OFFICIAL JOURNAL OF THE POLISH SOCIETY OF CLINICAL ONCOLOGY

Oncology IN CLINICAL PRACTICE

2020, Vol. 16, Number 6

ISSN 2450–1654

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Official Journal of the Polish Society of Clinical Oncology

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Oncology in Clinical Practice (ISSN 2450–1654) is published six times a year by
VM Media sp. z o.o. VM Group sp.k.
ul. Świętokrzyska 73, 80–180 Gdańsk, Poland
Phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60
e-mail: redakcja@viamedica.pl,
http://www.viamedica.pl, wap.viamedica.pl

19-0214.015.001

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Indexed in Index Copernicus (ICV 2019 = 89.65), Ulrich's Periodicals Directory and CAS.

According to the statement of the Polish Ministry of Science and Higher Education publication in the journal has been awarded with 20 points.

Editorial policies and author guidelines are published on journal website: http://journals.viamedica.pl/oncology_in_clinical_practice

The journal "Oncology in Clinical Practice" is financed under Contract No. 790/P-DUNdem/2019 by the funds of the Minister of Science and Higher Education for the science promotion activities.

Ministerstwo Nauki i Szkolnictwa Wyższego

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ONCOLOGY
IN CLINICAL PRACTICE
Official Journal of the Polish Society of Clinical Oncology
https://journals.viamedica.pl/oncology_in_clinical_practice 2020, Vol. 16, Number 6

GUIDELINES FOR DIAGNOSTIC AND THERAPEUTIC MANAGEMENT IN MALIGNANT NEOPLASMS

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Polish Society of Clinical Oncology and Polish Urological Association Guidelines for the diagnosis and treatment of renal cell cancer

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Key words: renal cell cancer, RCC, nephrectomy, targeted therapy, tyrosine kinase inhibitors, anti-angiogenic therapy, diagnostics

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Translation: dr n. med. Dariusz Stencel
Oncology in Clinical Practice 2020, Vol. 16, No. 6, 301–330. DOI: 10.5603/OCP.2020.0029, copyright © 2020 Via Medica, ISSN 2450–1654

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1. Evidence-based guidelines for the management

1.1. Introduction

For all diseases, diagnosis and treatment should follow evidence-based guidelines for management [1]. Prospective clinical trials are the most important source of scientific evidence. Management according to the guidelines is more effective and safe for patients, allows to compare the results obtained in various centers and assess the quality of diagnostic and therapeutic procedures, as well as it is important in terms of didactics.

1.2. Principles of creating guidelines for management

The results of properly designed and conducted clinical trials represent the most important element of guidelines development. The evaluation of research results should be comprehensive and take into consideration a variety of priority conditions. The results of phase III clinical trials with similar assumptions or their meta-analyses are of the greatest value. In special epidemiological justified situations (low cancer incidence rate), the results of non-randomized prospective studies or eventually observations from retrospective comparative studies and case reports may be valuable.

The analyzed prospective studies should use appropriate methods in control groups, it is also advisable to adopt clinically relevant main objectives of the research. Subgroup analyzes should be pre-planned (retrospective analyzes are less valuable). It is important to use adequate assumptions for statistical analyzes. The efficacy and safety of the assessed intervention should be equally evaluated (including the frequency and severity of adverse events [AEs] and toxicity-related treatment discontinuation rate). Determination of the impact on patients' quality of life (QoL) is specifically related to safety and particularly plays a role in palliative management.

An example of a comprehensive evaluation is launched by the European Society of Medical Oncology (ESMO) the ESMO — Magnitude of Clinical Benefit Scale (ESMO-MCBS) [2]. ESMO-MCBS classifies the value and clinical benefits of anti-cancer therapies based on the effect on survival rates, objective response rates, frequency of AEs and quality of life, and relates these parameters to the results obtained with standard treatment. However, radical and palliative treatment methods should be classified separately. The assessment of these parameters allows to determine the magnitude of clinical benefit and is the basis for reimbursement decisions-making. The algorithm for assessing the value of anticancer drugs was also developed by the Polish Society of Clinical Oncology (PTOK) and the Polish Society of Oncology (PTO) [3].

1.3. Level of evidence and strength of recommendation

International scientific societies (e.g. the American Society of Clinical Oncology — ASCO or the National Comprehensive Cancer Network — NCCN in the United States) and institutions evaluating new medical technologies (e.g. the National Institute for Health and Care Excellence — NICE in the United Kingdom) incorporates different methods to classify the quality of the evidence and the strength of recommendation used for the development of guidelines that apply to most patients. All classifications indicate, however, that when establishing guidelines, it is important to be aware of the occurrence of situations requiring an individual approach, taking into account all medical and socio-economic conditions. An example of individualization in the guideline development process is establishing the rules of management for patients with advanced age or concurrent, non-cancer, serious medical conditions.

The PTOK guidelines for the diagnostic and therapeutic management assume 4 levels of the quality of scientific evidence (I, II, III and IV) and 3 categories of recommendations for clinical practice (A, B and C). The aforementioned levels of the quality of evidence and categories of recommendations (detailed in Table 1) are used in the studies of PTOK devoted to particular neoplasms and methods of diagnostic and therapeutic management. Epidemiological conditions and the evolution of the possibilities of diagnosing and treating disease in oncology justify the use of reliable scientific evidence, which is the basis for guidelines development. The guidelines provide the basis for increasing the availability of medically and economically sound management.

Table 1. Evidence quality levels and recommendation categories according to the Polish Society of Clinical Oncology

Evidence quality levels	Recommendation categories
I — evidence from well-designed and conducted randomized controlled trials (RCTs) or meta-analysis of RCTs	A — indications clearly confirmed and absolutely useful in clinical practice
II — evidence from well-designed and conducted prospective observational studies	B — indications likely and potentially useful in clinical practice
III — evidence from retrospective observational or case-control studies	C — indications determined individually
IV — evidence from clinical practice and/or expert opinion	

Table 2. The most important hereditary syndromes associated with renal cell cancer

Syndrome	Gen	Morphological features
Von Hippel-Lindau syndrome	*VHL*	Clear cell carcinoma
Hereditary papillary renal carcinoma (HPRC)	*MET*	Papillary carcinoma, type 1
Hereditary leiomyomatosis and renal cell cancer (HLRCC)	*FH*	Papillary carcinoma, type 2
Birt-Hogg-Dubé syndrome	*FLCN*	Chromophobe carcinoma or oncocytoma
Tuberous sclerosis	*TSC1/2*	Clear cell, papillary, or chromophobe carcinoma
Cowden syndrome	*PTEN*	Clear cell, papillary, or chromophobe carcinoma
Hereditary pheochromocytoma syndrome (PCC)	*SDH B/C/D*	Clear cell carcinoma
Clear renal cell carcinoma associated with chromosome 3 translocations		Clear cell carcinoma

2. Epidemiology

Kidney cancer accounts for 5% of malignant neoplasms in men and 3% in women, and this statistic includes neoplasms originating from the renal cortex and some neoplasms originating from the urinary tract epithelium. Classic renal cell cancer (RCC), originating from the renal cortex, accounts for 80% of all kidney cancer. The highest incidence of RCC is reported in Western Europe and the United States. Overall, in the last 2 decades, there has been a 2% increase in the incidence of RCC annually in both worldwide and Europe. The male gender dominates (the male: female incidence ratio is 1.5: 1), and incidence peaks around age 60–70. according to the National Cancer Registry, in recent years in Poland, there are about 5,000 cases of RCC annually (men — about 3,000, women — about 2,000 cases), and about 2,500 patients die from kidney cancer each year (1,500 and 1,000 patients, respectively).

3. Etiopathogenesis

Kidney cancer occurs most frequently sporadically, and only 2–3% of cases are associated with some family conditions. The exact etiology of sporadic RCC has not been established, however, a higher incidence of RCC has been associated with nicotinism, obesity, and hypertension. In turn, consumption of coffee containing caffeine reduces the risk of RCC, and decaffeinated coffee increases the risk of developing clear cell RCC [4]. Renal cell carcinoma is also more common in patients with chronic kidney disease, dialyzed, undergoing kidney transplantation or in patients with tuberous sclerosis complex (TSC).

Genetic factors associated with an increased risk of developing RCC are primarily inactivating mutations of the von Hippel-Lindau (*VHL*) gene, determining the development of clear cell RCC. Autosomal dominant inherited von Hippel-Lindau disease with germline *VHL* mutations is associated with RCC, central nervous system (CNS) hemangiomas, adrenal medulla tumors and retinal hemangiomas. In turn, mutations in the *BHD* gene are associated with the occurrence of chromophobe RCC (CRCC) and eosinophilic adenoma (oncocytoma), and the *MET* and *FH* genes mutations — papillary carcinomas, type 1 and 2, respectively. The list of the most important hereditary syndromes associated with the occurrence of renal cell cancers is presented in Table 2.

4. Pathology

RCC subtypes arise from different parts of the nephron: proximal tubule — papillary carcinoma and clear cell carcinoma, distal tubule — oncocytoma and chromophobe tumor, collecting ducts of Bellini

— collecting duct carcinoma, renal medulla — renal medullary carcinoma (RMC). Clear cell RCC (ccRCC) accounts for 80% of kidney malignancies in adults, and the remaining 20% comprises a number of histological subtypes characterized by distinct different molecular, histological and cytogenetic features. Papillary and chromophobe carcinomas consist of 80% of non-clear cell carcinomas.

Clear cell renal cell carcinoma (ccRCC) — characterized by the presence of cells with abundant, bright cytoplasm, resulting from fats and glycogen deposits. A characteristic feature of ccRCC is the inactivation of the *VHL* gene, which is detected in 90% of tumors.

Papillary renal cell carcinoma — is the second most common histological subtype of RCC and in 10% of cases is bilateral. In microscopic evaluation papillary or tubulo-papillary structures, foci of calcification and necrosis are visible. Type 2 tumors are more aggressive (Fuhrman grade 2/3) and diagnosed at a higher stage.

Chromophobe renal cell carcinoma — cancer cells often with double nuclei surrounded by a characteristic halo. This tumor metastasizes relatively rarely, even when it is detected at significantly high stage (except the cases of sarcomatous transformation).

Collecting duct renal cell carcinoma — characteristic features include tubulo-papillary structure, a fibrotic stroma and mucinous content. This is highly aggressive neoplasm malignant, with often synchronous metastases at diagnosis. In 22% of cases, characteristic lymphocyte-rich infiltrates are observed.

Renal medullary carcinoma — is rare cancer that occurs most frequently in young black men with hemoglobinopathies and is more common in the right kidney for unknown reasons. It is associated with a very poor prognosis. Cancer cells are poorly differentiated, with eosinophilic cytoplasm. To date, less than 200 cases of renal medullary carcinoma have been described.

Microphthalmia-associated transcription factor (MiT) family translocational renal cell carcinoma — is characterized by the presence of translocations of genes encoding TFE3 and TFEB transcription factors, located on Xp11 and 6p11 chromosomes. This subtype is found in young people, more often in women. Tumors with translocation are very aggressive and associated with early lymph nodes involvement. Macroscopically, tumors are similar to clear cell carcinoma, with cells with very abundant, bright, granular cytoplasm, forming papillary systems or nests. However, these neoplasms are much less responsive to treatment compared to ccRCC.

Eosinophilic adenoma (oncocytoma) —is a benign tumor, accounting for 25% of small (< 3 cm) kidney tumors. In imaging diagnostics it is difficult to differentiate from renal cell carcinoma, and in the microscopic evaluation of biopsy material — from chromophobe carcinoma. Until recently, it was believed that due to the possible coexistence of RCC, the diagnosis of oncocytoma based on biopsy sample evaluation was not sufficient to exclude the malignant lesion. Recent studies have shown that the majority of complex (hybrid) tumors are associated with congenital genetic syndromes. Only less than 5% of sporadic monofocal oncocytomas have complex histologic structure.

According to the International Society of Urological Pathology (ISUP), WHO (2016) and the Polish Society of Pathologists recommendations, histopathological diagnostics of kidney tumors should include:

— tumor histological type;
— the degree of differentiation according to the Fuhrman grading system with ISUP modification (G1–4);
— presence of sarcomatous transformation (always G4 according to ISUP);
presence of necrosis;
— presence of vascular invasion;
— pathological stage according to pTNM (pathological tumor, node, metastasis) classification;
— surgical margin;
— description of non-neoplastic kidney tissue.

5. Diagnostics

Currently, the historical Virchow's triad, including hematuria, back pain in the lumbar region, and the presence of a tumor palpable through the abdominal wall, is rarely found in clinical practice. If present, the Virchow's triad indicates advanced or aggressive disease. In 30% of patients, atypical symptoms may be a consequence of the paraneoplastic syndrome. Now, most renal cancers are detected accidentally in imaging studies performed for other reasons. In the case of clearly suspicious results of imaging examinations (computed tomography — CT or magnetic resonance imagination — MRI), a biopsy prior to surgery is not necessary, but this examination should be performed when surgery is abandoned and systemic treatment is planned. Considering the fact that in approximately 25% of patients renal cancer will be diagnosed with distant metastasis, systematic staging is necessary already at diagnosis. This is particularly important due to the increasingly strong conditions for metastasectomy and the emerging controversy regarding the benefits of nephrectomy in patients with metastatic RCC. Described recommendations are summarized in Table 3.

5.1. Imaging diagnostics

5.1.1. Computed tomography

Computed tomography is the most important method of imaging diagnostics in RCC patients. A typical CT finding in this tumor type is contrast enhancement

Table 3. Diagnostic tests in renal cell cancer

Baseline tests in renal cell cancer
— Abdomen ± pelvis and chest CT
— General blood tests
— Urinalysis
Additional tests in specific clinical situations
— Abdomen ± pelvis MRI
• Contraindications for contrast-enhanced CT
• The need to exclude venous vessels infiltration
— Contrast-enhanced ultrasound (CEUS)
• Evaluation of a small or unclear lesion in the kidney
• Assessment of tumor thrombus extension
— Urine cytology, ureteroscopy, biopsy
• suspicion of pelvicalyceal system tumor
— MRI of central nervous system (CNDS)
• Clinical suspicion of CNS dissemination
— Bone imaging (scintigraphy or in some cases PET-CT)
• Clinical suspicion of bone dissemination
— Biopsy (preferably core needle)
• Primary tumor — when a nephrectomy is not planned
• Metastatic lesions — in case of diagnostic doubts
— Kidney scintigraphy
• Decreased GFR for elective nephrectomy or
• The need for a careful assessment of active renal parenchyma (patient with a single kidney, multifocal disease)
— Genetic tests
• Genetic syndrome suspected.

CT — computed tomography; GFR — glomerular filtration rate; MR — magnetic resonance imagination; PET — positron emission tomography; PET-CT — positron emission tomography-computed tomography; US — ultrasound

[5] — a lesion is considered to show enhancement if the radiodensity difference between pre- and post-contrast images is at least 20 Hounsfield units (HU); increase by 10–20 HU is considered ambiguous and requires further evaluation (MRI, control CT). In small tumors, the contrast enhancement is usually homogeneous, while in large tumors it is heterogeneous due to the presence of necrosis and hemorrhage. Despite the high accuracy in RCC diagnostics, CT may sometimes not be able to reliably distinguish cancer from eosinophilic adenoma (oncocytoma) [6]. In addition, in some cases, RCC shows very small foci of adipose tissue, which could preclude to reliably distinguish cancer from low-fat angiomyolipoma (AML) on CT scan [7]. On the other hand, the presence of minor calcifications/ossifications in the vicinity of adipose tissue foci is characteristic for cancer.

The risk of malignancy in cystic renal lesion visible in CT is stratified according to Bosniak classification [8] (Table 4). It enables the identification of "clearly benign" lesions (categories I, II), "probably benign" lesions requiring further control (IIF), lesions of an indeterminate nature (III) requiring surgery or active surveillance, and typical "clearly malignant" lesions (IV) requiring only surgery.

Both locally recurrent lesions and RCC distant metastases usually show high contrast enhancement on CT scans and progressive enlargement in subsequent examinations. Bone metastases are usually osteolytic — they are visible on CT as foci/areas of bone destruction. In the course of therapy, the nature of metastatic lesions may change from osteolytic to osteosclerotic, with possible enlargement. Such an image, however, may correspond to the focal reconstruction and reactive formation of bone tissue in the course of therapy, and not the progression, which must be taken into account during the radiological evaluation of the CT scan.

In the course of therapy, minor osteosclerotic metastatic lesions may also appear in locations where previously no changes were found. This may be the result of a reactive bone tissue reaction in the topography of previously present metastatic lesions in the bone marrow, which, however, were too small to cause bone destruction visible on CT.

5.1.2. Magnetic resonance imaging

Kidney cancer in T1-weighted MRI images is often isointense (approx. 60%), possibly hypointense. In T2-weighted images, clear cell carcinoma usually shows an increased signal, while papillary carcinoma — a decreased signal, which allows for preliminary determination of the histological subtype already in the imaging examination; in addition, papillary carcinoma is often characterized by the presence of a pseudocapsule. Diffusion weighted imaging (DWI) within neoplastic tissue usually shows diffusion restriction. However, in the case of kidney tumors, DWI has a moderate accuracy in differentiating between malignant and benign lesions [9]. In some cases, MRI can better than CT imaging the involvement of the venous vessels, especially the extent and nature (thrombus/tumor tissue) of the plug in inferior vena cava (IVC) [10]. MRI can also be used instead of CT in case of contraindications to the administration of iodinated contrast agents used in CT and pregnant women [11]. It is estimated that MRI is more accurate than CT in the assessment of cystic kidney lesions in categories IIF and III according to Bosniak, therefore it can be used in case of doubt in the assessment of CT [12]. MRI may also be the preferred imaging method in young patients with concerns about the use of X-rays, especially when multiple control assessments are required [13]. In MRI imaging an intravenous contrast agent containing gadolinium is used, which is contraindicated in the case of significant renal failure due to the risk of developing nephrogenic systemic fibrosis (NSF) [14].

Table 4. The Bosniak classification system of renal cystic masses

Category	Description	Risk of malignancy	Management
I	**A simple, benign cyst with a hairline-thin wall** No visible calcifications, septa or solid elements. No contrast enhancement and homogeneous simple fluid [< 20 Hounsfield units (HU)]	0%	Treatment usually not required. Re-assessment may be considered after 6–12 months to verify the diagnosis.
II	**A benign cyst with thin septum** May contain few hairline-thin septa without measurable contrast enhancement and fine calcification in the wall or septa. This category also includes homogeneous, well-defined, markedly hyperintense cysts ≤ 3 cm in diameter, without contrast enhancement	0–10%	Treatment usually not required. Re-assessment may be considered after 6–12 months to verify the diagnosis.
IIF (*follow up*)	**Cyst not meeting all category II criteria. A well-defined lesion with features requiring further observation** May contain many hairline-thin or minimally thickened septa, with discrete — perceived but not measurable — contrast enhancement, thicker or nodular calcifications of walls or partitions. This category also includes markedly hyperintense intrarenal cysts > 3 cm in diameter, without contrast enhancement	4.7–24%	Extension of diagnostics is necessary Access to previous imaging studies to assess dynamics MRI consideration Thereby, observation every 3–6 months, and every year if a stable image is confirmed
III	**Indeterminate lesions that usually require surgery, but a significant part of them turns out to be mild** With thickened or irregular wall or septa, with measurable contrast enhancement	40–60%	Surgical treatment is usually indicated. In case of contraindications, fine needle biopsy or active surveillance may be considered
IV	**Usually malignant lesions** All category III criteria and a contrast-enhanced soft-tissue component independent of the wall or septa	85–100%	Surgical treatment

5.1.3. Ultrasonography

Ultrasonography (US) is the most frequently used method of imaging diagnostics of the abdominal cavity organs, including the kidneys, therefore it is often the first examination to find focal lesions in the kidneys, including accidentally — without any connection with the underlying disorder being the indication to US examination. In the RCC assessment, ultrasound is characterized by a much lower sensitivity and specificity than CT or MRI: ultrasound detects approx. 85% of kidney cancers > 3 cm in diameter, but only up to 60% of lesions < 2 cm; some of the suspected lesions in ultrasound are verified in CT as pseudotumors [hypertrophic column of Bertin (HCB), dromedary hump). Renal cell carcinoma in approximately 48% of cases is hyperechoic, in 42% of cases isoechogenic, and 10% of cases hypoechoic mass. Small lesions usually show a homogeneous echogram, and the larger ones, similar to on CT, heterogeneous structure related to necrosis and bleeding foci; some of the lesions may show a presence of pseudocapsule.

