters M, Beets-Tan RGH, et al. Three-dimensional analysis of recurrence patterns in rectal cancer: the cranial border in hypofractionated preoperative radiotherapy can be lowered. Int J Radiat Oncol Biol Phys. 2011; 80(1): 103–110, doi: 10.1016/j.ijrobp.2010.01.046, indexed in Pubmed: 20646849.
51. Socha J, Pietrzak L, Zawadzka A, et al. A systematic review and meta-analysis of pT2 rectal cancer spread and recurrence pattern: Implications for target design in radiation therapy for organ preservation. Radiother Oncol. 2019; 133: 20–27, doi: 10.1016/j.radonc.2018.12.024, indexed in Pubmed: 30935577.
52. Peters FP, Teo MTW, Appelt AL, et al. Mesorectal radiotherapy for early stage rectal cancer: A novel target volume. Clin Transl Radiat Oncol. 2020; 21: 104–111, doi: 10.1016/j.ctro.2020.02.001, indexed in Pubmed: 32099912.
53. Wang Y, Cummings B, Catton P, et al. Primary radical external beam radiotherapy of rectal adenocarcinoma: long term outcome of 271 patients. Radiother Oncol. 2005; 77(2): 126–132, doi: 10.1016/j.radonc.2005.09.001, indexed in Pubmed: 16216364.
54. Sprawka A, Pietrzak L, Garmol D, et al. Definitive radical external beam radiotherapy for rectal cancer: evaluation of local effectiveness and risk of late small bowel damage. Acta Oncol. 2013; 52(4): 816–823, doi: 10.3109/0284186X.2012.707786, indexed in Pubmed: 22860980.
55. Rijkmans EC, Marijnen CAM, van Triest B, et al. Endorectal Brachytherapy Boost After External Beam Radiation Therapy in Elderly or Medically Inoperable Patients With Rectal Cancer: Primary Outcomes of the Phase 1 HERBERT Study. Int J Radiat Oncol Biol Phys. 2017; 98(4): 908–917, doi: 10.1016/j.ijrobp.2017.01.033, indexed in Pubmed: 28366579.
56. Heald RJ, Beets G, Carvalho C. Report from a consensus meeting: response to chemoradiotherapy in rectal cancer — predictor of cure and a crucial new choice for the patient: on behalf of the Champalimaud 2014 Faculty for 'Rectal cancer: when NOT to operate'. Colorectal Dis. 2014; 16(5): 334–337, doi: 10.1111/codi.12627, indexed in Pubmed: 24725662.

57. Chadi SA, Malcomson L, Ensor J, et al. Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis. Lancet Gastroenterol Hepatol. 2018; 3(12): 825–836, doi: 10.1016/S2468-1253(18)30301-7, indexed in Pubmed: 30318451.
58. Dossa F, Chesney TR, Acuna SA, et al. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2017; 2(7): 501–513, doi: 10.1016/S2468-1253(17)30074-2, indexed in Pubmed: 28479372.
59. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010; 11(9): 835–844, doi: 10.1016/S1470-2045(10)70172-8, indexed in Pubmed: 20692872.
60. Bujko K, Michalski W, Kepka L, et al. Polish Colorectal Study Group. Association between pathologic response in metastatic lymph nodes after preoperative chemoradiotherapy and risk of distant metastases in rectal cancer: An analysis of outcomes in a randomized trial. Int J Radiat Oncol Biol Phys. 2007; 67(2): 369–377, doi: 10.1016/j.ijrobp.2006.08.065, indexed in Pubmed: 17118570.
61. Socha J, Kępka L, Michalski W, et al. The risk of distant metastases in rectal cancer managed by a watch-and-wait strategy — A systematic review and meta-analysis. Radiother Oncol. 2020; 144: 1–6, doi: 10.1016/j.radonc.2019.10.009, indexed in Pubmed: 31710938.
62. Smith FM, Rao C, Oliva Perez R, et al. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. Dis Colon Rectum. 2015; 58(2): 159–171, doi: 10.1097/DCR.0000000000000281, indexed in Pubmed: 25585073.
63. Bujko K, Wyrwicz L, Rutkowski A, et al. Polish Colorectal Study Group. Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study. Ann Oncol. 2016; 27(5): 834–842, doi: 10.1093/annonc/mdw062, indexed in Pubmed: 26884592.
64. Conroy T, Lamfichekh N, Etienne PL, et al. Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: Final results of PRODIGE 23 phase III trial, a UNICANCER GI trial. J Clin Oncol. 2020; 38(15_suppl): 4007, doi: 10.1200/jco.2020.38.15_suppl.4007.
65. Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol. 2015; 16(2): 200–207, doi: 10.1016/S1470-2045(14)71199-4, indexed in Pubmed: 25589192.
66. Bujko K, Glimelius B, Valentini V, et al. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo) therapy: A meta-analysis of randomized trials comparing surgery ± a fluoropyrimidine and surgery + a fluoropyrimidine ± oxaliplatin. Eur J Surg Oncol. 2015; 41(6): 713–723, doi: 10.1016/j.ejso.2015.03.233, indexed in Pubmed: 25911110.
67. Poulsen LØ, Qvortrup C, Pfeiffer P, et al. Review on adjuvant chemotherapy for rectal cancer - why do treatment guidelines differ so much? Acta Oncol. 2015; 54(4): 437–446, doi: 10.3109/0284186X.2014.993768, indexed in Pubmed: 25597332.
68. Hong YS, Kim SY, Lee JiS, et al. Oxaliplatin-Based Adjuvant Chemotherapy for Rectal Cancer After Preoperative Chemoradiotherapy (ADORE): Long-Term Results of a Randomized Controlled Trial. J Clin Oncol. 2019; 37(33): 3111–3123, doi: 10.1200/JCO.19.00016, indexed in Pubmed: 31593484.
69. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, et al. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. Br J Surg. 2014; 101(10): 1280–1289, doi: 10.1002/bjs.9569, indexed in Pubmed: 25049111.
70. Valentini V, Morganti AG, Gambacorta MA, et al. Study Group for Therapies of Rectal Malignancies (STORM). Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. Int J Radiat Oncol Biol Phys. 2006; 64(4): 1129–1139, doi: 10.1016/j.ijrobp.2005.09.017, indexed in Pubmed: 16414206.
71. Guren MG, Undseth C, Rekstad BL, et al. Reirradiation of locally recurrent rectal cancer: a systematic review. Radiother Oncol. 2014; 113(2): 151–157, doi: 10.1016/j.radonc.2014.11.021, indexed in Pubmed: 25613395.
72. Tyc-Szczepaniak D, Wyrwicz L, Kepka L, et al. Palliative radiotherapy and chemotherapy instead of surgery in symptomatic rectal cancer with synchronous unresectable metastases: a phase II study. Ann Oncol. 2013; 24(11): 2829–2834, doi: 10.1093/annonc/mdt363, indexed in Pubmed: 24013512.
73. van Dijk TH, Tamas K, Beukema JC, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. Ann Oncol. 2013; 24(7): 1762–1769, doi: 10.1093/annonc/mdt124, indexed in Pubmed: 23524865.