5.1.4. Radiography

Conventional X-ray examination of bone and chest structures can be used as a method of the initial assessment of metastatic lesions, but then diagnostics should be continued with more advanced techniques (CT).

5.1.5. Bone scintigraphy

Technetium-99m-methyl diphosphonate (99mTc — MDP) scintigraphy is a nuclear medicine technique that has been available for many years and allows for the simultaneous assessment of the entire skeleton, including the search for metastatic lesions. However, in the case of RCC, such lesions are usually osteolytic, which significantly reduces the sensitivity of scintigraphy, indicating the osteoblastic bone reaction to neoplastic tissue [15].

5.1.6. PET-CT

The use of positron emission tomography (PET) combined with computed tomography (PET-CT) in the diagnosis of kidney cancer is quite limited [16]

— compared to other cancers, RCC may not exhibit significant accumulation of the tracer most commonly used in PET — deoxy-glucose labelled with the isotope ^{18}F (FDG), which forces the use of other markers — ^{11}C or ^{18}F-labeled choline or acetate.

Recommendations

— In the detection and staging of RCC, contrast-enhanced multiphase abdominal and thoracic CT should be used (invasion, tumor plug and metastatic lesions) (II, A).
— Due to the slightly higher sensitivity and specificity of MRI compared to CT in neoplastic plugs detection, MRI should be performed to better assess venous involvement, and to reduce total radiation exposure or to avoid administration of an intravenous contrast agent used in CT (II, A).
— Contrast-enhanced ultrasound (CEUS) is highly sensitive and specific in the assessment of kidney abnormalities. Therefore, it can be used to further assess small kidney lesions, neoplastic plug and differentiate of unclear kidney lesions without the need for exposure to ionizing radiation (II, A).
— PET-CT and scintigraphy are characterized by low sensitivity and specificity in the detection and staging of RCC, and therefore should not be routinely used in RCC staging (II, B).

6. Staging and prognostic factors assessment

Clinical stage is the single strongest prognostic factor in renal cell cancer. Five-year survival rates are at the level of 81%, 73%, 53%, and 8% for grades I, II, III and IV according to TNM, respectively [17].

Anatomical cancer staging should consider the risk factors that are not included in the TNM classification. For stages I/II, infiltration of the renal collecting system is a strong negative prognostic factor [hazard ratio (HR) 3.2; 95% confidence interval (CI) 1.4–7.1] [18]. In stage III, the infiltration of the renal collecting system also seems to be a negative prognostic factor (HR 1.49; 95% CI 1.02–2.17) [19]. For stage III, prognostic significance has not been established for the presence of perirenal fat infiltration [20].

Due to the potential benefits of local treatment in oligometastatic disease [21], it is also necessary to perform a detailed staging in patients with stage IV disease. This may allow the selection of a group of patients who may benefit from this local treatment.

The current staging assessment guidelines are included in the 8th Edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM classification 2017 (Table 5).

6.1. Histological subtype

The role of RCC histological subtype as an independent prognostic factor is debatable, especially when taking into account the impact of other variables, however, most analyzes have shown that patients with cancer have a worse prognosis compared to patients with chromophobe and papillary subtypes. Some less frequent subtypes, such as medullary carcinoma, collecting duct carcinoma, and renal cell carcinoma with Xp11.2 translocation, are considered the most aggressive. Additionally, the presence of the sarcomatous component is an independent negative prognostic factor increasing the aggressiveness and risk of tumor dissemination.

The malignancy grade is also an independent prognostic factor, from many years assessed according to Fuhrman scale. The 5-year survival rates for grade 1, 2, and 3/4 were 89%, 65%, and 46%, respectively [22]. The presence of necrosis is an additional unfavorable prognostic factor for clear cell and chromophobe carcinomas [23].

6.2. Molecular biomarkers

Different molecular markers have been assessed in RCC patients, including carbonic anhydrase IX (CAIX), hypoxia-inducible factor 1α (HIF1α), Ki67 proliferation index and 9p chromosome deletion; however, any of them did not affect the accuracy of prognostic models. Currently, none of the described molecular markers are used in clinical practice.

6.3. Clinical factors

The prognostic impact was described for other factors, such as performance status (PS), the presence of cancer symptoms (fever, weight loss), paraneoplastic syndromes, obesity, laboratory abnormalities (anemia, thrombocytosis, hypercalcemia), systemic inflammatory reaction (CRP, C-reactive protein), neutrophil-lymphocyte ratio (NLR). Based on these observations, numerous models and nomograms were developed and validated for the comprehensive analysis of independent prognostic factors in order to assess the risk of recurrence in patients after radical treatment of RCC. However, the use of UISS system (UCLA Integrated Staging System) [TNM, ECOG (Eastern Cooperative Oncology Group) PS, Fuhrman scale], SSIGN (Stage, Size, Grade, and Necrosis Score) or the Karakiewicz nomogram (TNM, tumor symptoms, Fuhrman scale, tumor size) in making therapeutic decisions is limited due to the lack of adjuvant treatment options and the lack of the highest level data on optimal follow-up after treatment.

Table 5. TNM classification of RCC staging according to AJCC/UICC, 8th edition

T — primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidney		
T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidney		
T1b	Tumor > 4 cm but ≤ 7 cm in greatest dimension, limited to the kidney		
T2	Tumor > 7 cm in greatest dimension, limited to the kidney		
T2a	Tumor > 7 cm but ≤ 10 cm in greatest dimension, limited to the kidney		
T2b	Tumor > 10 cm, limited to the kidney		
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia		
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia		
T3b	Tumor grossly extends into the vena cava below the diaphragm		
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)		
N — regional lymph node			
Hilar, abdominal periaortic and vena cava lymph nodes. Category N is not affected by the side with the nodes			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
M — distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
Clinical staging			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
T1, T2, T3	N1	M0	
Stage IV	T4	Any N	M0
Any T	Any N	M1	

6.4. Prognostic factors in metastatic renal cell carcinoma

In the case of stage IV RCC, in which the patient's assignment to one of the prognostic groups is the basis for qualification for systemic treatment, it is currently recommended to use the IMDC (International Metastatic RCC Database Consortium) prognostic model (Table 6), but it should be remembered that in the majority of systemic therapies available in Poland, qualification for treatment is based on the older MSKCC (Memorial Sloan Kettering Cancer Center) criteria. The accuracy of these scales has been validated, but it should be remembered that the MSKCC is based on database dedicated to interferon-alpha (IFN-α) effectiveness, and the IMDC scale is based on data on the use of anti-angiogenic therapies, hence their nature may not keep up with the rapidly changing treatment landscape of generalized kidney cancer.

7. Treatment

7.1. Management of localized RCC

7.1.1. Active surveillance

Elderly patients or patients with comorbidities and a small kidney tumor have a relatively low risk of RCC-related death compared to the risk of death from other causes [27, 28]. Therefore, in such patients, it is advisable to use active surveillance (AS), which consists in monitoring the disease with the use of available imaging

Table 6. The prognostic scales in RCC

MSKCC scale (developed on the basis of studies with IFN-α) [24]		
Risk factors	**Prognostic category**	**Median overall s urvival (months)**
— Karnofsky performance status score < 80%	Favorable: 0 factors	30
— Time from diagnosis to systemic treatment < 1-year	Intermediate: 1–2 factors	14
— Hemoglobin level < LLN	Unfavorable: ≥ 3 factors	5
— Corrected calcium concentration > ULN		
— Lactate dehydrogenase (LDH) concentration > ULN		
IMDC scale (developed on the basis of studies with TKI-VEGFR) [25, 26]		
Risk factors	**Prognostic category**	**Median overall s urvival (months): first-line [25]; second line [26]**
— Karnofsky performance status score < 80%	Favorable: 0 factors	**43.2;** 35.3
— Time from diagnosis to systemic treatment < 1 year	Intermediate: 1–2 factors	**22.5;** 16.6
— Hemoglobin level < LLN	Unfavorable: ≥ 3 factors	**7.8;** 5.4
— Corrected calcium concentration > ULN		
— Neutrophil count > ULN		
— Platelets count > ULN		

LLN — the lower limit of normal; ULN — lower limit of normal

tests (USG, CT or MRI) and possible implementation of oncological treatment in the case of a clearly progressed neoplastic process. The growth rate of kidney tumors is usually slow, and generalization of the disease is rarely observed during AS [29]. In 2015, the results of a prospective, multicenter study on AS in patients with incidentally detected kidney tumors DISSRM (Delayed Intervention and Surveillance for Small Renal Masses) were published [30]. Almost 500 patients with kidney tumors <4 cm participated in the study and were qualified for either surgery or AS. Patients assigned to AS group were usually older and had worse PS, more comorbidities, smaller tumors and more often multifocal or bilateral lesions. The tumor growth dynamics in the AS population was (median) 0.09 cm/year and decreased with the follow-up. None of the patients with AS died, and none developed metastatic disease. The percentage of patients surviving 2 and 5 years was 98% and 92% (surgical treatment) and 96% and 75% (AS), respectively, and there were no statistically significant differences. Moreover, the 5-year cancer-specific survival rates were 99% (surgical treatment) and 100% (AS) [30, 31].

Active surveillance should be distinguished from close monitoring, i.e. management of patients with contraindications to oncological treatment, in whom diagnostic imaging should be carried out only in case of clinical indications.

7.1.2. Ablative methods

One of the treatment modalities for small renal masses (SRM) is a thermal ablation in the form of cryoablation (CA) or radiofrequency ablation (RFA). The evidence regarding the effectiveness of thermal ablation methods in the treatment of SRM come mainly from retrospective studies and systematic reviews.

7.1.2.1. Cryoablation (CA)

Cryoablation can be performed by both percutaneous and laparoscopic methods. The available — mainly retrospective — studies comparing the two techniques do not indicate any advantage of either of them in terms of perioperative as well as oncological outcomes, except for a shorter hospitalization time with the use of percutaneous method [32, 33]. The results of studies comparing nephron sparing surgery (NSS) performed by different techniques (open, laparoscopic or robot-assisted) with CA of kidney tumor (percutaneous or laparoscopic technique) are inconclusive. Some of them show no differences in overall survival (OS), cancer specific survival (CSS), recurrence-free survival (RFS) and disease-free survival (DFS), local recurrence rate of progression to metastatic disease [34, 35], while others demonstrate the advantage of NSS [36, 37]. Importantly, none of the published studies indicates a prognostic advantage of CA over NSS. Studies comparing the perioperative NSS and CA outcomes are also inconclusive. Some of them show shorter hospitalization time and lower blood loss in patients undergoing CA [34, 35], with no differences in other perioperative outcomes, such as recovery time, complication rate, postoperative serum creatinine concentration. Based on the available studies, it is not

possible to assess which of these methods is associated with a lower risk of developing a newly diagnosed chronic kidney disease.

7.1.2.2. Radiofrequency ablation (RFA)

As with CA, RFA can be performed either percutaneously or laparoscopically. Both techniques show no differences in both the complication rate and oncological outcomes [38–40]. One study found a higher percentage of incomplete ablations with percutaneous access than with laparoscopic method [41]. The results of studies comparing RFA and NSS are inconclusive. One study showed comparable OS and CSS for both treatment methods [42]. Another study, on the other hand, suggests improved OS in patients undergoing NSS, but those patients were younger [43]. A systematic review [44] showed a higher local recurrence rate for RFA compared to NSS, with no difference in terms of distant metastases. A 2018 systematic review comparing thermal ablation (RFA or CA) with NSS showed higher total mortality and cancer-specific mortality for ablation methods, with no difference in the risk of metastasis and local recurrence [45]. The RFA and NSS methods show no differences in the complication rates and the postoperative glomerular filtration rate (GFR) [44], while a systematic review comparing ablative techniques (RFA or CA) with NSS showed a lower complication rate and a lower GRF reduction for ablation methods [45]. The available studies comparing RFA and CA [46, 47] show comparable OS, CSS and RFS for both thermal ablation techniques. The local recurrence rates in one of the studies are higher for RFA [47], and in the other for CA [46]. Postoperative complications rates are comparable [46].

Other ablation techniques, such as microwave, ultrasound, and laser ablation, are considered experimental in the treatment of kidney tumors due to the lack of sufficient scientific evidence.

Recommendations

— Thermal ablation is an alternative to partial nephrectomy in elderly and/or burdened with concomitant abnormalities (e.g. impaired renal function) patients with single T1a cortical renal tumors (III, C).
— Prior to treatment, a tumor biopsy should be performed using the thermal ablation method (IV, A).

7.1.3. Nephrectomy

7.1.3.1. Total versus partial nephrectomy

There is little evidence regarding the direct comparison of NSS and radical nephrectomy (RN) with respect to oncological outcomes, and the available evidence comes mainly from retrospective studies. One randomized trial [48] and several retrospective series [49–51] found comparable results for CSS after NSS and RN in patients with small renal masses (pT1). Due to conflicting results, the beneficial effect of NSS on OS compared to RN suggested in some studies remains unconfirmed [52–54]. A Cochrane systematic review found that NSS was associated with a shorter OS compared to RN in renal cancer limited to the kidney, while CSS and time to relapse and serious complication rates were similar [52]. In comparisons of NSS and RN the complication rate, length of hospital stay estimated blood loss, and blood product transfusions were similar [50–52, 55, 56]. A randomized trial showed that in patients with small kidney tumors and a properly functioning second kidney, NSS can be performed safely, with a slightly higher complication rate compared to RN [57]. Partial nephrectomy is associated with better preservation of renal function than RN [55]. Some studies suggest a reduced risk of cardiovascular disease after NSS [55, 58]. The quality of life after NSS is rated higher than after RN [55].

In a systematic review and meta-analysis of studies comparing NSS in relation to RN, cT1b and T2 tumors were less likely to relapse and cancer-specific and total mortality were lower after NSS. For T2 tumors, NSS was associated with greater blood loss, a greater risk of complications, a lower relapse rate, and lower cancer-specific mortality [59]. In a retrospective long-term, follow-up (LTFU) study (median 102 months) assessing survival in patients with renal tumors ≥ 7 cm undergoing NSS or RN, significantly better median OS and CSS were found [60].

7.1.3.2. Laparoscopic versus open nephrectomy

There are no randomized trials comparing the oncological outcomes of laparoscopic and open RN. A cohort study [61] and retrospective studies have shown that laparoscopic nephrectomy is associated with similar oncological outcomes in relation to open nephrectomy [51]. One randomized study and several non-randomized trials have shown that laparoscopic nephrectomy was associated with shorter hospitalization, less need for painkillers, and less blood loss (but with no difference in blood transfusions) compared to open nephrectomy [51, 62]. However, there were no differences in delayed complications or in postoperative quality of life, and the surgery duration was shorter in the case of open nephrectomy. A systematic review reported fewer complications in patients undergoing laparoscopic RN [55]. There were no significant differences between the transperitoneal and retroperitoneal approach [63, 64]. In a systematic review, no significant differences were found in local recurrence rates between laparoscopic and robot-assisted RN [65].

7.1.3.3. Laparoscopic versus open partial nephrectomy

In centers with extensive experience in laparoscopy, there were no differences between open and laparoscopic partial nephrectomy with regard to RFS and OS

[66, 67]. Blood loss was lower with laparoscopic surgery, but there were no differences in postoperative mortality, thrombosis or pulmonary embolism (PE) [67, 68]. The duration of surgery and the duration of warm ischemia are longer with laparoscopy [67, 68]. Retroperitoneal and transperitoneal approach in laparoscopy is associated with similar perioperative outcomes. Simple enucleation is associated with similar progression-free survival (PFS) and CSS compared to standard NSS and RN [69]. A retrospective analysis comparing open, laparoscopic and robot-assisted NSS with a median follow-up of 5 years showed similar rates of local recurrences, distant metastases, and cancer deaths [70]. In a prospective study comparing the perioperative outcomes of open and robot-assisted partial nephrectomy, the latter was associated with less blood loss and shorter hospitalization stay. Other parameters were similar [71]. In the analysis of the results of 1800 open and robot-assisted NSS, a lower percentage of complications and transfusions, as well as, a shorter hospitalization stay were found in the group undergoing robot-assisted NSS [72]. A meta-analysis comparing the perioperative outcomes of robot-assisted and laparoscopic NSS found that conversion to open surgery and RN was less frequently required in the case of robotic surgery, warm ischemia time and hospitalization stay were shorter, and the magnitude of GFR changes after surgery was also smaller. There were no significant differences in complications, duration of surgery, blood loss, changes in serum creatinine levels after surgery, or positive surgical margins. There were no significant differences in complications, duration of surgery, blood loss, changes in serum creatinine levels after surgery, or positive surgical margins [73]. The studies suggest that the number of procedures (NSS in general/robot-assisted NSS) performed in a clinical center (hospital volume) influences outcomes in terms of surgical complications and margins [74, 75].

7.1.3.4. Management of positive surgical margins

Positive surgical margins are found after about 2–8% of NSS [73], and more often in the case of forced indications and the presence of unfavorable pathological features [76, 77].

The influence of positive margins on oncological outcomes has not been clearly defined, however, based on the literature data, it can be concluded that their presence is not associated with a higher recurrence risk [78]. This is most likely due to the thermal destruction of tissues, including neoplastic cells, located in the immediate vicinity of the surgical incision line. Therefore, in the case of positive margins, only closer monitoring is recommended [77, 79].

7.1.3.5. Lymphadenectomy

The indications for lymphadenectomy in patients without clinically suspicious lymph nodes undergoing NSS and RN are under discussion. Clinical evaluation is based on imaging studies and intraoperative palpation. The value of lymphadenectomy in patients with clinically unsuspected lymph nodes (cN0) was assessed primarily in a single randomized trial (EORTC 30881) [80] which showed that nodal metastases are rare (4%) and the benefit of extended lymphadenectomy is limited only to determine the degree of pathological disease stage. In a large retrospective study, lymphadenectomy in high-risk renal cancer patients was not found to be associated with a reduced risk of distant metastasis, cancer-specific and overall mortality [81]. In other studies, lymphadenectomy has been associated with improved disease-specific survival outcomes in patients with pN+ feature or unfavorable prognostic factors [82, 83]. Retrospective studies indicate that extended lymphadenectomy should involve the lymph nodes surrounding the adjacent large vessel and the area between the aorta and inferior vena cava (IVC). At least 15 lymph nodes should be removed [83].

7.1.3.6. Adrenalectomy

In a prospective, non-randomized clinical trial, tumor size was found to be predictive for adrenal involvement, contrary to tumor location in the upper kidney pole. Adrenalectomy has not been found to affect the prognosis of OS [84].

7.1.3.7. Embolization

There is no benefit associated with tumor embolization prior to routine nephrectomy [85, 86]. In patients not eligible for surgery or with unresectable disease, embolization may help control symptoms (e.g. hematuria or pain in the lumbar region) [87].

Recommendations

— Active surveillance should be considered in elderly patients with ECOG performance status ≥ 2, with comorbidities and a small (< 4 cm) lesion in the kidney (II, B).
— Partial nephrectomy should be performed in patients with T1 tumors (III, B).
— Laparoscopic radical nephrectomy should be performed in patients with T2 tumors and tumors limited to the kidney for whom partial nephrectomy cannot be performed (II, B).
— Minimally invasive radical nephrectomy should not be performed in patients with T1 tumors for whom partial nephrectomy is possible (this includes any approach, including open) (II, B).
— Minimally invasive surgery should not be performed if such approach may worsen oncological and functional or perioperative outcomes (III, B).

Table 7. Comparison of the most frequently used classification of kidney cancer extension

The outreach of kidney cancer extension	Pritchett [89]	Wilkinson [90]	Libertino [91]	Neves [92]	Novick [93]	Hinmann [94]
IVC	1	I	1	0	I	1
IVC < 2 cm above RV	1	II	1	II #1		
IVC > 2 cm above RV and below HVs	1	II	1	II	II	1
IVC above HVs and below the diaphragm	2	II	1	III	III	2
IVC above the diaphragm	3	III	2	IV	IV	2 or 3

IVC — inferior vena cava; RV — renal vein; HVs — hepatic veins

— Extended lymphadenectomy should be considered in patients with unfavorable clinical features, including a large diameter of primary tumor (II, C).
— If positive margins are found after partial nephrectomy, it is not recommended to extend the procedure, but only closer monitoring (III, C).
— Adrenalectomy should not be performed on the kidney tumor side if the preoperative imaging studies do not reveal adrenal involvement (III, B).
— In patients not eligible for surgical treatment with massive hematuria or pain in the lumbar region, tumor embolization should be considered (III, C).

7.2. Treatment of RCC with tumor extension

Tumor extension (TE) that grows into the lumen of the venous system is an unfavorable prognostic factor, while the outreach of tumor extension within the renal vein, inferior vena cava and/or cardiac cavities is not proportional to the risk of metastases [88] (Table 7).

Surgery is the treatment of choice in patients with RCC with tumor extension and without metastases, regardless of the outreach (level) of TE [92, 95, 96]. The choice of the surgical technique depends on tumor extension level (Table 8).

In patients with RCC with TE, minimally invasive surgeries are characterized by a shorter recovery time compared to open surgeries (including and/or sternotomy with the use of extracorporeal circulation). No significant differences were observed in the oncological outcomes after surgery with the use of peripheral cardiopulmonary circulation in deep hypothermia and under normothermic conditions with IVC clamping without supporting by extracorporeal circulation [97]. Preoperative embolization of the renal arteries is not justified, as in patients undergoing such procedure, a longer duration of surgery, greater blood loss, longer hospitalization time and higher perioperative mortality have been reported [97].

As in the case of RCC without TE, lymph node involvement or distant metastases in RCC patients with TE in the venous system is an unfavorable prognostic factor. The 5-year cancer-specific survival rate in the case of metastatic lymph nodes is 0–27%, while in patients with N0 feature it is 17–63% [98–100]. The presence of distant metastases in RCC patients, regardless of venous system involvement by TE, is a negative prognostic factor. The 5-year overall survival rate in RCC patients with N0M0 feature, depending on the outreach of tumor extension, is 55% (TE limited to the sub-diaphragmatic inferior vena cava) or 36% (TE above the diaphragm), and 35% in patients with N1 or M1 feature (TE in renal vein), 24% (TE in IVC below the diaphragm) and 23% (TE above the diaphragm).

Recommendations

— In the case of non-metastatic renal cell cancer with neoplastic extension growing into the lumen of the venous system, surgical excision of the kidney and TE is recommended, regardless of its outreach (II, B).
— It is not recommended to embolize renal arteries prior to excision of RCC with TE growing into the venous system, regardless of its outreach (II, C).

7.3. Treatment of inoperable/metastatic RCC

7.3.1. Choosing the optimal strategy

When deciding on the optimal management strategy in patients with advanced RCC, a number of factors related to both the patient's general condition and the features of disease should be taken into account. First, it is necessary to assess the possibility and justifiability of local treatment (primary tumor resection, resection/radiosurgery of metastatic lesions), and only in the next step to consider the systemic treatment strategy (Fig. 1). The decision regarding the introduction of systemic treatment must take into account stage and dynamics of the disease, accompanying symptoms and the possible presence of an immediate threat to the patient's life, related, for example, to the so-called organ crisis. In the case of high disease dynamics, massive advancement or symptoms of an organ crisis, systemic treatment must

Table 8. Types of approaches and surgical technique depending on the outreach of kidney cancer extension (according to the Neves classification [92])

Incision	Technique
Tumor extension level: 0	
Lumbar	IVC control below and above TE
Subcostal	
Middle abdominal	
Possible 3- or 5-port laparoscopy	
Possible robotic surgery	
Tumor extension level: I	
Lumbar (only for tumor of the right kidney)	IVC control below and above TE and RV of the healthy side and performing thrombectomy
Subcostal	
Middle abdominal	
Possible 3- or 5-port laparoscopy	
Possible robotic surgery	
Tumor extension level: II	
Chevron incision	IVC control below and above TE and RV of the healthy side and performing thrombectomy
Chevron incision with a median extension	
Middle abdominal	
Possible laparoscopy	
Possible robotic surgery	
Tumor extension level: III	
Chevron incision with a median extension	IVC control below and above TE, RV of the healthy side and HVs and performing thrombectomy
Middle abdominal	
Thoracoabdominal	
Tumor extension level: IV	
Chevron incision with a median extension	Removal of TE from the right atrium using a Foley catheter, manual fingers technique: "up-down", or lowering of the TE into the sub-diaphragmatic part of IVC
Thoracoabdominal	
Middle abdominal with sternotomy	
Possible laparoscopy with open atriotomy	

TE — tumor extension; IVC — inferior vena cava; RV — renal vein; HVs — hepatic veins. The tumor extension level was classified by [6]

be implemented as soon as possible (even in patients without prior nephrectomy). In the case of patients with oligometastatic disease or multiple, but asymptomatic and potentially slowly growing metastases, especially located in a single site, the first delay in the introduction of systemic treatment and leaving the patient under active surveillance (AS) or referring to local treatment (nephrectomy, metastasectomy, stereotactic radiotherapy of metastatic lesions) should be considered. In such a situation, it is possible to safely postpone systemic treatment for up to several months without its effectiveness adversely affected. The phase II study assessed the safety of AS in previously untreated, asymptomatic patients with metastatic RCC [101]. A group of 52 patients underwent control imaging examinations every 3 months in the first year, every 4 months in the second year, and every 6 months in the following years. The median follow-up was 38.1 months, and the median time from the start of AS to systemic treatment was 14.9 months. The prognostic factors suggesting the advantage of AS include the presence of up to one unfavorable prognosis factor according to the IMDC scale and metastases located in no more than two organ sites. In the group of patients with favorable prognostic factors, the median AS time was 22 months, while in patients with unfavorable factors — 8.4 months [101]. In any other case, adequate systemic treatment should be implemented (Fig. 2).

7.3.2. Cytoreductive nephrectomy

The role of cytoreductive nephrectomy (CN) in patients with metastatic RCC is currently the subject under many debates. Historically, nephrectomy in patients with metastatic RCC undergoing IFN-α-based

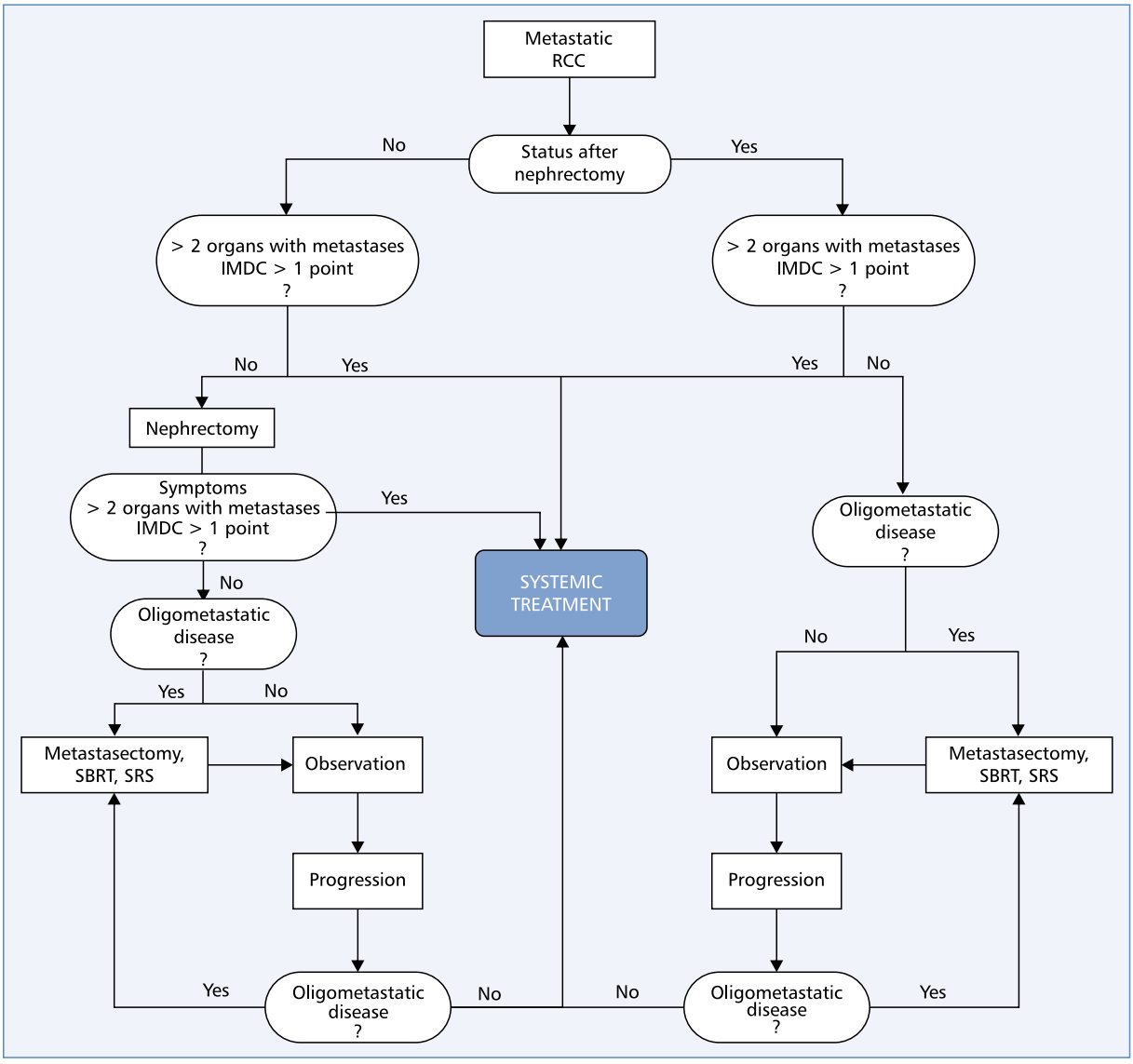


Figure 1. Management strategy in patients with advanced RCC. SBRT — stereotactic body radiation therapy; SRS — stereotactic radiosurgery

immunotherapy has been shown to significantly improve prognosis, reducing the relative risk of death by more than 30% [102]. Due to this fact, primary tumor resection has become a standard procedure in all RCC patients, regardless of disease stage. Thus, at the time of the commencement of studies on targeted therapies in the treatment of RCC, the absolute majority of patients qualified for these studies underwent nephrectomy of radical or cytoreductive intent. Therefore, it was very difficult to conclude about the value of CN in the era of molecularly targeted treatment. Retrospective analysis of the US National Cancer Data Base, covering the years 2006–2013 [15.4 thousand patients treated with tyrosine kinase inhibitors (TKIs), including 35% of patients undergoing CN] showed that CN was associated with a significant reduction of the relative risk of death by 55% (HR 0.45; 95% CI 0.40–0.50) with OS median of 17.1 months (patients after CN) and 7.7 months (patients without CN), respectively [103].

So far, only two prospective clinical trials (CARMENA and SURTIME) with incomplete recruitment have been conducted to assess the role of CN in patients with metastatic RCC receiving sunitinib [104, 105]. The CARMENA study verified whether systemic treatment without preceding CN is non-inferior to systemic treatment after CN. The study included 450 patients (intermediate and poor prognosis according to MSKCC scale) randomly assigned to the experimental arm with CN and sunitinib or to the control arm with sunitinib alone. In the experimental arm, CN was performed

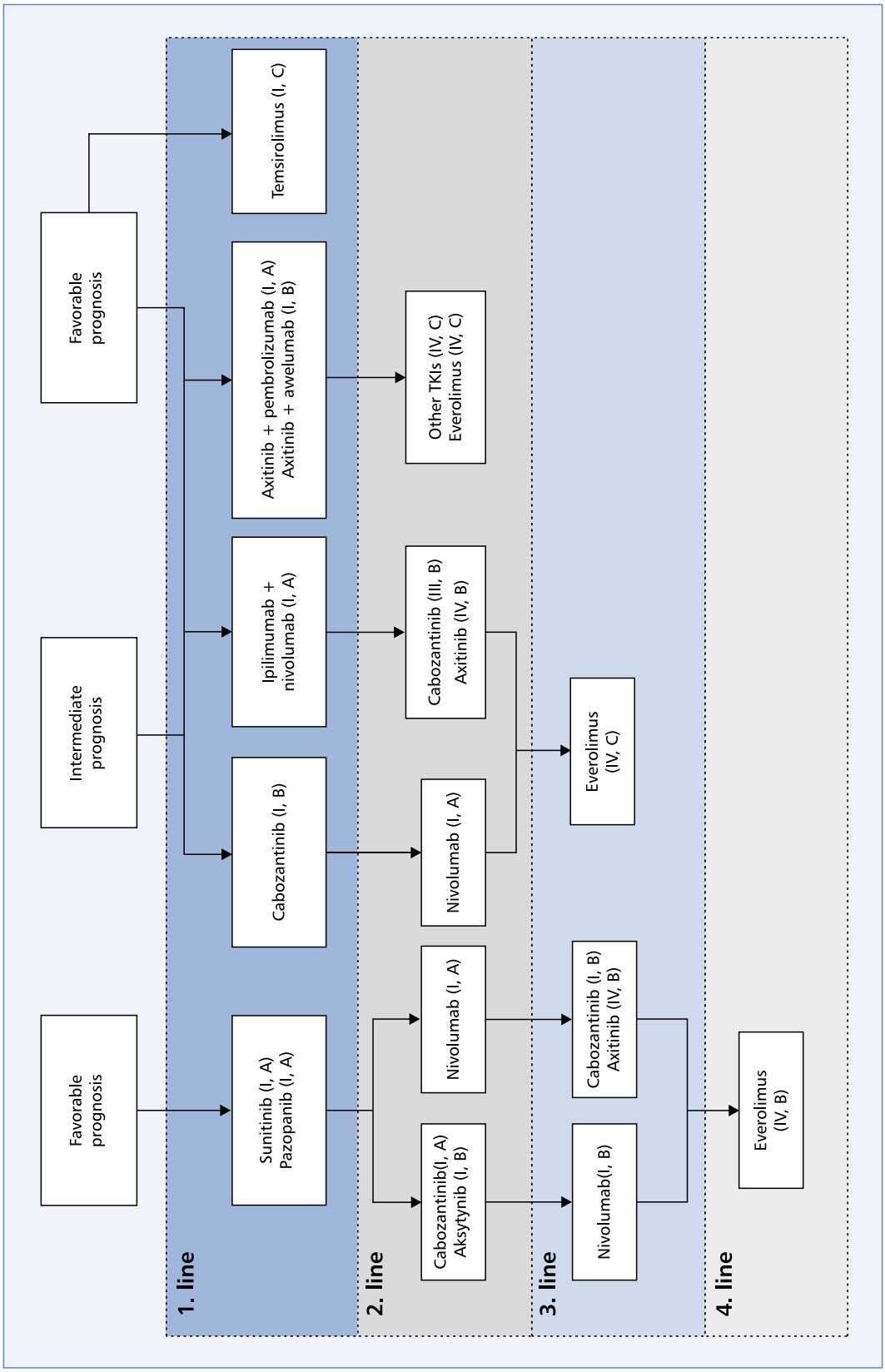


Figure 2. Systemic treatment of advanced ccRCC. TKI — tyrosine kinase inhibitors

within 4 weeks of randomization, and sunitinib was administered within 3-6 weeks after CN. In the control arm, sunitinib was started within 3 weeks of randomization. In the intention-to-treat (ITT) population, the median OS (18.4 months) was not significantly higher in the non-CN arm than in the CN arm (13.9 months), which met the assumed non-inferiority boundary. In turn, the SURTIME study compared the effects of immediate and deferred CN in RCC patients receiving sunitinib on 28-week PFS. In a population of 99 patients participating in this study, no significant differences in relation to the indicated parameter were found, however, a significant reduction in the relative risk of death was demonstrated in patients undergoing delayed CN (HR = 0.57; 95% CI 0.34–0.95) with a median of OS 32.4 months (deferred CN) and 15 months (immediate CN), respectively. Summarizing the results of the CARMENA and SURTIME studies, it can be unequivocally concluded that CN is not necessary in patients with metastatic RCC. However, a detailed analysis of the CARMENA study indicates that the adverse effect of CN on prognosis is particularly evident in the group of patients with ≥ 2 factors of poor prognosis according to IMDC scale [106]. In clinical practice, this means that taking into account the beneficial impact of CN on the immune system functions, manifested by spontaneous remissions or long-term disease stabilization [107, 108], CN is a valuable option in patients with good performance status and tumor-related symptoms or patients without massive dissemination and metastases-related symptoms.

7.3.3. Metastasectomy

Surgical treatment or radiosurgery/stereotaxic radiotherapy of metastatic lesions is an increasingly used procedure in the oncological treatment of patients with oligometastatic neoplastic disease. The basic assumption of such a procedure is to reduce the overall tumor mass, which should translate into improved prognosis. Additionally, in many cases, local treatment may delay the implementation or change of systemic treatment strategy. First mentions of a metastasectomy (MX) in RCC patients appeared over 80 years ago [109]. Although no randomized clinical trials have been conducted so far, it is assumed based on numerous observational studies that such a procedure may improve the prognosis. A systematic review of 56 studies showed that the median OS in patients undergoing MX ranged from 36 to 142 months compared to patients not undergoing MX, in whom it ranged from 8 to 27 months [110]. Performing MX was associated with a significant (more than 2-fold) reduction in the risk of death (HR 2.37; 95% CI 2.03–2.87). The most important prognostic factor was the radical resection of the metastases. Other favorable prognostic factors were: ECOG performance status 0-1, clear cell histology, ISUP grade 1–2, time from nephrectomy to relapse > 12 months, presence of metastases in the lungs, pancreas, liver, thyroid gland and adrenal glands. Patients with metastases limited to the lungs had the best prognosis [110]. Radical MX of lung metastases compared to non-radical management is associated with a significant prognosis improvement with median OS of 69 months (radical MX) *versus* 19 months (non-radical MX; P < 0.00001) and a 5-year CSS of 73,6% versus 19%, respectively [111]. Slightly worse results of surgical MX were obtained in cases of metastases of unusual or rare location (skin, muscles, salivary glands, breast, nasopharynx, stomach). In daily practice, it is difficult to define individual indications for surgical treatment of metastases. However, it can be assumed that before implementing systemic therapy, the patient should be carefully assessed in terms of the feasibility and benefits of MX.

Recommendations

— Active surveillance and deferring of systemic treatment may be considered in RCC patients with IMDC risk factor ≤ 1 and metastases in ≤ 2 organs (II, B).
— Cytoreductive nephrectomy should be considered in RCC patients with synchronous metastases and IMDC risk factor ≤ 1 (I, B).
— In RCC patients with synchronous metastases and IMDC risk factors ≥ 2 cytoreductive nephrectomy is contraindicated (I, B).
— Surgical metastasectomy or radiosurgery should be considered in RCC patients with oligometastatic dissemination (II, C).

7.3.4. Adjuvant systemic therapy

The appropriateness of adjuvant systemic therapy after radical surgery in RCC patients has been assessed in numerous phase III studies. The phase III PROTECT study enrolled patients after radical surgery due to pT2, high-grade renal cell carcinoma or stage ≥ pT3 or pN1 RCC. Patients were randomly assigned to receive either pazopanib or placebo for one year. In the primary endpoint analysis, no significant effect of pazopanib on the time to disease progression was demonstrated [112]. The ASSURE study evaluated the effect of sorafenib or sunitinib treatment on DFS versus placebo. The study included patients without distant metastases, after radical surgery in the pT1b G3–4 N0 stage (patients with N0 feature were allowed to participate based on imaging tests) and with higher local advancement with any grade and patients after radical surgery with metastatic lymph nodes. There were no significant differences in DFS [113]. The only positive study on adjuvant ccRCC treatment remains the phase III S-TRAC study, in which patients received sunitinib or placebo for one year. The study included 615 patients with pT3 tumor or lymph

node involvement after radical surgery. The median DFS was 6.8 years in the sunitinib group and 5.6 years in the placebo group, which translated into a significant reduction in the relative risk of disease recurrence or death by 24% (HR = 0.76; P = 0.03) [114]. In the summary of studies on the effectiveness of TKIs in adjuvant treatment, attention should be paid to the different inclusion criteria in individual studies. However, these differences and distinctness in imaging evaluation methodology make it difficult to fully explain the conflicting results of the ASSURE and S-TRAC studies. Due to these doubts, the European Medicines Agency, in relation to the significant toxicity of TKIs treatment, did not register any drug from this group for the adjuvant treatment of ccRCC.

7.3.5. First-line treatment for patients with clear cell RCC

7.3.5.1. VEGFR tyrosine kinase inhibitors

In patients with metastatic RCC, there are many systemic treatments with proven effectiveness. The evaluation of the studies is made difficult by the inconsistent application of prognostic criteria (earlier — MSKCC criteria, later — IMDC criteria) — both scales distinguish three prognostic groups, but due to slightly different criteria there are some differences in the characteristics of patients in individual studies. Moreover, the inclusion criteria differed in terms of histological type. Only the study on the efficacy of temsirolimus included the patients with neoplasms other than clear cell carcinoma; other studies required to indicate clear cell histology, but the volume of this component in relation to the whole tumor was different in individual studies. Additionally, in some studies, primary tumor resection was required, while in others only confirmation the histological diagnosis was sufficient. In view of the discussion on the role of nephrectomy in metastatic RCC, these differences make it difficult to compare the results of individual studies. Moreover, allowing the patients from comparative group to switch after disease progression to the group receiving an experimental drug (crossover) significantly complicates the inference regarding the impact of the new treatment on OS.

In older studies on the effectiveness of systemic treatment, the comparator was IFN-α — the first drug with proven effectiveness in the treatment of patients with metastatic RCC, but currently of historical importance. In current first-line studies, the comparator is usually sunitinib, the first drug to be more effective than IFN-α.

The Phase III AVOREN study compared the combination of bevacizumab and IFN-α with INF-α monotherapy in metastatic ccRCC. The median PFS increased from 5.4 months for IFN-α to 10.2 months for the bevacizumab plus IFN-α combination. The median OS in this study did not differ significantly for both groups of patients, however, in the AVOREN study, bevacizumab + IFN-α was allowed after progression to IFN-α [115].

Monotherapy with sunitinib in the first-line treatment of advanced RCC was compared with IFN-α in the phase III study, which enrolled patients after surgical treatment of a primary tumor with dominant clear cell histology from favorable and intermediate prognostic group according to the MSKCC scale. Overall survival was longer in patients treated with sunitinib (26.4 months) compared to those receiving IFN-α (21.8 months) despite sunitinib treatment in patients with progression in the group primary treated with IFN-α. The median PFS was 11 months for sunitinib compared with 5 months for IFN-α, which was also statistically significant. The objective response rates were 47% for sunitinib and 12% for IFN-α. All observed differences were statistically significant [116]. The results of this study ultimately resulted in the ccRCC treatment with IFN-α monotherapy being no longer recommended, and sunitinib becoming the first TKI used in first-line treatment. Another TKI used in the first-line treatment was pazopanib. This drug was compared with sunitinib in the non-inferiority phase III COMPARTZ study. This study demonstrated that pazopanib is not significantly inferior to sunitinib in terms of PFS and OS. The authors of the study raised the issue of better tolerance of pazopanib treatment [117], which to some extent was confirmed in the PISCES study, comparing patients' treatment preferences. Patients preferred pazopanib (70% *vs.* 22%) because of less symptomatic toxicity associated with this drug [118]. Pazopanib is approved in Europe for the first-line treatment of adult patients with advanced RCC and for the treatment of patients who have previously received cytokines for advanced RCC.

Tivozanib was compared with sorafenib in a phase III study in patients with advanced ccRCC. The comparator used — sorafenib — raises doubts because no phase III study has shown its superiority to IFN-α in first-line treatment in terms of efficacy. Although the median PFS after first-line treatment was significantly better for tivozanib than for sorafenib (12.7 months *vs*. 9.1 months), no significant differences in OS were observed [119]. It was surprising that the median OS was higher for sorafenib (29.3 months) than for tivozanib (28.8 months). Tivozanib is approved for the first-line treatment of patients with advanced RCC, but in Poland, this drug is not reimbursed.

In a phase III study comparing axitinib with sorafenib in first-line treatment in metastatic clear cell RCC, no significant difference in the median PFS between the treatment groups was shown — as a result, axitinib was not registered in this indication [120].

In the phase II CABOSUN study, which included 157 patients with advanced RCC with intermediate and high risk according to IMDC, cabozantinib and sunitinib were compared in first-line treatment. Cabozantinib increased median PFS by 3.2 months (8.6 *vs.* 5.3 months, respectively), which translated into a significant reduction in the relative risk of disease progression or death by 52% (HR = 0.48; 95% CI 0.31–0.74). The objective response and clinical benefit rates were 20% and 74%, respectively, for cabozantinib, compared to 9% and 47%, respectively, for sunitinib. Early disease progression occurred in 18% of patients treated with cabozantinib compared to 29% of patients treated with sunitinib. However, the CABOSUN study did not show an improvement in OS with cabozantinib versus sunitinib. Grade 3 or 4 adverse events rates were comparable for cabozantinib and sunitinib. Due to the limitations of the statistical analyzes in phase II study, the evidence is of lower quality and a benefit was only shown for PFS and objective responses [121].

7.3.5.2. mTOR kinase inhibitor

Temsirolimus — mammalian target of rapamycin (mTOR) serine-threonine kinase inhibitor was evaluated in a phase III study in patients with advanced RCC (also with histology other than ccRCC) with an unfavorable prognosis according to the MSKCC scale. Patients were randomized to three treatment arms: (i) temsirolimus monotherapy, (ii) IFN-α monotherapy, or (iii) temsirolimus plus IFN-α combination. Patients receiving temsirolimus achieved significantly better median OS and PFS than patients in the other arms. Median PFS and OS were 5.5 months, 4.7 months, and 3.1 months, and 10.9 months, 8.4 months, and 7.3 months for temsirolimus, IFN-α, and temsirolimus with IFN-α, respectively [122]. Based on this study, temsirolimus has been approved for first-line treatment in patients with advanced RCC with at least 3 risk factors according to MSKCC.

7.3.5.3. Checkpoint inhibitors

In the CheckMate 214 study, two-drug immunotherapy with immune checkpoint inhibitors (ICI): programmed death receptor 1 (PD-1) (nivolumab) and cytotoxic T cell antigen 4 (CTLA-4) (ipilimumab) was compared with sunitinib in patients with metastatic RCC containing a clear cell component. The study showed that immunotherapy is significantly more effective in patients with intermediate and unfavorable prognosis according to the IMDC scale (77% of participants in the study), and the subgroup analysis confirmed these results for both intermediate and unfavorable prognosis [123]. For patients with intermediate and unfavorable prognosis (considered together), median PFS was similar and accounted for 8.2 months (immunotherapy) and 8.4 months (sunitinib), but the use of immunotherapy resulted in a significant reduction of the risk of progression by 23% (HR = 0.77, 95% CI 0.65–0.90). In the unfavorable and intermediate prognostic population according to IMDC, the objective response rates were 42% and 27%, and the complete response rates were 9% and 1% for immunotherapy and sunitinib, respectively. The median OS in the immunotherapy arm was not reached, and in the sunitinib arm was 26.6 months, which translated into a significant reduction in the risk of death in patients with intermediate and poor prognosis by 34% (HR = 0.66; 95% CI 0.54–0.80). The quality of life in patients undergoing immunotherapy was significantly better than that in patients receiving sunitinib. The improvement in prognosis after immunotherapy was independent of programmed death-ligand 1 (PD-L1) expression [124]. The delay in registration of this treatment by the European Medicinal Agency was due to the unclear role of ipilimumab in combination with a PD-1 inhibitor and, according to the recommendation, a study is currently conducted that directly compares the value of nivolumab with or without ipilimumab. Ultimately, based on the study, nivolumab in combination with ipilimumab has been approved in Europe for the first-line treatment of advanced RCC in adult patients with intermediate or poor prognosis.

7.3.5.4. Checkpoint inhibitors in combination with kinase inhibitors

In the phase III Keynote-426 study, the combination of axitinib and pembrolizumab with sunitinib monotherapy was compared in the first-line treatment of patients with advanced ccRCC. The study showed that the estimated percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab/axitinib arm and 78.3% in the sunitinib arm. The corresponding estimates for the 18-month OS rate were 82.3% and 72.1%, respectively. Median OS was not reached in either group. The combination of pembrolizumab and axitinib was associated with a significant reduction in the relative risk of death by 47% compared with sunitinib (HR = 0.53; 95% CI 0.38–0.74). Median PFS was 15.1 months in the experimental group and 11.1 months in the sunitinib group, which translated into a significant reduction in the relative risk of disease progression by 31% (HR = 0.69; 95% CI 0.57–0.84). The benefits of pembrolizumab and axitinib in relation to OS and PFS were observed in all IMDC risk categories (however, only in the intermediate and unfavorable groups these differences were statistically significant), regardless of PD-L1 expression [125]. Based on this study, pembrolizumab in combination with axitinib has been approved for the first-line treatment of patients with advanced ccRCC.

In another phase III study, the effectiveness of axitinib in combination with avelumab in patients with metastatic RCC with a clear cell component was

compared with sunitinib in the first-line treatment. The median PFS was 13.8 months in the avelumab plus axitinib arm compared with 8.4 months in the sunitinib arm (hazard ratio of progression or death 0.69). Among patients in the overall population with high, intermediate and low risk according to IMDC who received avelumab with axitinib, 68.1%, 51.3%, and 30.6%, respectively, achieved objective responses compared with 37.5%, 25.4 % and 11.3% of patients who received sunitinib. There are no data on OS in this study [126]. In Europe, avelumab is approved in combination with axitinib for the first-line treatment of adult patients with advanced RCC.

Recommendations

— In patients after radical surgery due to renal cell carcinoma, systemic adjuvant therapy is not recommended (I, A).
— Treatment with bevacizumab in combination with interferon-α does not improve overall survival compared to interferon- α alone and is not the treatment of choice (I, C).
— Sunitinib and pazopanib are drugs of comparable activity in advanced renal cell carcinoma patients with favorable and intermediate prognosis (I, A).
— Sunitinib and pazopanib have proven value, but in some patients, immunotherapy or immunotherapy in combination with kinase inhibitors should be considered first (I, B).
— Axitinib monotherapy should not be used in the first-line treatment of patients with advanced renal cell carcinoma (I, A).
— Cabozantinib is more active than sunitinib in the treatment of RCC patients in intermediate and unfavorable prognosis in terms of progression-free survival, but an effect on overall survival has not been proven (I, B).
— The use of cabozantinib should be considered in patients with clear cell renal cell carcinoma, intermediate and poor prognosis, and with contraindications to checkpoint inhibitor-based therapies, especially if a rapid response is required (I, B).
— Temsirolimus improves the prognosis of RCC patients in poor prognosis group but compared to other treatments the clinical benefit is very limited (I, C).
— The use of the combination of nivolumab and ipilimumab in patients with renal cell carcinoma in intermediate and poor prognosis groups significantly improves the prognosis in terms of progression-free and overall survival compared to sunitinib (I, A).
— The combination of pembrolizumab with axitinib in relation to sunitinib in patients with RCC significantly improves the prognosis in terms of progression-free and overall survival, while being associated with a very low risk of lack of benefit from the treatment (I, A).

7.3.6. Second-line treatment for patients with clear cell RCC

Historically, second-line treatment has only been considered in patients with advanced ccRCC after the failure of cytokines (e.g. IFN-α). Drugs with significant activity compared to placebo on PFS — but not OS — were sorafenib, pazopanib and axitinib. It should be remembered that cytokines, which are no longer used in practice in RCC patients, have a completely different mechanism of action than ICI. Therefore, the extrapolation of data regarding TKIs activity after cytokines to their usefulness after ICIs is unjustified.

7.3.6.1. Treatment after tyrosine kinase inhibitors

The first drug with proven activity in patients after failure of TKI treatment was everolimus, which is an mTOR kinase inhibitor. In the phase III RECORD-1 study, in patients who failed therapy with sunitinib and/or sorafenib, everolimus significantly increased the median PFS by 3 months (4.9 months versus 1.9 months) compared with placebo, reducing the relative risk of progression by 67% (HR = 0.33; P < 0.001) [127]. In this study, however, no significant benefit of everolimus treatment was observed in relation to OS (the study assumed the administration of active drug after progression on placebo). Although the drug was associated with side effects, no significant differences in terms of patients' quality of life were found. Axitinib was the first TKI with marked second-line treatment activity following the failure of TKI therapy. In the phase III study, axitinib significantly increased median PFS from 5.7 months to 8.3 months compared to sorafenib, which translated into a 35% reduction in the relative risk of progression (HR = 0.65; P < 0.0001). However, no significant differences were observed with regard to OS (median 19.2 months and 20.1 months, respectively) [128].

Significant progress in the treatment of second-line RCC patients occurred with the advent of nivolumab and cabozantinib. In parallel clinical trials, both drugs for the first time in history significantly increased OS in patients with ccRCC after failure of TKI therapy compared to the active comparator, everolimus [129, 130]. In the Check-Mate 025 study, the use of nivolumab versus everolimus resulted in a significant reduction the risk of death by 27% (HR = 0.73; 95% CI 0.62–0.85) with no significant effect on PFS (HR = 0.88; P = 0.11). Nivolumab also provides a clinical benefit in 60% of patients with an objective response rate of 26%, however, in over one-third of patients (35%) no benefit was observed from the use of nivolumab (disease progression at the first assessment) [130]. Nivolumab caused typical side effects related to the activation of autoimmune mechanisms, but the quality of life of patients was better compared to patients taking everolimus [131].

In turn, the use of cabozantinib in the METEOR study compared to everolimus was associated with a significant reduction the risk of both death — by 30% (HR = 0.70; 95% CI 0.58–0.85) and progression — by 42% (HR = 0.58; 95% CI 0.45–0.75) [129]. Cabozantinib led to clinical benefit in 87% of patients with an objective response rate of 24%, and only less than 10% of patients did not benefit from the treatment. Clinically significant side effects of cabozantinib were mainly diarrheas, which were more frequent and severe than for other TKIs. On the other hand, the profile of other side effects can be considered typical for this drug class. Despite the higher incidence of adverse events in the arm receiving cabozantinib, the quality of life of patients treated with this drug did not differ significantly in relation to everolimus. Additionally, the time to significant deterioration in the quality of life of patients was significantly longer for cabozantinib [132].

Currently, nivolumab and cabozantinib are the drugs of choice for the second-line treatment of patients with advanced ccRCC. Both drugs significantly improve the prognosis, and the drug should be selected carefully with regard to potential benefits and risks. The subgroup analyzes in the study with nivolumab found that the drug is active in intermediate and poor prognosis group according to IMDC scale. As nivolumab did not show a significant effect on PFS, and more than 30% of patients will not benefit from its use, it is the optimal choice in patients without cachexia, asymptomatic or poorly symptomatic, without the risk of organ crisis, and not receiving antibiotic therapy within the preceding month. On the other hand, cabozantinib seems to be a better option for second-line treatment in patients with favorable and intermediate prognosis according to IMDC scale, with cancer-related symptoms and advanced disease, and requiring a quick and profound response to treatment.

7.3.6.2. Treatment after immunotherapy with nivolumab and ipilimumab

Due to the lack of prospective clinical trials assessing the effectiveness of systemic treatment of patients receiving modern immunotherapy based on the combination of ipilimumab and nivolumab, the use of cabozantinib seems to be the optimal management. Retrospective analyzes of the METEOR study showed that cabozantinib was more active than everolimus in patients receiving prior-line immunotherapy based on ICI.

7.3.6.3. Treatment after immunotherapy combined with a tyrosine kinase inhibitor

There is currently no evidence of the effectiveness of any systemic therapy in RCC patients after failure of ICI and TKI containing therapy (e.g. pembrolizumab and axitinib). Therefore, the procedure of choice is to enroll patients previously receiving such treatment for clinical trials. If impossible, the use of other TKIs (especially cabozantinib, if not used as part of combination therapy) or everolimus could be considered.

Recommendations

— Cabozantinib and nivolumab are the drugs of choice in the second-line treatment of patients with clear cell renal cell carcinoma (I, A).
— Patients who received a multi-kinase inhibitor (sunitinib, pazopanib) in the first line should receive cabozantinib (I, A) or nivolumab in the second line (I, A).
— Patients who received nivolumab with ipilimumab in the first line should receive cabozantinib (III, B) or axitinib in the second line (IV, B).
— In patients who received a combination of immunotherapy and a tyrosine kinase inhibitor in the first line, the use of another TKI (if not used as part of combination therapy) or everolimus may be considered in the second line (IV, C).
— The use of cabozantinib in the second-line treatment is associated with the lowest risk of treatment failure (I, C).

7.3.7. Third-line treatment for patients with clear cell RCC

Third-line treatment should be considered in patients in good performance status and with preserved organ capacity, with no contraindications to systemic treatment. This procedure prolongs the OS [133, 134]. The benefits of fourth and subsequent lines of treatment are limited [135–137] and should only be considered in selected patients. The choice of the appropriate therapeutic strategy depends on the clinical situation and the type and tolerability of previous treatment. Including patients in clinical trials is preferable option.

7.3.7.1. Molecularly targeted drugs

In the phase III study, which compared the efficacy of cabozantinib and everolimus after failure of anti-angiogenic treatment, 29% of patients had previously received two or more treatment lines (including ICI in nearly 5%). In this group, the efficacy of cabozantinib was significantly higher — the reduction in the relative risk of progression was 49% (HR 0.51; 0.35–0.74) [129]. Cabozantinib activity in the third and subsequent lines of treatment, including after previous ICI use, has also been demonstrated in retrospective studies [138, 139]. On the other hand, the GOLD study confirmed the activity of sorafenib in the third-line treatment in the population of patients previously treated with TKI-VEGFR and everolimus. The use of sorafenib was associated with a reduction in tumor mass in 46% of patients, and objective response was observed in 4% of patients [140].

In the population included in the aforementioned RECORD-1 study, 26% of patients had previously received two lines of TKI-VEGFR treatment (sunitinib and sorafenib) [127]. Everolimus was associated with an increase in PFS compared to placebo (median 4 months and 1.8 months, respectively). However, considering the lower activity of everolimus in relation to cabozantinib and nivolumab, it seems rational to use it in patients after failure of sequential therapy with the use of the above-mentioned drugs or when the above-mentioned drugs cannot be used.

7.3.7.2. Immunotherapy

Currently, nivolumab is the only ICI approved for the treatment of patients with advanced RCC after failure of prior therapy. In the already mentioned pivotal study, Check-Mate 025, 28% of patients received nivolumab in third-line treatment [130]. The relative risk of death in this group decreased by 11% (HR 0.89; 95% CI 0.61–1.29), while a post-hoc analysis showed a reduction in the risk of death by 35% (HR 0,65; 95% CI 0.43–0.99) [141].

In fourth or subsequent treatment line, the decision regarding treatment strategy should be made on an individual basis, taking into account prior management, response to treatment, and tolerability (including persistent complications of prior treatment). It is acceptable to use everolimus, TKI-VEGFR other than previously used or re-use of TKI-VEGFR, if such treatment was effective in the past. Re-use of immunotherapy is not recommended.

Recommendations

— Third-line treatment should be considered in patients with metastatic renal cell carcinoma in good performance status, with no contraindications to systemic therapy (III, A).
— The decision to use the fourth or subsequent treatment lines should be made on an individual basis (IV, C).
— Patients with metastatic renal cell carcinoma after sequential use of multi-kinase inhibitors should receive nivolumab in third-line treatment (I, B).
— Patients with metastatic renal cell carcinoma after sequential treatment with a tyrosine kinase inhibitor and nivolumab should receive cabozantinib in third-line treatment (I, B).
— In patients with metastatic renal cell carcinoma, sorafenib (I, B), cabozantinib (IV, B) or nivolumab may be used in third-line treatment after treatment with a multi-kinase inhibitor and everolimus.
— Patients with metastatic renal cell carcinoma after sequential treatment with ipilimumab plus nivolumab, followed by a multi-kinase inhibitor, should receive cabozantinib in third-line treatment (IV, B).
— Patients with metastatic renal cell carcinoma after sequential treatment with ipilimumab plus nivolumab followed by cabozantinib should receive everolimus in third-line treatment (IV, C).
— Patients with metastatic clear cell renal cell carcinoma after sequential treatment with a multi-kinase inhibitor combined with immunotherapy followed by cabozantinib should receive everolimus in third-line treatment (IV, C).

7.3.8. Treatment for patients with advanced non-clear cell RCC

Data on the effectiveness of systemic treatment of advanced RCCs other than clear cell histology (non-ccRCC) are limited. Due to their relatively rare occurrence, their representation in the populations of patients included in prospective phase III clinical trials was small or the protocols completely excluded the possibility of their recruitment. For this reason, in non-ccRCC cases, it is advisable to qualify patients for controlled clinical trials. Current knowledge about the efficacy of available therapeutic options in the treatment of non-ccRCC is based primarily on the results of small prospective studies or subgroup analyzes in larger studies that generally assessed the effectiveness of TKI or serine-threonine kinase inhibitors [142, 143].

The greatest amount of data in the non-ccRCC patient population relates to the use of sunitinib. Due to the design of these studies and their statistical assumptions, the obtained results could not provide unambiguous answers regarding the efficacy of the tested drugs in patients with non-ccRCC; a trend suggesting the advantage of sunitinib over everolimus was observed. These data were confirmed in further expanded access studies, subsequent retrospective analyzes, and subgroup analysis in the registration process for temsirolimus.

The available data also suggest the effectiveness of other molecularly targeted drugs (everolimus, sorafenib, pazopanib, and temsirolimus), with most studies including only patients with papillary or chromophobe RCC. Recently published results of prospective clinical trials using ICI suggests the clinical activity of this form of immunotherapy in patients with non-ccRCC previously receiving another form of treatment.

Figure 3 presented the algorithm of first-line systemic treatment developed on the basis of the above-mentioned studies and compliant with the ESMO recommendations.

Currently, there are no data based on which the recommendations regarding second-line systemic treatment of patients with non-ccRCC could be developed. Nevertheless, for the most common papillary RCC, the use of drugs as for ccRCC is acceptable.

cMET inhibitors have shown activity in papillary tumors with a confirmed mutation or amplification

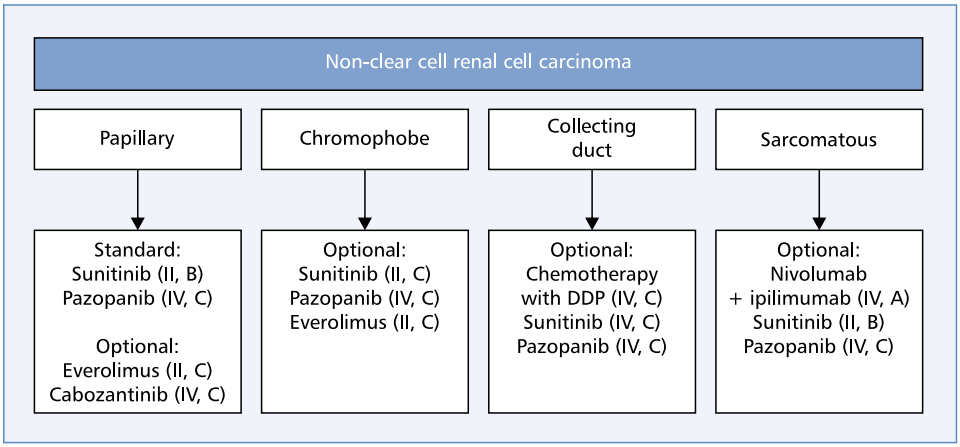


Figure 3. Management of patients with advanced non-clear cell renal cell carcinoma

in the *cMET* gene [144]. In turn, crizotinib and other cMET inhibitors may be an important alternative to classic TKIs with anti-angiogenic activity (anti-VEGF).

Some patients with chromophobe RCC may benefit from treatment with mTOR inhibitors, as it has been shown that mutations in chromosome 7 lead to loss of the functional folliculin gene and, secondly, to increased activity of the mTOR complex.

The available data suggest the presence of excessive inflammatory infiltration within tumors with sarcomatous component, being a histological feature associated with poor prognosis. Renal cell carcinomas with a sarcomatous component appear susceptible to ICI therapy. In this situation, therapeutic strategies such as the combination of nivolumab with ipilimumab or pembrolizumab with axitinib should be considered as an option of choice [124, 125].

Due to the fact that the biology of RCC originating from collective ducts and medullary renal cell carcinomas is very similar to the biology of aggressive forms of cancers originating from transitional epithelial cells, classical chemotherapy is used in patients with these tumor types (e.g. MVAC regimen with cisplatin gemcitabine) [145–147]. Unfortunately, treatment outcomes for these RCC subtypes remain unsatisfactory, with objective response rates below 30%. There is also no direct comparison of the individual regimens in these indications [148, 149]. However, scant data on the effectiveness of immunotherapy in this group of patients suggest a negligible clinical benefit of the available therapeutic options [148].

7.3.9. Anti-osteolytic drugs

The use of zoledronic acid in RCC patients with multiple bone metastases is a palliative approach that reduces the incidence of skeletal complications and prolongs the time their onset without significant affecting OS. Renal function monitoring is essential when taking zoledronic acid. Administration of zoledronic acid may be considered in patients with metastatic RCC with longer survival expected. A comparable value was demonstrated for denosumab.

7.4. Radiotherapy

Renal cell carcinoma is considered to be radioresistant and radiotherapy is not a routinely recommended treatment.

Preoperative radiotherapy

The results of the only prospective studies of the use of preoperative radiotherapy in the treatment of primary operable RCC were published in the 1970s. In both of them, low total doses of radiation were administered: 30 Gy in 15 fractions of 2 Gy each or 33 Gy in 15 fractions of 2.2 Gy each using standard radiotherapy techniques. There has been no evidence of improvement in 5-year survival compared to standalone nephrectomy [150]. Currently, such a strategy is not recommended.

Intraoperative radiotherapy

There are only single reports of intraoperative radiotherapy in RCC patients, mainly locally advanced or with local tumor recurrence. A study involving the largest group of 98 patients showed results comparable to standalone nephrectomy in cancer-related and asymptomatic survival [151]. Due to the scarcity of data, intraoperative radiotherapy is not recommended and should only be used in clinical trials.

Postoperative radiotherapy

The role of radiotherapy in the adjuvant treatment of patients with locally not advanced RCC after nephrectomy has not been clearly established. The experiences from the 1970s and 1980s showed that the treatment results deteriorated after adjuvant radiotherapy [152].

However, studies from that period are vitiated by methodological errors (e.g. small groups of incorrectly selected patients) and used radiotherapy techniques that did not allow for effective dose reduction in critical organs — this was a likely cause of higher toxicity of treatment and a lower 5-year survival rate in patients undergoing radiotherapy compared to the group undergoing surgery alone. Later studies also failed to confirm the value of adjuvant radiotherapy [153]. A meta-analysis of data from seven studies (two prospective and five retrospectives) showed an increase in local cure rates after postoperative radiotherapy but with no effect on OS [154]. Coming to conclusion, postoperative radiotherapy may be considered in patients with a high risk of local recurrence, mainly with positive surgical margins and metastases to regional lymph nodes. However, it should only be used in clinical trials until its value is confirmed in randomized trials using modern radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT).

Standalone radiotherapy

The opinion about RCC radioresistance may be wrong because the use of modern radiotherapy techniques allows the administration of high radiation doses in one (stereotactic radiosurgery, SRS) or several fractions (stereotactic body radiotherapy, SBRT). Therefore, it allows also to overcome radioresistance while reducing the risk of damage to healthy tissues. This procedure, apart from direct destruction of cancer cells by activation of the ceramide signaling pathway, may also induce the so-called abscopal effect. Released products of tumor cell lysis become visible to the immune system, causing its "unmasking" and effective destruction of cancer cells. This effect can be enhanced by the simultaneous use of molecularly targeted therapies. The experience regarding stereotactic radiotherapy of RCC brain metastases, showing local control improvement, has become the basis for using this method in patients with locally advanced RCC who are not eligible for nephrectomy [155]. Several prospective studies have shown promising 2-year local cure rates of over 90% with acceptable toxicity. The lack of evidence from randomized trials does not allow to determine neither the optimal dose of radiation nor the method of fractionation or to recommend such a treatment in routine clinical practice. Primary RCC radiosurgery and stereotactic radiotherapy should only be used in clinical trials.

Radiotherapy in oligometastatic disease

Many retrospective studies show improved treatment outcomes in patients with RCC after primary nephrectomy who underwent metastasectomy, radiosurgery, or stereotactic radiotherapy after oligometastatic disease recurrence [156, 157]. For both intracranial and extracranial metastases, local control rates account for up to 90%, and the median OS is 7 to 26 months. In prospective randomized studies, the effect of tumor bed postoperative radiosurgery on the reduction of local recurrence risk in patients with brain metastases after complete metastasectomy compared to observation was confirmed. Additionally, it has been shown reduced cognitive impairment compared with total brain irradiation [158, 159].

Radiosurgery and stereotactic radiotherapy are recommended treatment methods in patients with RCC brain metastases.

Achieving control of metastatic lesions in the brain with radiotherapy is indicated before starting anti-angiogenic treatment.

Palliative radiotherapy

Numerous reports indicate that radiotherapy is an effective method of controlling symptoms related to local progression or dissemination of RCC. It enables the reduction of pain caused by spreading to the bone or infiltration of nerve plexuses and managing the symptoms associated with multiple metastases in the brain. The administered total doses and applied fractionation methods depend mainly on patient's performance status, location of metastases and the volume of irradiated tissues. Response to radiotherapy is achieved in more than 50% of patients [160, 161]. Radiotherapy is the method recommended for symptom control in patients with metastatic RCC.

Recommendations

— Stereotactic radiotherapy is the recommended treatment option in patients with renal cell carcinoma with metastases to the central nervous system (II, A).
— Radiotherapy is a valuable therapeutic option in the symptomatic treatment of patients with metastatic renal cell carcinoma (III, B).
— Stereotactic radiotherapy is an alternative to surgical metastasectomy (III, B).

8. Follow-up after treatment completion

The objectives of observation of RCC patients after the completion of surgical treatment include monitoring and/or diagnosing the nature of postoperative complications and dysfunction, as well as the detection of local recurrences or contralateral RCC and distant metastases.

There is no consensus on the post-treatment monitoring principles in RCC patients. There are also no prospective studies analyzing the prognosis of patients depending on the time of relapse diagnosis. Intensive surveillance with the use of imaging tests is not necessary

in all patients, but follow-up after treatment completion is warranted (especially in patients receiving treatment with radical intent). Large long-term cohort observational studies are available [162, 163]. They demonstrated a benefit in terms of survival in patients undergoing a structured observation protocol compared to unobserved patients [164]. The long-term results after surgery for low-stage tumors (T1a) are almost always excellent. Therefore, a gradation in the intensity of monitoring based on the risk of relapse and/or disease generalization is warranted. The risk should be determined based on the UCLA Integrated Staging System (UISS) for Renal Cell Carcinoma [165, 166] (Table 9). Therefore, personalized and risk-based monitoring after treatment completion with regular imaging examinations is currently recommended (Table 10).

CT is most commonly used for oncological monitoring, and ultrasound is used only in some cases. PET-CT, PET-MR and scintigraphy are not routinely recommended. In low-risk patients, follow-up should take into account the expected benefits and exposure to ionizing radiation. MR imaging can be used to reduce

Table 9. UCLA Integrated Staging System (UISS) for renal cell carcinoma

Localized disease (any T, N0, M0)			
Primary tumor (T)	**Differentiation**	**ECOG performance status**	**Risk**
T1	Fuhrman 1–2	0	Low
		≥ 1	Intermediate
	Fuhrman 3–4	Any	
T2	Any	Any	
T3	Fuhrman 1	0	
		≥ 1	
	Fuhrman > 1	0	
		≥ 1	High
Metastases (N1, N2 or M1)			
N1M0	Any	Any	Low
N2M0/M1	Fuhrman 1	0	
		≥ 1	Intermediate
	Fuhrman 2	0	Low
		≥ 1	Intermediate
	Fuhrman 3	Any	
	Fuhrman 4	0	
		≥ 1	High
Prognosis			
Stage	**Risk**	**5-year survival rate**	
Localized disease	Low	91.1%	
	Intermediate	80.4%	
	High	54.7%	
Metastatic disease	Low	32%	
	Intermediate	19.5%	
	High	0%	

Table 10. Schedule of follow-up of RCC patients after completion of surgical treatment

Risk profile	**Observation**				
6 months	**1 year**	**2 years**	**3 years**	**> 3 years**	
Low	US	CT	US	CT	CT every 2 years, patient education about the risk of recurrence accounting for app. 10%
Intermediate/high	CT	CT	CT	CT	CT every 2 years

CT — computed tomography of chest and abdomen, alternatively abdominal imaging with the use of magnetic resonance imaging; US — ultrasound of abdominal cavity, kidney/kidneys and/or postoperative tumor bed

radiation exposure. Chest, abdominal and pelvic CT scans should be performed in patients from moderate or high-risk groups.

Post-treatment follow-up should also include monitoring of renal function, including the measurement of serum creatinine concentration along with GFR. Repeated and long-term monitoring of upper urinary tract functioning is indicated in the presence of renal dysfunction both before and after surgery [167]. Regular evaluation of cardiovascular risk factors is also recommended.

In patients undergoing partial nephrectomy, local disease recurrence is rare, but it is important to recognize it early, due to the potential qualification for radical re-treatment [168, 169]. Relapse of the underlying disease in the second kidney is also rare (1–2%), and it may occur late (median 5–6 years) and may be associated with positive surgical margins, multifocal lesions, and higher histopathological grade [170]. In addition to early detection of local recurrence, proper monitoring of patients with RCC after treatment is also aimed at early detection of distant metastases. In late-diagnosed metastatic disease, local treatment options are usually limited (surgical metastasectomy, stereotactic radiotherapy), which are the treatment of choice in oligometastatic disease. Furthermore, detecting relapse/cancer generalization with a low total tumor mass can increase the effectiveness of systemic therapy.

Controversies concern the optimal duration of observations. According to some authors, continuing imaging tests beyond 5 years is cost-ineffective; however, late metastases occur more often as single lesions, which justifies an aggressive treatment approach with curative intent. In turn, in patients with newly diagnosed tumor in contralateral kidney, the detection of the tumor at an early stage often enables nephron-sparing surgery. For tumors <4 cm, there is no difference between partial and radical nephrectomy in relation to recurrence during follow-up [171]. Currently, various nomograms are available to estimate the likelihood of cancer recurrence, metastasis development, or later death, which can be used in everyday clinical practice [172, 173].

Recommendations

— The strategy for monitoring RCC patients after treatment completion should be based on the relapse risk (III, A).
— Patients should be closely monitored after NSS with a positive surgical margin or if the tumor size exceeds 7 cm (III, C).

Conflict of interest

PW — speaker, scientific advisor, presenter - Roche, Ipsen, Pfizer, Novartis, MSD, BMS, Merck

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Carcinoma of the anal canal and anal margin

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Key words: anal canal carcinoma, anal margin carcinoma, diagnosis, treatment, follow-up, recommendations

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According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. *The quality of scientific evidence*
   I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-randomizedcohort studies)
   III — Scientific evidence obtained from retrospective observational studies or case-control studies
   IV — Scientific evidence obtained from clinical experiences and/or experts, opinions
2. *Category of recommendations*
   A — Indications confirmed unambiguously and absolutely useful in clinical practice
   B — Indications probable and potentially useful indications in clinical practice
   C — Indications determined individually

Translation: dr n. med. Dariusz Stencel
Oncology in Clinical Practice 2020, Vol. 16, No. 6, 331–337. DOI: 10.5603/OCP.2020.0036, copyright © 2020 Via Medica, ISSN 2450–1654

Epidemiology

Anal canal and anal margin cancers are rare, accounting for 1–2% of all gastrointestinal (GI) cancers. In 2017, there were 286 newly diagnosed cases in Poland [1]. This type of GI cancers is more frequent in women than in men and the age of onset is usually 60–65 years. As anal canal and anal margin cancers are different clinical entities with different treatments they will be separately discussed. In doubtful cases, when the tumor infiltrates both the skin of the anal margin and the anal canal, the diagnosis is determined by the location of the main tumor mass.

Etiopathogenesis

The risk factors of the anal canal and anal margin cancers include human papilloma virus (HPV) and human immunodeficiency virus (HIV) infection, sexual habits (passive anal intercourses), previous cervical cancer and immunosuppressive treatment after organ transplantation. HPV infection is detected in 84% of patients and therefore is considered to be the most important. Anal marginal cancer may arise from condylomas.

Anal margin carcinoma is a skin cancer that occurs within 5 cm from the anal verge. The anal canal extends 3–5 cm from the anal verge to the superior border of the puborectalis muscle, palpable *per rectum*, where it connects to the rectum. The anal margin is lined with multi-layered squamous keratinizing epithelium, and the initial segment of the anal canal is lined with multi-layered squamous non-keratinizing epithelium. The pectinate (dentate) line is the upper border of the anal canal. Above this line, the transitional epithelium begins which passes without a clear border into the typical, single-layered, cylindrical intestinal epithelium. Anal canal cancer most often arises from the transitional epithelium and therefore is usually located in the upper part of the anal canal. Sometimes, due to the lack of anatomical barriers, the tumor spreads towards the rectum, where its main mass could be palpable. If squamous cell carcinoma is detected in histological evaluation, the anal canal carcinoma should be diagnosed, rather than rectal cancer. Rectal squamous cell carcinomas are very rare and should be diagnosed only when the tumor does not connect to the superior border of the anal canal.

The lymphatic drainage pathways of anal margin skin include the inguinal, external iliac, and common iliac lymph nodes.

Lymphatic flow from anal canal goes in three principal directions:

— cephalad, initially through the perianal lymph nodes in the mesorectum, then to the lymph nodes located along the course of the upper rectal and lower mesenteric vessels;
— lateral, along the course of the middle rectal vessels to the internal iliac lymph nodes, then the common iliac and periaortic lymph nodes;
— to the inguinal, then to the external iliac and finally to the common iliac lymph nodes.

Pathology

The most common histological type of anal canal neoplasms is squamous cell carcinoma (SCC), which may arise from the so-called high grade anal intraepithelial neoplasia (HG-AIN). Previously diagnosed types of squamous cell carcinoma — carcinoma basaloides, transitionale, cloacogenes, and keratodes — are now grouped under the common name of squamous cell carcinoma because their differentiation is not clinically relevant (no difference in prognosis by cancer subtype for the same stage and identical treatment). A type of squamous cell carcinoma is verrucous carcinoma, a special form of which is malignant giant genital warts (GGWs) (the so-called Buschke-Loewenstein tumor).

Anal canal adenocarcinoma is diagnosed in 5–10% of patients. Melanoma is much less common.

The most common histological type of anal margin cancer is squamous cell carcinoma. Less common are basal cell carcinoma, extramammary Paget disease or Bowen's disease (currently perianal squamous intraepithelial neoplasia, PSIN).

Diagnosis — general principles

Rectal bleeding is the most common symptom. This is followed by pain and fecal incontinence and a visible or palpable tumor in the anus or groin area. Signs and symptoms of high tumor stage include pain in the pelvic area, symptoms of partial obstruction, rectovaginal fistula, the involvement of the ischioanal fossa and buttock skin fistulas. Metastases to the regional lymph nodes (inguinal and pelvic) occur in approximately 30% of patients, and synchronous distant metastases in approximately 10% of patients. Incorrect diagnosis of varicose veins, anal fissure or abscess, quite frequent in the first period of the disease leads to proper treatment delay.

Staging

The clinical assessment is based on a detailed *per rectum* examination and — performed under anesthesia — anoscopy with taking a specimen for histological examination. In women, *per vaginam* examination and two-handed examination (*per rectum* and *per vaginam*) are mandatory and performed in order to assess the rectovaginal septum and infiltration of the mucosa.

Description of *per rectum* examination, necessary when planning radiotherapy (RTH) to determine gross tumor volume (GTV), should include the assessment of the distance of lower and upper tumor edge from anal margin, as well as the length of the rectal involvement above the upper border of the anal canal. The anal canal wall involved, the percentage of circumference involved, and the degree of tumor mobility should be determined. Description of *per rectum* examination should also include the assessment of the mesorectal lymph nodes. They can be palpable through the unchanged rectal mucosa in the form of hard nodules, which proves their metastatic nature. The description of *per vaginam* examination should include the condition of the vaginal mucosa — when it is involved, the patient should be informed about the risk of rectovaginal fistula development after or during treatment. Careful diagnostics of the inguinal lymph nodes is essential, which is important for precise RTH planning. Histological verification is not necessary in the case of enlarged inguinal lymph nodes if clinical examination indicates their metastatic nature. In doubtful cases, a fine-needle aspiration biopsy is performed.

The diagnostic tests necessary for the diagnosis and staging of anal canal and anal margin cancer are presented in Table 1. Colonoscopy is not necessary as the lesions in the colon are not related to anal canal cancer. Table 2 presents the staging of anal canal cancer according to TNM classification [2]. It applies both to anal canal and anal margin cancer [3].

Treatment of anal canal squamous cell carcinoma (SCC)

The treatment of choice for anal canal squamous cell carcinoma is concurrent radical chemoradiotherapy (CRTH), which is indicated even in more locally advanced cases (II, A). Generally, patients with HIV do not require the modifications of the treatment regimens listed below. CRTH should also be administered in elderly patients with use of standard doses of radiotherapy and irradiated volumes as well as the regimen of cytotoxic treatment.

Principles of radiation therapy

According to the patient's general condition (PS, performance status), radiotherapy is combined with chemotherapy (CTH). Two atlases detailing the contouring principles have been published so far [4, 5]. Additionally, useful information on the practical aspects of contouring is provided in the publication on the pelvic

Table 1. Diagnostic tests essential to diagnose and stage anal canal and anal margin cancer

Diagnostic tests	The most important information
Anoscopy with taking a sample for histological examination	Assessment of tumor location and extent Histological verification of the tumor — Excision biopsy should be avoided as healing may prolong the time to initiate causal treatment
High-resolution MRI of the pelvis	Local advancement assessment Necessary for RTH planning, mainly for GTV contouring — Pelvic CT scan is not sufficient as small anal canal tumors are not visible
Abdominal and chest CT	Exclusion of metastatic changes Necessary before treatment in all patients — Chest X-ray instead of CT is allowed
PET-CT (if available)	Improves the effectiveness in detecting metastases to regional lymph nodes Facilitates contouring of the primary lesion Is not strictly necessary
Blood tests	Complete blood count Biochemical panel The clinical usefulness of squamous cell carcinoma antigen (SCCAg) has not been proven
Assessment of the presence of anti-HIV antibodies	Exclusion of active infection
Gynecological examination	Collection of material from the cervix for cytological examination — HPV — a common etiological factor in the development of anal canal, cervical and vaginal cancers

GTV — gross tumor volume; HIV — human immunodeficiency virus; HPV — human papilloma virus; CT — computed tomography; MRI — magnetic resonance imaging; PET-CT — positron emission tomography-computed tomography

Table 2. Anal canal cancer staging according to TNM classification (8th edition, 2017) [2]

T	Primary tumor
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II–III, high-grade anal intraepithelial neoplasia)
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s) (e.g., vagina, urethra, bladder)
N	**Regional lymph nodes**
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes
M	**Distant metastasis**
M0	No distant metastasis
M1	distant metastasis
Clinical stages	
0	TisN0M0
I	T1N0M0
IIA	T2N0M0
IIB	T3N0M0
IIIA	T1-2N1M0
IIIB	T4N0M0
IIIC	T3-4N1M0
IV	Any T, Any N, M1

lymph nodes location [6]. Basic information is provided below. Intensity-modulated radiation therapy (IMRT) or its arc variant (V-MAT, volumetric modulated arc therapy) should be routinely used [7]. This allows for the reduction of acute toxicity, mainly in the perineal skin area, therefore a break in irradiation caused by skin radiation reaction is currently very rare. Studies have shown that interruptions in treatment reduce the effectiveness of local radiotherapy, so they should be avoided or shortened whenever possible [8]. Depending on the stage the most frequently used doses are 50–60 Gy in fractionated doses of 1.8 or 2 Gy. The use of irradiation doses higher than 60 Gy does not improve treatment outcomes [9]. The traditional and best-documented regimen is two-stage irradiation. Not infiltrated regional lymph nodes in the groin and the pelvis are always irradiated; the dose of 30.6–36 Gy in fractions of 1.8 Gy is given to this volume in the first stage of treatment. In the second stage of treatment, the volume irradiated with a high dose is limited to macroscopically detected lesions in the anal canal and margin as well as enlarged inguinal and pelvic lymph nodes; the fractional dose may be increased to 2 Gy. Depending on the size of these lesions, the total irradiation dose ranges from 50 Gy to 54 Gy. In patients with a residual tumor identified at the end of treatment, increasing the dose by 5.4–6 Gy may be considered, although this has not been proven (IV, B). An optional regimen is a single-stage radiotherapy using a simultaneous integrated boost (SIB) technique, assessed in a US prospective phase II study with a historical control group [7]. In patients with T3-4 or N1 stage cancers, the dose of 54 Gy in 30 fractions was administered to the primary tumor and lymph nodes over 3 cm, 50.4 Gy to enlarged lymph nodes ≤ 3 cm and 45 Gy to the elective volume; the fractional doses were 1.8 Gy, 1.7 Gy and 1.5 Gy, respectively. In patients with cancer stage T1–2N0, the dose of 50.4 Gy in 28 fractions to the primary tumor and 42 Gy to the elective volume was administered; the fractional doses were 1.8 Gy and 1.5 Gy, respectively.

Some centers use brachytherapy to the residual primary tumor instead of the second stage of irradiation with an external beam (IV, C). However, approximately 5% of these patients develop radiation necrosis of the anal canal, necessitating the creation of a stoma; this complication is practically not observed after the use of irradiation with only external beams. Furthermore, there is no evidence of an improvement in local efficacy with brachytherapy compared to treatment with only external beams.

In patients ineligible to CTH due to concomitant diseases, stand-alone RTH is used. The doses must then be increased by 5 Gy to 10 Gy compared to the above-mentioned doses. When one instead of two courses of CTH is administered due to toxicity, increasing of the total irradiation dose should be also considered.

Principles of simultaneous chemoradiotherapy

The CTH regimen consists of 2 cycles of fluorouracil in continuous infusion and mitomycin (I, A). The randomized clinical trials with cisplatin instead of mitomycin have shown similar treatment outcomes (I, A) [10, 11]. The use of neoadjuvant or adjuvant CTH does not improve treatment outcomes (I, A) [9–11]. The superiority of CRTH has been shown compared to RTH alone in

terms of better local efficacy in prolonging stoma-free survival but with no impact on overall survival (I, A) [12]. The value of mitomycin as a component of CTH was also confirmed (I, A) [13]. Retrospective studies suggest similar treatment efficacy when fluorouracil is replaced by capecitabine (III, B).

The routine CTH regimen given during irradiation consists of two cycles of fluorouracil and mitomycin given at week 1 and 5 of radiotherapy. Fluorouracil is administered at a dose of 1000 mg/m^2/24 h in a 96-hour continuous intravenous infusion. Mitomycin is administered on cycle day 1 or 2 at a dose of 10 mg/m^2 (the maximum dose is 20 mg). The cycle is repeated after 28 days. In order to reduce the toxicity, it is possible to administer mitomycin only in the first course. Retrospective studies have shown that this does not reduce treatment effectiveness (III, B) [14].

The value of consolidating CTH after completion of CRTH is not proven.

There is some controversy regarding the advisability of concurrent CRTH use in patients with cancer stage T1–2N0. However, it should be considered, because without CRTH the irradiation doses should be higher than those described above.

Surgery

A primary abdominosacral resection is a mistake; this operation is performed only as part of salvage therapy after CRTH failure and in patients with contraindications to RTH (e.g. after RTH of the pelvic region). CRTH rapidly reduces discomfort caused by the tumor, so the indications for a pre-treatment bypass stoma creation are rare; the typical indication is a vaginal fistula. The value of local resection of confirmed anal canal squamous cell carcinoma is questionable even in stage I tumors, due to frequent relapses in local or regional lymph nodes.

Surgical treatment can only be used in the case of recurrent disease, and examinations should always be performed to assess the condition of abdominal and thoracic organs in order to exclude the metastases.

Complications

CRTH is associated with a high risk of acute radiation complications. Grade 3–4 early complications occur in approximately 70% of patients and include painful radiation dermatitis, weakness, diarrhea, nausea, vomiting, pollakiuria, leukopenia, and anemia. Most patients require opioid analgesics. It is advisable to use antibacterial ointments (e.g. argosulfan) on the skin affected by radiation. The use of topical lidocaine can relieve the symptoms. The acute radiation reaction lasts for about 2–3 weeks after treatment. Due to the high risk of leukopenia, it is necessary to perform a complete blood count once a week. There is a common admixture of blood in the stools due to radiation telangiectasias in the rectum. A colonoscopy should then be performed to rule out other causes. Treatment with argon beamer to stop bleeding is not frequently necessary. The risk of femur fracture is increased. Erectile dysfunctions in men are also possible. Even small doses of radiation dispersed in the testes can cause infertility and hypogonadism. Young and middle-aged men should be informed about this complication in order to possibly deposit sperm in a sperm bank. In women, radiation-induced vaginal dryness causes painful intercourse. In those who do not have intercourse, the vaginal encroachment can occur, so artificial expansion is recommended. Young women will experience early menopause soon after CRTH. It is then advisable to consult a gynecologist regarding the advisability of using hormone replacement therapy.

Prognosis

Unfavorable prognostic factors are large primary tumor size, metastases to regional lymph nodes, male gender and skin ulceration. It should be emphasized, however, that anal margin and anal canal squamous cell carcinoma is a radiosensitive tumor. Even patients with locally advanced cancer can be cured; these patients should be treated radically. Local or regional lymph node recurrence usually occurs within the first 3 years after treatment completion. The local effectiveness of CRTH in patients with anal canal or anal margin cancer is similar and accounts for approximately 80%. After treatment, distant metastases are rare and occur in approximately 10–15% of patients.

Follow-up examinations

Post-treatment follow-up is recommended every 3 months for the first 2 years, then every 4 months for up to 3–4 years (II, B). Almost all relapses appear up to 3 years after treatment. *Per rectum* and groin examination is basic with the description of *per rectum* examination at the end of irradiation as a baseline. The presence of a residual, non-growing tumor in the follow-up examination does not justify the diagnosis of treatment failure. Biopsy of such lesions is not recommended. The tumor sample is taken only in case of progression suspected prior to salvage abdominoperineal resection. The residual tumor may shrink slowly, up to 6 months after treatment [15]. In some cases of initially very advanced cancers, it is advisable to perform a pelvic MRI examination during the first follow-up as a starting point for an objective comparison of the residual lesions in subsequent examinations performed at 1–2 month intervals until complete regression is achieved. This is especially

true in case of ulcerated anal margin cancers, which leave large scarring lesions during healing. As distant metastases are rare and usually occur together with local recurrence, the value of periodic pelvic, abdominal and chest CT examinations is doubtful. In women, a cytological examination of the material collected from the cervix is recommended once a year due Hto PV infection which is the common etiological factor of anal canal and cervical cancer.

Surgical salvage therapy

CRTH ineffectiveness most often occurs in the primary tumor, both as a result of its failure to regress completely and as a result of its recurrence after complete regression. Then, in the case of histologically confirmed local recurrence, a salvage abdominosacral resection is performed (III, A). Due to the rapid cancer progression after irradiation, these patients should be operated urgently. According to the previous high dose irradiation, this procedure is associated with a high (> 50%) risk of complications consisting in long-term impairment of perineal wound healing. For this reason, it is recommended to perform surgery in a specialized center, with perineal reconstruction, for example with a myocutaneous flap from the rectus abdominis muscle. 5-year survival rates after this treatment are approximately 50%.

Much less often, cancer recurrence can occur in the inguinal lymph nodes. In such a case, radical inguinal lymphadenectomy should be considered. In some cases, when the previously used irradiation dose does not exceed 40 Gy, pre- or postoperative CRTH is possible.

Treatment of patients with distant metastases

In patients with synchronous distant metastases, CRTH is still indicated for lesions located in the pelvis with the radical doses mentioned earlier. This is aimed at obtaining a local cure and therefore the quality of life improvement. Then, elective irradiation is applied to a limited volume.

The appearance of distant metastases is an indication for palliative CTH — the standard CTH regimen has not been clearly established, but fluorouracil (± calcium folinate) with cisplatin or carboplatin with paclitaxel is usually used (II, A). The decision to use palliative CTH should take into account the patient's age and PS, concomitant diseases and the tumor dynamics (including disease-free survival after primary treatment). The median overall survival in patients undergoing CTH is 12–20 months. There is no evidence that metastasectomy is effective.

Treatment of the oligometastatic disease is individualized. A metastasectomy should be considered. Stereotactic radiotherapy alone or in combination with irradiation of the adjacent region with an elective dose may also be used (it is possible, for example, to cure nearly 50% of patients with isolated metastases in the periaortic lymph nodes, with no distant metastases in other organs [16]). This method is also used in the case of isolated relapses in the pelvis outside the irradiation volume or in the elective volume.

Treatment of anal canal adenocarcinoma

Abdominoperineal resection is a standard of care, as in most patients, adenocarcinoma is not highly radiosensitive. Preoperative CRTH is routinely used according to the same principles as in patients with rectal cancer (III, B). The elective volume should additionally include inguinal nodes.

In patients with tumors ≤ 4 cm without lymph node metastases, encouraging results were obtained by combining local excision with CRTH or by using only a high dose of CRTH (IV, C). Then, the abdominoperineal resection is performed only in case of failure. However, this is not considered standard practice.

Chemotherapy in metastatic disease is used similarly to that in patients with colorectal cancer.

Treatment of anal margin squamous cell carcinoma

Treatment of patients with low stage anal margin cancer (≤ 4 cm without metastases to regional lymph nodes) is based on radical surgical resection of the tumor, similar to that in patients with skin cancer of a different location. The possibility to preserve free macroscopic surgical margin of at least 1 cm is a prerequisite. Patients with a narrow (< 1 cm) or positive surgical margin in microscopic evaluation require extended resection or postoperative CRTH. In patients with more advanced cancer or when local resection would impair the function of the sphincters CRTH is used, as in patients with anal canal cancer.

Conflict of interest

The authors declare no conflict of interest.

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Rectal cancer (C20)

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Key words: rectal cancer, diagnosis, treatment, follow-up, recommendations

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Translation: prof. Ewa Bartnik
Oncology in Clinical Practice 2020, Vol. 16, No. 6, 338–357. DOI: 10.5603/OCP.2020.0042, copyright © 2020 Via Medica, ISSN 2450–1654

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.

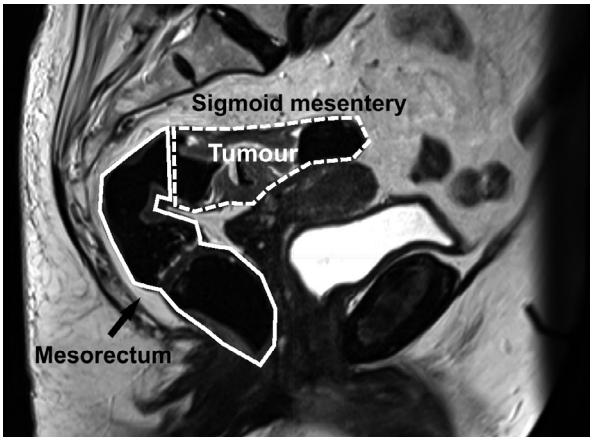


Figure 1. Boundary between the rectum and the sigmoid; after [14]. Rectum is marked by a continuous line; the sigmoid by a dashed line. The boundary between the rectum and sigmoid runs through the rectosigmoid junction, which is at the site where the intestine which runs initially mainly extraperitoneally 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);

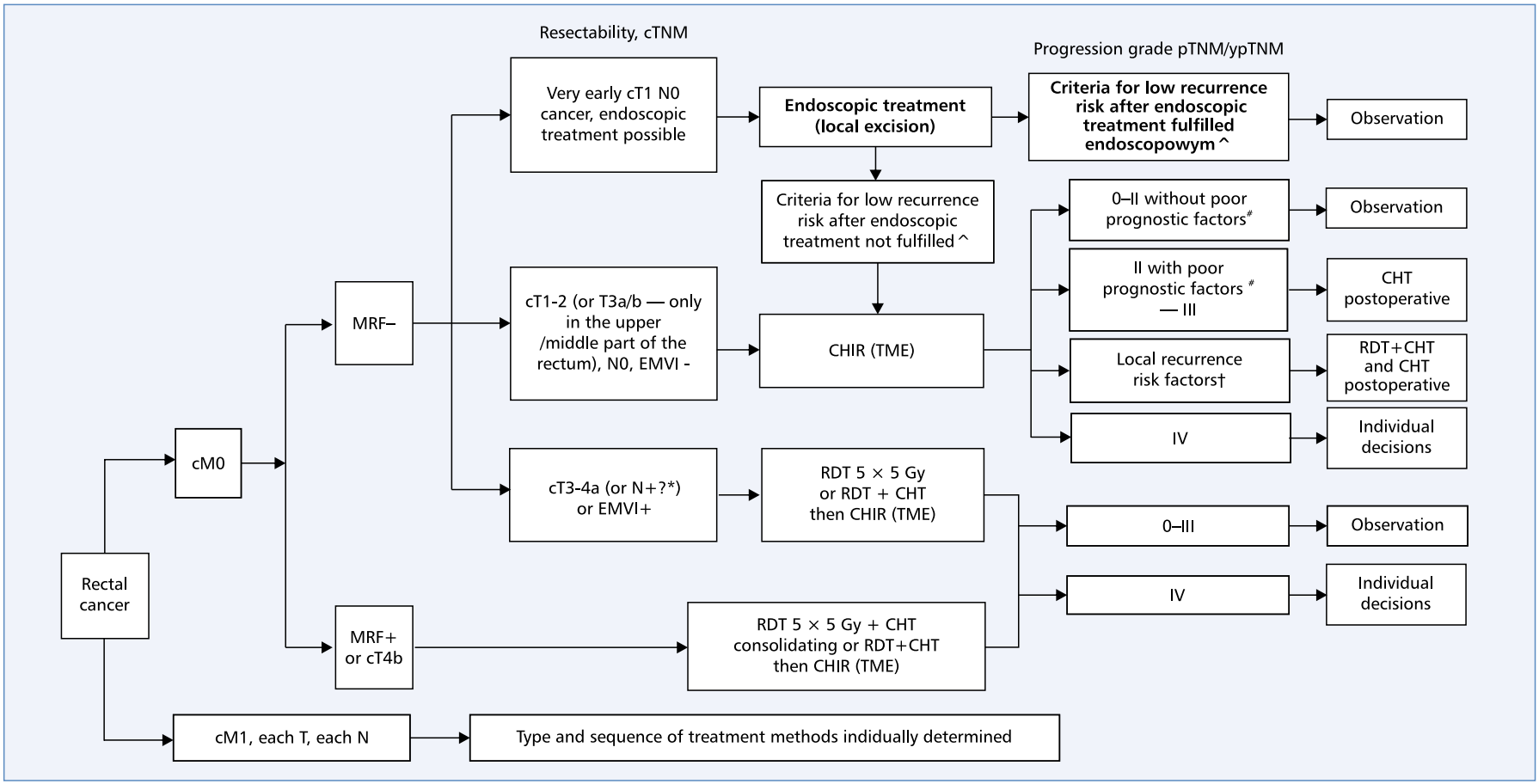


Figure 2. Scheme of therapeutic procedure in patient with rectal cancer depending on the evaluation of tumour resectabillity and the clinical stage evaluated by (cTNM) and pathomorphologically (pTNM or ypTNM). *Characteristic cN+ as an indication for preoperative radiotherapy is the subject of controversy — 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

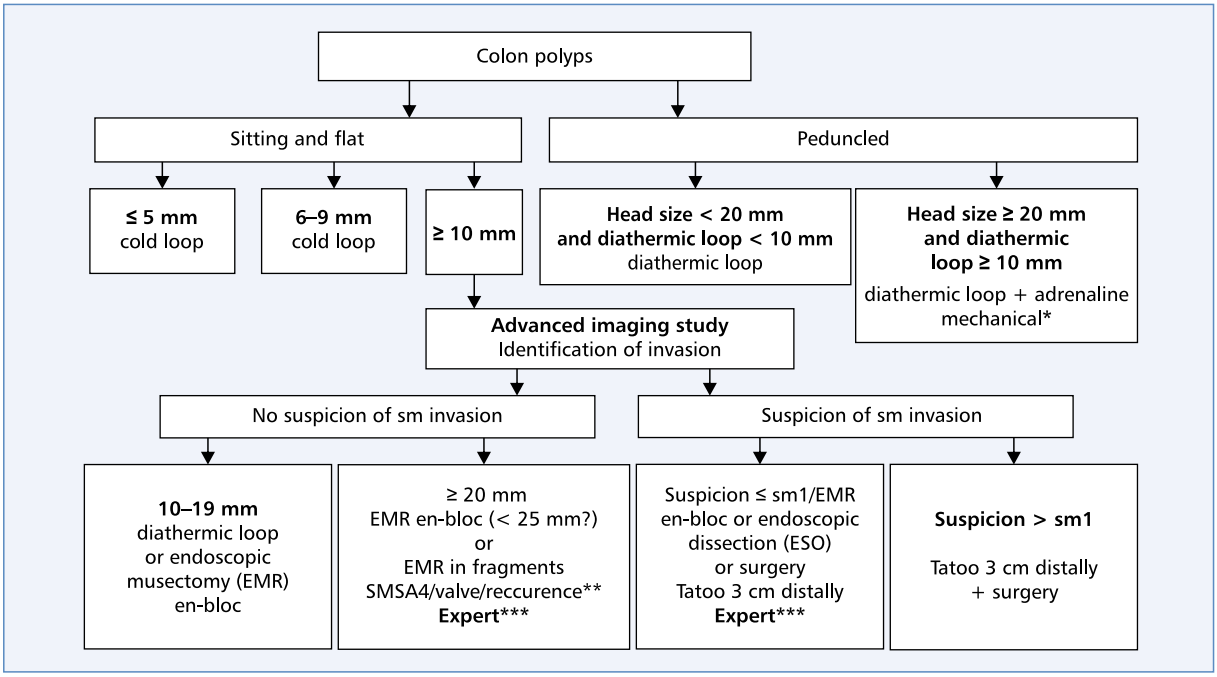


Figure 3. Scheme of selection of the technique of treating colon polyps depending on the size, shape, suspicion of submucosal invasion (sm) according to ESGE guidelines [6] (Ferlitsch et al., Endoscopy 2017). *As the head of the polyp is large and the peduncle thick — it is recommended prophylactically 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.

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VIA MEDICA

REVIEW ARTICLE

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New dosing schedule of pembrolizumab — theoretical basis and scientific evidence

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Oncology in Clinical Practice
2020, Vol. 16, No. 6, 358–363
DOI: 10.5603/OCP.2020.0033
Translation: prof. Ewa Bartnik
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ISSN 2450–1654

ABSTRACT

Pembrolizumab among other immunotherapy agents is a breakthrough drug in oncology. Its wide therapeutic index allowed evolution from a dosing schedule based on body mass 2 mg/kg to a fixed-dose 200 mg every 3 weeks. In 2019 the European Medicines Agency approved dosing 400 mg every 6 weeks, despite lack of evidence from clinical trials on safety and efficacy, based only on pharmacokinetic data derived from previous clinical studies. This year, facing the SARS-CoV-2 pandemic, international oncology societies recommended a new dosing schedule in order to minimise patient exposition to health care units. In April 2020 the US Food and Drug Administration also approved a new dosing schedule, based on an interim analysis of clinical trial Keynote-555.
Key words: pembrolizumab, immunotherapy, dosing schedule

Oncol Clin Pract 2020; 16, 6: 358–363

Introduction

Pembrolizumab is a monoclonal humanized antibody against the programmed death 1 receptor (PD-1). This receptor is present on activated T, B and NK lymphocytes and monocytes. Its binding to ligands (PD-L1 and PD-L2) prevents excessive activation of immunological system and the associated inflammatory reaction. It also causes immunological tolerance of own tissues, and in case of neoplasms, it inhibits the effects of immunological system on neoplastic cells.

Blocking the binding of PD-1 receptor with its ligands present on antigen presenting cells (APC) and the cells of some neoplasms favors the cytotoxic reaction and apoptosis of neoplastic cells. At the same time, this reaction may take place in healthy tissues which is responsible for adverse effects on autoimmunological basis [1].

The first clinical trial using pembrolizumab (Keynote-001) in solid tumors was initiated in 2011. On the basis of the results of this trial this drug was acknowledged as a breakthrough in 2013 and in 2014 in an accelerated mode it was registered for melanoma treatment and in 2015 for non-small cell lung cancer [2]. Currently, pembrolizumab is registered for multiple indications (Table 1). It is used in monotherapy or together with chemotherapy or in molecularly targeted treatment.

The effectiveness and safety of pembrolizumab have been confirmed in numerous trials [3]. 2019 brought publication of 5-year observations of patients with advanced melanoma and non-small cell lung cancer, who received pembrolizumab at a dose of 2 mg/kg body mass (b.m.) every 3 weeks (Q3W) or 10 mg/kg b.m. Q3W or every 2 weeks (Q2W) in the Keynote-001 trial. An objective response was reached in 41% of patients with melanoma and 26% with non-small cell lung cancer, whereas the percentage of disease control was 65% and 63%, respectively. After five years the response was maintained in 73% of the patients with melanoma and 54% with non-small cell lung cancer, and in respect to disease control, this percentage was 61% and 23%, respectively [4, 5].

Adverse effects of pembrolizumab concern 63–96% of treated patients (including 10–41% with grade 3–4).

Table 1. Registration indications for pembrolizumab

Registration indications according to EMA	Registration indications according to FDA
Palliative treatment	**Palliative treatment**
Melanoma	Melanoma
Non-small cell lung cancer	Non-small cell lung cancer
Classical Hodgkin lymphoma	Small cell lung cancer
Urothelial cancer	Classical Hodgkin lymphoma
Squamous cell head and neck carcinoma	Mediastinal large B cell lymphona
Renal cell carcinoma	Solid tumors with microsatellite instability Stomach cancer
	Esophageal cancer
	Cervical cancer
	Hepatocellular carcinoma
	Merkel cell cancer
	Endometrial carcinoma
	Urothelial cancer
	Squamous cell head and neck carcinoma
	Renal cell carcinoma
	Skin spinocellular carcinoma
Adjuvant treatment	**Adjuvant treatment**
Stage III melanoma	Stage III melanoma

EMA — European Medicines Agency; FDA — Food and Drug Administration

According to the Keytruda Summary of Product Characteristics in force in Poland, the registered indications for the use of the drug include the following diseases: melanoma, non-small cell lung cancer, classical Hodgkin's lymphoma, urothelial carcinoma, squamous cell carcinoma, head and neck cancer, renal cell carcinoma.

The dosage of Keytruda is as follows:

1. The recommended dose of KEYTRUDA monotherapy is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as a intravenous infusion lasting 30 minutes;
2. The recommended dose of KEYTRUDA in combination therapy is 200 mg every 3 weeks, administered as an intravenous infusion over a period of 30 minutes

The most common adverse effects include weakness, pruritis, diarrhea and disorders of thyroid gland function (grade 3 and 4 — immunological pneumonia, diarrhea and colon inflammation, hypopituitarism and liver toxicity). Mortality associated with treatment is estimated to be 0.45% and is most commonly the result of immunological pneumonia, cardiotoxicity and hepatotoxicity and infections. Among rarely occurring adverse effects are neurological complications (including encephalitis, Guillian-Barre syndrome, myasthenia, uveitis, type 1 diabetes) [6–8].

Pembrolizumab dosing

Pembrolizumab dosing changed over time. Initially, the drug was registered at a dose of 2 mg/kg b.w. Q3W. Currently in all indications for adults pembrolizumab is used at a constant dose of 200 mg Q3W intravenously during a 30-minute infusion (in children the dosing is 2 mg/kg b.w.). In 2019 the European Medicines Agency (EMA) additionally registered the dosing schedule 400 mg every 6 weeks (Q6W), and the American Food and Drug Administration (FDA) accepted it in April 2020 in an accelerated mode even though it initially rejected this dosing schedule. Dosing every 6 weeks only concerns pembrolizumab in monotherapy. In combined treatment, only the dosing schedule 200 mg Q3W is accepted. This paper will present the stages of dosing evolution and the evidence justifying current pembrolizumab dosing.

Pharmacokinetics

Data concerning pharmacokinetics are derived from 5 clinical trials involving 2993 patients, which were the basis of a population pharmacokinetic model (Keynote-001, Keynote-002, Keynote-006, Kenote-010, Keynote-024). In these trials the following dosing schedules were evaluated: 2 mg/kg Q3W, 10 mg/kg Q3W and Q2W and 200 mg Q3W regardless of body mass [9, 10].

The potential of pembrolizumab activity was evaluated on the basis of the dynamics of interleukin-2 after stimulation *ex vivo* with Staphylococcus endotoxin in peripheral blood taken before and in different time intervals after pembrolizumab administration. Maximal activity measured this way was found to be reached at a minimal concentration (C_{min}) of 10 μg/ml. This is possible with dosing of at least 1 mg/kg Q3W without further advantage with doses of 3 and 10 mg/kg. During further simulations, the highest potential effect was evaluated to be with a dose of 2 mg/kg mc Q3W [11].

Pembrolizumab concentration in blood increases in a linear fashion in the dose range of 0.1–10 mg/kg. The distribution volume is about 6 liters, which means a small degree of passage into the non-vascular space. Pem-

Table 2. Exposure to pembrolizumab depending on the dosing schedule [16]

Dosing schedule (number of patients)	C_{min} [μg/mL]	AUC [μg·day/mL]	C_{max} [μg/mL]
2 mg/kg Q3W (755)	21.1 (9.18–35.7)	1316.5 (724.9–2038.5)	66.3 (48.3–88.2)
10 mg/kg Q3W (1403)	120.4 (59.8–200.2)	7436.0 (4354.0–11 172.8)	357.6 (257.7–466.8)
10 mg/kg Q2W (652)	217.8 (111.8–325.3)	11 993.5 (6834.7–16895.5)	457.7 (315.9–599.9)
200 mg Q3W (830)	27.6 14.9–46.2	1787.0 1120.6–2730.9	89.1 66.4–124.3

Values presented as median (10–90 percentile). AUC — area under the curve of change in concentration in time; C_{min} — minimal concentration; C_{max} — maximal concentration

Table 3. Effectiveness of pembrolizumab in NSCLC Keynote-001 trial [17]

Parameter	2 mg/kg Q3W n = 52	10 mg/kg Q3W n = 155	10 mg/kg Q2W n = 105
ORR, % (95%CI)	15 (7–28)	25 (8–33)	21 (14–30)
DCR, % (95% CI)	50 (36–64)	48 (40–56)	50 (40–60)

CI — confidence interval; DCR — percentage of disease control; n — number of patients analyzed; ORR — percentage of objective responses

brolizumab concentration in blood reaches a stationary state after 6–16 weeks of treatment. As pembrolizumab catabolism is via non-specific protein catabolism, the velocity of drug elimination does not significantly depend on liver and kidney function and is 195 ml/day in the stationary phase, whereas the half-life is 14–22 days [10, 12, 13]. Drug clearance is affected by body mass, albumin and bilirubin concentration, the size and type of neoplasm, the index of glomerular filtration and the sex — but the clinical significance of these factors has not been demonstrated. These factors may, however, affect the individual variation in exposure to the drug, thus they have been used in pharmacokinetic models evaluated in search for an optimal dosing schedule [12, 14]. In spite of the lack of known factors affecting pembrolizumab clearance, an unfavorable effect of rapid drug elimination in relation to overall survival has been demonstrated, but a higher dose of pembrolizumab (10 mg/kg Q3W) did not give a better prognosis [15]. This correlation may be associated with increased protein catabolism in advanced stages of the disease or in persons with severe comorbidities which would explain lack of benefits of immunotherapy in persons in a worse performance status.

Parameters used for evaluation of exposure to the drug — maximal concentration after finishing the infusion (C_{max}), the area under the curve of the change in concentration of the drug with time (AUC) and Cmin before the next infusion for particular dosing schedules are presented in Table 2.

In spite of clear differences in the extent of exposure to pembrolizumab depending on the dosing schedule, in the Keynote-001, Keynote-002, Keynote-006, Keynote-010 trials comparing dosing schedules 2 mg/kg Q3W and 10 mg/kg Q2W or Q3W [16], no significant differences were observed in the efficacy and the toxicity of the applied treatment in a direct comparison of Keynote-001 results (Tables 3 and 4) [17]. Also in the meta-analysis evaluating the frequency of adverse effects no statistically significant differences were observed between the clinical trials evaluated so far [7]. Taking into consideration data from the first three mentioned trials, Chatterjee et al. analyzed the correlation between the exposure to pembrolizumab, expressed as AUC, and the response to treatment, expressed by the degree of decrease of the dimensions of the lesions evaluated in imaging tests. In two publications concerning patients with melanoma and non-small cell lung cancer, no significant differences were found in the dynamics of the lesion sizes for individual schedules and it was concluded that dosing 2 mg/kg Q3W allows obtaining the best response to treatment [17, 18].

Dosing 200 mg every 3 weeks

Aiming at simplifying the dosage schedule and to limit errors in calculating and dispensing the dose depending on body mass, from 2016 a fixed dose of 200 mg has been used in clinical trials regardless of body mass.

Table 4. Adverse effects associated with treating patients with NSCLC in the Keynote-001 trial [17]

Adverse effects	2 mg/kg Q3W n = 61	10 mg/kg Q3W n = 287	10 mg/kg Q2W n = 202
All grades n (%)	31 (51)	201 (70)	148 (73)
Grade 3–4 n (%)	5 (8)	34 (12)	8 (4)
Mortal n (%)	1 (2)	1 (< 1)	0
Immunological n (%)	9 (15)	39 (14)	32 (16)

n — number of analyzed patients

The analysis of available data allowed a mathematical model to be created in which exposure to pembrolizumab was calculated in clinical trials in which a constant dose of 200 mg Q3W was used. The values observed in clinical trials were convergent with those estimated on the basis of the mathematical model. Moreover, on their basis, it was observed that a constant dose of 154 mg allows an AUC in the stationary phase which is the same as that with the dose of 2 mg/kg body mass, whereas the dose of 200 mg allows to reach an AUC ensuring effectiveness with acceptable toxicity, both in persons with a low body mass as well as in the subgroup of patients with body mass > 90 kg [17].

Dosing 400 mg every 6 weeks

Financial and logistic considerations were decisive in the next step in decreasing the frequency of drug administration, and thus the visits of patients in healthcare units, which is particularly desirable during the SARS-CoV-2 pandemic. During the ASCO conference in 2018, the results of mathematical analysis were presented forecasting the approximated parameters of exposure to pembrolizumab with a dose of 400 mg Q6W [19]. In a model elaborated on the basis of data from Keynote-001, Keynote-002, Keynote-006 and Keynote-010 clinical trials simulations of C_{min}, C_{max} and AUC were performed, evaluated during the first 6 weeks of treatment and the same parameters evaluated between 25 and 30 weeks of treatment (during the 5^{th} cycle). According to the performed simulations, AUC in the stationary stage between consecutive doses will be close to AUC reached with dosing 2 mg/kg Q3W and 200 mg Q2W, and the stationary state will be reached earlier than with Q3W dosing. In the context of adverse effects, the foreseen C_{max} does not exceed values reached in the cohort of patients receiving 10 mg/kg Q2W, in which the safety profile did not diverge from other dosing schedules. In turn, the simulated C_{min} will be lower than the minimal value with potential effectiveness only in approximately 0.5% of patients in a time not longer than 3 days. According to the authors of the cited work, this brief decrease in concentration does not result in a decrease of clinical effectiveness as according to the physiological model of monoclonal antibody pharmacokinetics in the stationary state the fraction of the drug bound to its receptor ensures its saturation for about 7 days (longer than the decrease in drug concentration) [17, 20].

A different position was presented in the report of the Canadian Agency for Drugs and Technologies in Health (CADTH) concerning dosing schedules in immunotherapy. According to the performed simulation, the 400 mg Q6W schedule translates into a lower saturation of target molecules, expressed as the dynamics in the changes of interleukin-2 concentration in peripheral blood and depending on the weight it is 95.88–98.16% (400 mg Q3W) as compared to the values of 98.47–99.95%, calculated for dosing 2 mg/kg body weight considered to be optimal [15]. There were, however, no data about the clinical significance of the mentioned differences.

The above reports require confirmation in trials and clinical practice. Despite that EMA registered 400 mg Q6W dosing schedule already in 2019 only on the basis of the evidence presented above. The results of a preliminary analysis of data from the Keynote-555 trial which evaluated the effectiveness and safety of the above schedule in advanced melanoma were presented during 2020 Virtual AACR meeting. Among the first 44 patients, the parameters of exposure to the drug were found to be comparable with those observed in the schedules which have been registered so far. The percentage of objective responses at this stage is 39%, grade 3 and 4 adverse effects were noted so far in 25% patients, which is comparable to data obtained in clinical conditions with different dosing schedules. The result should, however, be interpreted carefully especially in relation to adverse effects, as this is a preliminary analysis of the first group of patients with a median time of observation of 6.7 months [21].

Potential dosing schedules

Taking clinical, logistic and financial matters into consideration it seems that the recommended dosage schedule will continue to evolve. Currently, in the Keynote-555 trial (cohort B) a subcutaneous form of administering the drug is being evaluated, more com-

fortable for many patients and possible to use outside a healthcare unit.

Financial matters are also worth mentioning. Bach et al. calculated that in case of dosing depending on body mass in the USA about 16–24% of the drug is utilized which is due to the availability of vials containing 50 or 100 mg pembrolizumab. Even if the drug from an opened vial was given to the next patient (a practice not recommended by the CDC because of the risk of a blood-derived infection) the value of the unused drug was estimated close to 200 million dollars per year [22]. In order to minimize treatment costs, various dosing models were studied, allowing to ensure optimal exposure to the drug and their costs were estimated in relation to dosing 2 mg/kg b.m. The constant dose of 200 mg Q3W was found to generate costs 7% higher than the initial dosing schedule. A constant dose of 150 mg would allow savings of 25%. An intermediate form was dosing calculated on the basis of body mass ± 10% so that the dose would be a multiple of 25 mg, which would minimize the amount of the utilized drug (*dose banding*). The last strategy was based on pharmacokinetics simulations depending on the body mass and is based on adjusting the dose to the available vials (*PK-derived dose banding*). Dosing depending on the body mass interval was presented in easy to use tables which decrease the risk of an error. Economic analysis indicated the costs of both strategies were lower by 15 and 16%, respectively, in comparison to 2 mg/kg b.m. dosing [14].

A strategy taking into consideration the needs of the reduction of exposure to contact with SARS-CoV-2 and economic problems in the context of the pandemic is based on dosing 4 mg/kg Q6W to a maximal dose of 400 mg. On the basis of data from mathematical simulations such dosing will enable the maintenance of high saturation of target molecules [23], however, it differs from that obtained for dosing at 2 mg/kg Q3W. Nevertheless, in the face of the SARS-CoV-2 pandemic many international oncological societies have recommended dosing of pembrolizumab 400 mg Q6W in order to minimize the contact of patients with healthcare units.

Summary

The evolution of the pembrolizumab dosing schedules reflects the interactions between theoretical models and the results of clinical trials and everyday clinical practice. The aim to obtain a mode of drug dosing which is economical and acceptable for patients is indispensable. However only appropriately conducted clinical trials can defermine the value of a new schedule from it in all patients or can lead to determining the profile of patients who can benefit.

Conflict of interest

The authors declare no conflict of interest.

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CASE REPORT

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The search for causes of resistance to pembrolizumab in lung adenocarcinoma with PD-L1 expression — focus on intestinal microbiome

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Oncology in Clinical Practice
2020, Vol. 16, No. 6, 364–368
DOI: 10.5603/OCP.2020.0031
Translation: dr n. med. Dariusz Stencel
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ISSN 2450–1654

ABSTRACT

Anti-PD-1 or PD-L1 immunotherapy in some patients with non-small cell lung cancer (NSCLC) may not be effective, despite the high percentage of cancer cells with PD-L1 expression (≥ 50%). TMB (tumor mutation burden), smoking status and low intestinal microbiome diversity may be associated with lack of efficacy of immune checkpoints inhibitors treatment in NSCLC patients. The case presented here concerns a non-smoking female patient with lung adenocarcinoma, in whom, despite the high percentage of PD-L1 positive tumor cells (50%), pembrolizumab therapy was ineffective. Next generation sequencing (NGS) was performed using the FOCUS panel allowing the analysis of 52 genes whose damage is associated with various types of solid tumors, including lung cancer. Benign genetic changes clinically irrelevant for patients with non-small cell lung cancer have been observed. In the meantime, profiling of the patient's intestinal microbiome was performed, due to the fact that the composition of the intestinal microbiome may be a decisive factor in the lack of response to immunotherapy in patients with high PD-L1 expression and no driver mutations. Low diversity of bacteria in the intestines, with a noticeable dysbiosis (dysbacteriosis), was observed. The presence of bacteria *Akkermansia, Enterococcaceae, Bifidobacteriaceae* or *Coriobacteriaceae*, especially the presence of *Akkermansia mucinifila* seems to be a favourable factor of the possibility of obtaining response to immunotherapy and prolongation of progression-free survival (PFS). In the intestinal microbiome of the presented case, no bacteria from the *Verrucomicrobia phylum*, to which *A. mucinifila belongs*, were found. In addition, only 0.011% of *Enterococcaceae* were found. Studies on the intestinal microbiome in cancer patients receiving immunotherapy appear to be necessary to correctly understand the effect of microbiome composition on the effectiveness of this treatment method.

Key words: immunotherapy, intestinal microbiome, NGS, NSCLC

Oncol Clin Pract 2020; 16, 6: 364–368

Case report

In August 2019, a 48-year-old patient came to the Department of Pneumonology, Oncology and Allergology in Lublin due to severely increased dyspnea, highly reduced exercise tolerance and a dry, persistent cough. She never smoked. Chest x-ray revealed a large amount of fluid in the left pleural cavity with atelectasis above the fluid level and left hilar enlargement. Thoracentesis was performed several times during hospitalization, however pathomorphological examination of pleural effusion did not allow for definitive diagnosis. Computed tomography (CT) scans revealed tumor in a left lung (13 × 10 cm), constricting the left upper lobe and lower

lobe bronchi, fluid in the left pleural cavity, and significant pleural thickening. In the preserved lower lobe of the left lung multiple small metastatic nodules were visible. In the abdominal cavity numerous enlarged hepatic hilar and periaortic lymph nodes were found. Magnetic resonance imaging of the spine also revealed numerous metastases with pathological vertebral compression fractures (Th3–Th4 and Th8–Th10). In September, the patient underwent bronchofiberoscopy with transbronchial biopsy of the mediastinal lymph nodes. Specimens were obtained from infiltrated carina and right main bronchus, transesophageal and transesophageal fine-needle aspiration of the tumor as well as left mediastinal lymph nodes (station 7) were also performed.

The tissue samples were preserved in formalin and embedded in paraffin wax blocks. Histological examination confirmed adenocarcinoma with thyroid transcription factor 1 (TTF1) expression on cancer cells. In the fixed cytological material all predictive factors for therapies registered in European Union countries were examined. The *EGFR* (epidermal growth factor receptor) and *BRAF* (B-Raf Proto-Oncogene) genes mutations were excluded using real-time polymerase chain reaction (RT-PCR), *ROS1* gene rearrangement was excluded using fluorescent in situ hybridization (FISH), and the expression of ALK (anaplastic lymphoma kinase) fusion protein using immunohistochemistry (IHC). Programmed cell-death ligand 1 (PD-L1, CD274) expression was also analyzed by IHC (antibody clone SP263). Surface PD-L1 expression was detected in 50% of tumor cells.

Based on the results of the aforementioned examinations and the clinical factors (stage IV lung adenocarcinoma) it was decided to use pembrolizumab in first-line treatment. Unfortunately, after two cycles of immunotherapy, the disease progressed and the patient's clinical condition worsened. The patient consistently refused chemotherapy. Therefore, only local treatment of the obstructive bronchus lesion with brachytherapy, radiotherapy and the best supportive care was used.

Searching for the causes of resistance to immunotherapy

This is one of the examples when immunotherapy is not effective despite the high PD-L1 expression on cancer cells. The reason for this could be the occurrence of a single rare driver mutation that could not be detected by monogenic tests. Low tumor mutation burden (TMB) may result in ineffectiveness of immunotherapy. Low TMB is also affected by smoking history and the ability to repair damaged cellular DNA, determined by germinal or somatic mutations or polymorphisms of genes encoding DNA repair pathway proteins. Therefore, it was decided to perform next-generation sequencing (NGS) to look for driver mutations qualifying to molecularly targeted therapies. Sequencing was carried out with Ion Torrent technology in the S5 (Thermo Fisher Scientific) apparatus using the FOCUS Oncomine™ (Thermo Fisher Scientific) panel, which allows simultaneous analysis of single nucleotide polymorphisms (SNPs), copy number variation (CNV) , INDEL-type aberrations (insertions/deletions) in tumor DNA, as well as gene rearrangements in mRNA (including the rearrangement of *ALK*, *ROS1*, and *NTRK1-3* genes). The FOCUS panel allows the identification of abnormalities in selected 52 genes associated with various types of solid tumors including lung cancer. From a technical perspective, sequencing was successful. Genetic abnormalities with the status "benign" were detected, being currently of no clinical significance for patients with non-small cell lung cancer (NSCLC). No personalized therapies have been developed so far for patients with such genetic variation; on the other hand, it has not been proven that such genetic abnormalities can cause malignancies. There were substitutions in exon 29 of *ALK* gene: c.4587C>G (p.Asp1529Glu) and c.4381A>G (p.Ile1461Val), occurring outside the tyrosine kinase domain coding region. In addition, an aberration in exon 4 of *FGFR4* (fibroblast growth factor receptor 4) gene was found: c.407C>T (p.Pro136Leu). These abnormalities did not predispose to targeted molecular treatment registered in European Union countries or used in clinical trials.

In the meantime, profiling of the patient's intestinal microbiome was carried out as part of scientific research (consent of the Bioethics Committee of the Medical University of Lublin No. KE-0254/58/2019). The study was performed on the Illumina MiSeq apparatus (Illumina) using Nextera (Illumina) kits, dedicated to small, including bacterial genomes. The composition of the gut microbiome may be a decisive factor in the lack of response to immunotherapy in patients with high PD-L1 expression and no driver mutations. In our patient, we observed a low diversity of particular types of bacteria found in the intestines with a noticeable state of dysbiosis (dysbacteriosis). The majority of the gut microbiome of the examined stool sample (as much as 80.6%) was *Firmicutes* bacterium, including *Lactobacillus*, *Streptococcus*, *Clostridium*, *Veilonella*, *Enterococcus* and *Ruminicoccus* spp. [1]. In healthy people, this group of bacteria accounts for about 45–60% of microbiome bacteria 1]. *Firmicutes* and *Bacteroidetes* together should constitute about 90% of the intestinal microbiome [1]. In our patient it was 88.5%, however, a large disproportion between these two groups of bacteria was visible because *Bacteroidetes* constituted only 7.9%. In a normal biotic state, *Bacteroidetes* should account for 25–45% of the microbiome composition. *Bacteroidetes* include primarily *Bacteroides* and *Prevotella* [1–4]. Figure 1 presents graphically representation of the percentage microbiome composition (at *Phylum* level) in our patient compared to patients with disease control during immunotherapy.

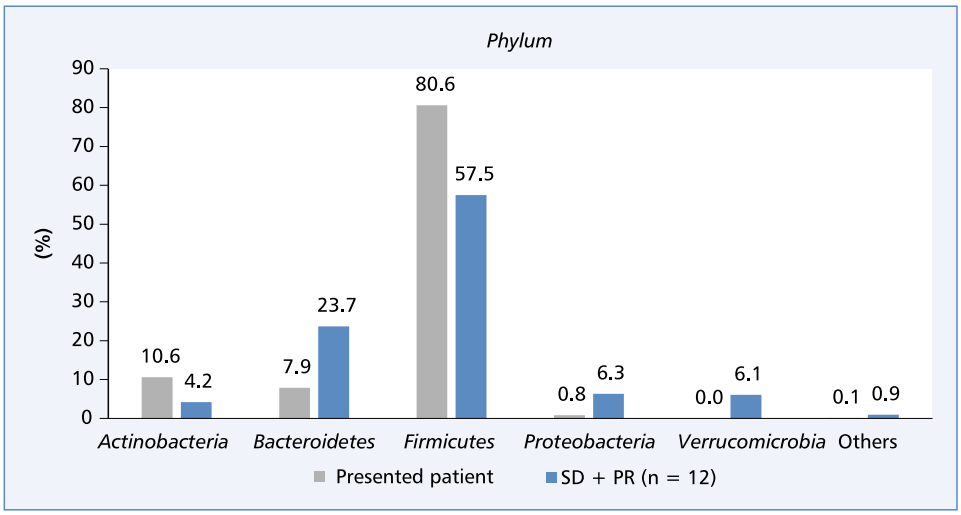


Figure 1. Percentage composition of the gut microbiome at *Phylum* level (bacterial type) in a patient with the progression of adenocarcinoma after two administrations of pembrolizumab and 12 NSCLC patients with disease stabilization during immunotherapy. A microbiome was examined in the specimen collected prior to immunotherapy. SD — stable disease; PR — partial response

Discussion

Vetizou and Trinchieri point to several factors that affect the composition of the gut microbiome [5]: genetic factors, lifestyle, the state of the immune system or the use of antibiotics. According to their opinion, all these factors and the composition of the gut microbiome are connected with the possibility of obtaining a response to immunotherapy in cancer patients. The more diverse the microbiome and the higher the percentage of "beneficial" bacteria in the intestine, the more likely it is to achieve the response to immunotherapy associated with the higher percentage of CD8 + T cells infiltrating the tumor stroma [6]. The "beneficial" bacteria include *Akkermansia muciniphila* (*Verrucomicrobia*, *Akkermansia* spp.), *Enterococcus hirae* (*Firmicutes, Enterococcocae* spp.), *Bifidobacterium longum* (*Actinobacteria*, *Bifidobacteriaceae* spp.), *Collinsella aerofaciens* (*Actinobacteria*, *Coriobacteriaceae* spp.), *Enterococcus faecium* (*Firmicutes*, *Enterococcocae* spp.) [5, 6]. The presence of *Akkermansia mucinifila* seems to be an especially beneficial factor for the possibility of achieving a response to immunotherapy and improving progression-free survival (PFS), which is also indicated by Routy et al. [7]. We did not find *Verrucomicrobia* spp., to which *A. mucinifila* belongs, in the gut microbiome of our patient (0%). In addition, we found only 0.011% of *Enteroccocae* spp., to which *E. hirae* and *E. faecium* belong.

Gopalakrishnan et al. point to an unfavorable intestinal microbiome that may affect the ineffectiveness of anti-PD-1 immunotherapy in patients with skin melanoma [6]. First of all, they indicate a low diversity of intestinal bacteria as a negative predictor of response to anti-PD-1 treatment. They also state that a high percentage of *Bacterioidates* spp. may have an impact on impaired systemic and anti-tumor immune responses, with limited tumor infiltration by immune cells, and inhibited antigen presenting ability of antigen-presenting cells (APCs) [6]. The authors also indicate a positive correlation between the percentage of TCD8 + lymphocytes infiltrating the tumor stroma and the participation of bacteria from the *Ruminococcae* family in the gut microbiome [6]. In our patient's microbiome, we observed 26.1% of this type of microorganisms (Fig. 2), which could be a beneficial predictor for immunotherapy.

Further research on the gut microbiome in cancer patients receiving immunotherapy seems to be necessary to correctly understand the effect of microbiome composition on the effectiveness of this treatment method. It should be remembered that prior to immunotherapy our patient received antibiotics and steroid therapy with methylprednisolone, which has been described in the literature as a negative predictive factor for immunotherapy. Antibiotic therapy was probably responsible for dysbiosis of the gut microbiome, and steroid therapy could additionally inhibit the immune system. On the other hand, many other causes of resistance to immunotherapy cannot be excluded. One of them may be the transformation of commensal bacteria into pathogenic ones. In addition, despite advanced genetic testing, including NGS, low TMB cannot be excluded, and this genetic abnormality requires examination of several hundred genes, not several dozen. Such a study could confirm the existence of a very rare genetic abnormality leading to cancer development. The probability of such a mutation is high due to the young age of the patient and the fact that she does not smoke cigarettes. NSCLC patients with high TMB are mostly heavy smokers. The

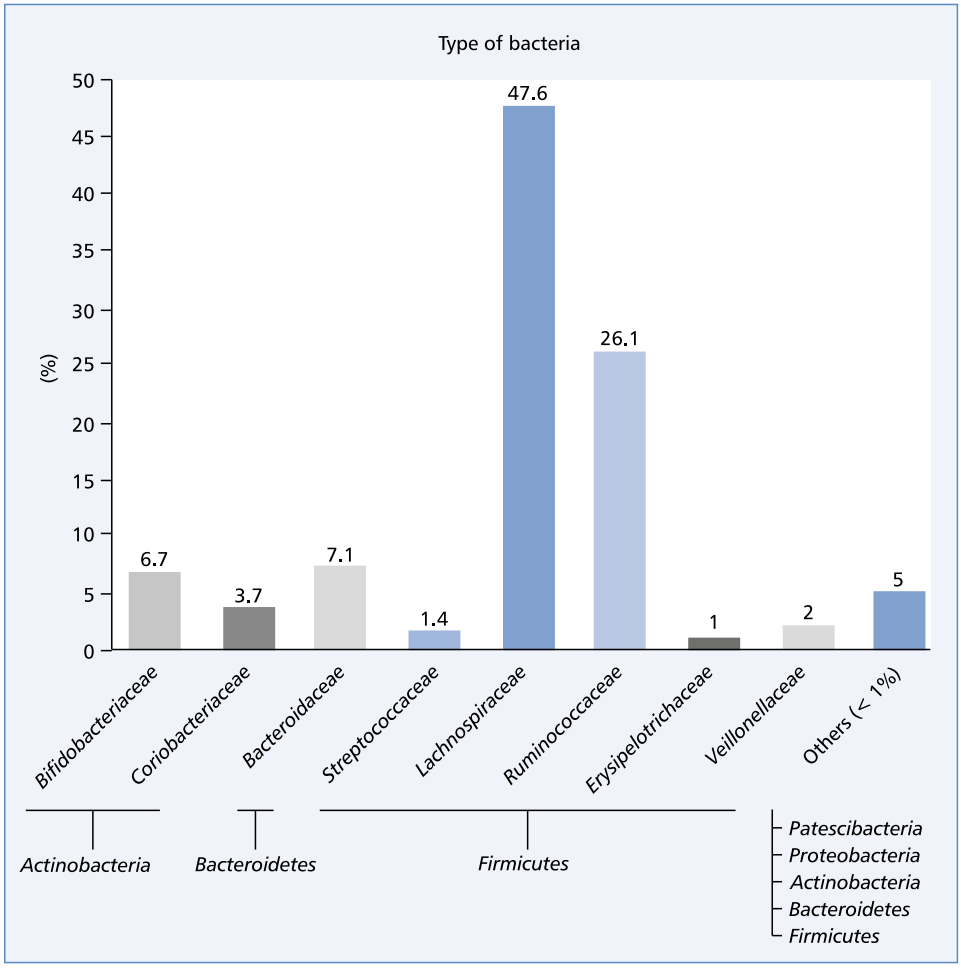


Figure 2. Percentage composition of the gut microbiome at the level of bacterial type (family) in a patient with the progression of adenocarcinoma after two administrations of pembrolizumab

carcinogenic effect of tobacco smoke promotes the formation of many somatic mutations in bronchial epithelial cells. A low TMB occurs in non-smokers and is associated with the occurrence of single driver mutations or rearrangements in such genes as *EGFR*, *ALK*, *ERBB2*, *ROS1*, *RET*, *MET*, *NTRK* [9, 10]. A response rate to PD-1 or PD-L1 inhibitors among NSCLC patients was higher in current or former smokers than in non-smokers [11–13]. Therefore, low TMB, smoking status and low diversity of the gut microbiome may be associated with a lack of effectiveness of treatment with immune checkpoints inhibitors in NSCLC patients.

The variety of potential causes of primary resistance to immunotherapy makes us realize how little we know about this method of treatment.

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