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Colorectal neuroendocrine neoplasms — management guidelines (recommended by the Polish Network of Neuroendocrine Tumours)

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Abstract
Neuroendocrine neoplasms/tumours (NENs/NETs) of the large intestine are detected increasingly often, especially rectal tumours, which is probably associated with the widespread use of screening colonoscopy.
There is a growing body of evidence supporting the thesis that the NENs of the rectum and the NENs of the colon are two different diseases. Rectal NENs are usually small lesions, of low to moderate histological malignancy, associated with good prognosis, and most may be treated endoscopically. NENs of the colon, however, are often aggressive, poorly differentiated, associated with a poor or uncertain prognosis, and require surgical treatment. The management guidelines regarding these groups of patients are constantly changing. On the basis of the recent literature data and conclusions reached by the working meeting of the Polish Network of Neuroendocrine Tumours (December 2016), this study completes and updates the data and management guidelines regarding colorectal NENs published in Endokrynologia Polska 2013; 64: 358–368.
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Key words: *colorectal neuroendocrine neoplasms; epidemiology; diagnosis; treatment; follow-up*

1. Epidemiology

1.1. Introduction

The rate of detection of colorectal neuroendocrine neoplasms (NENs) is increasing, and this tendency is likely to continue due to the widespread use of colonoscopy, including as a screening tool, and the removal of all diagnosed lesions [1–9]. The authors of the recent ENETS consensus state that there is a growing body of evidence supporting the thesis that the NEN of the rectum and the NEN of the colon are two different diseases [9].

1.2. Epidemiology

Rectal NENs are usually small lesions (most < 1 cm), and their histological malignancy is low to moderate (G1, G2), whereas NENs of the colon are often aggressive, poorly differentiated, and more malignant (G3). Colonic NENs account for 7.8% and rectal NENs for 13.7% of all neuroendocrine neoplasms [2]. The most common site for colonic tumours is the caecum, and this location is more frequent in females [2]. The mean age at disease onset is 70 years [3]. Rectal tumours are the third largest group of gastrointestinal NENs. They account for approximately 1% of all rectal tumours. They are detected by one in 1000–2000 endoscopic examinations [1, 5, 6, 10]. Since the year 2000, rectal NENs occur or are detected more frequently than small intestinal NENs [9]. This is probably associated with the widespread use of screening colonoscopy [1, 8, 9]. According to Japanese and Korean data, rectal NENs are slightly more common in the male population (M/F ratio — 1.5 and OR 1.9) [11], whereas American and Polish data demonstrate a similar prevalence of these neoplasms in both sexes [2, 5, 9]. In the USA, the highest incidence of these neoplasms is found in Asian (OR = 10) and black patients (OR = 1.96) [8, 11].

The mean age of patients with rectal NENs is 56 years. The statistical data records 4.2 cases of rectal NENs per 1,000,000 citizens [8, 11].

Rectal NENs are typically single lesions, although multiple lesions have also been described in the literature. Complete colonoscopy is recommended if neuroendocrine lesions are found in the rectum [12].

2. Clinical characteristics

2.1. Clinical characteristics and symptomatology

Colorectal neuroendocrine neoplasms arise from two types of cell:

— EC (enterochromaffin) cells, which secrete serotonin, and are typically located in the ascending colon;
— L cells, which secrete glucagon-like peptide (GLP) and YY peptide, and are found in the remaining part of the colon and rectum [8].

Colorectal NENs characteristically do not secrete specific hormones, and their clinical symptoms correlate with their location and stage of advancement [8].

The symptoms associated with colonic neuroendocrine neoplasms are non-specific. They mainly include changes in bowel movements (mostly diarrhoea) and, in the case of advanced disease, abdominal pain, weight loss, and palpable lesions in the abdominal cavity. Weakness and decreased effort tolerance, often associated with gastrointestinal blood loss, may also occur. Moreover, patients may suffer from gastrointestinal obstruction, which often requires an urgent surgical intervention. The above symptoms are similar for all neoplasms occurring in this part of the gastrointestinal tract, suggesting the initial diagnosis of adenocarcinoma, the most common neoplasm affecting the large intestine. Despite the presence of serotonin-producing cells, carcinoid syndrome with its characteristic symptoms is rarely observed (< 5%) [3]. According to the largest database, SEER, the local lesions account for approximately 45% at the moment of diagnosis [13]. Distant metastases are found in 16–40% of patients. The five-year survival rate in colonic tumours, the lowest of all the gastrointestinal neuroendocrine neoplasms, is 40–70%, depending on the size of the primary tumour, histological grade, and clinical stage [2, 13]. The mean survival time is 261 months for locally advanced lesions, and less in the case of regional lymph node metastases or distant metastases (36 months and 5 months, respectively) [8, 13].

Rectal neuroendocrine neoplasms are most frequently detected accidentally during an endoscopic

examination. The symptoms are also non-specific, including changes in bowel movement, gastrointestinal bleeding, or tenesmus. Carcinoid syndrome almost never occurs, due to the very rare presence of EC serotonin-secreting cells in this location (0.1%). At the moment of diagnosis, the majority (75–85%) of detected lesions are localised. The five-year survival rate is 75–100%, depending on the histological grade, proliferation index, and clinical stage [2].

Multiple Endocrine Neoplasia (MEN) syndrome and other genetically conditioned syndromes are very rarely associated with colorectal NENs [7, 8]. NENs in first-line family members increase the risk of the disease by a factor of four.

In 13% of patients with a colorectal NEN, another neoplasm develops [2, 4, 5]. The gastrointestinal tract, including the colon, is the most common site for synchronous tumours, while metachronous neoplasms primarily affect the lungs, prostate gland, and urinary tract. The detection of gastric GIST as a metachronous tumour in a patient with rectal NEN has been presented by Polish authors [14].

3. Diagnostics

3.1. Biochemical diagnostics

There is no specific marker for colorectal neuroendocrine neoplasms. Determination of serum chromogranin A concentration is still the most valuable method of monitoring, treating, and anticipating the course of the disease. CgA concentration may be elevated and correlate with the severity of the neoplastic disease [15, 16] *(*evidence level 3).*

As tumours in this part of the gastrointestinal tract rarely secrete serotonin, the concentration of 5-hydroxyindoleacetic acid in the 24-hour urine collection usually remains normal. The concentration of serum acid phosphatase may be elevated in the case of neoplasms demonstrating expression of the prostate-specific fraction [8, 17, 18] *(* evidence level 5).*

Minimal consensus statement on biochemical tests:

— serum CgA remains the most important biochemical marker in the diagnostics, monitoring, and establishing the prognosis in colorectal NENs.

3.2. Pathomorphological diagnostics

3.2.1. Pathogenesis

Similarly to the above discussed NENs in different gastrointestinal locations, colorectal neuroendocrine neoplasms are divided into well-differentiated neuroendocrine neoplasms with Ki-67 below 3% — NET G1, with Ki-67 index between 3 and 20% — NET G2, and with Ki-67 over 20% – neuroendocrine carcinomas (NECs): large- or small-cell, as well as mixed neuroendocrine non-neuroendocrine neoplasms (MINENs). There is also a small group of well-differentiated tumours with Ki-67 index over 20%, which in the AJCC eighth edition 2017 are referred to as NET G3 [19]. The diagnostic criteria are discussed in Chapter 2.2 and (Table V, VI and VII) (*see* p. 82–86).

Colonic neuroendocrine neoplasms are potentially malignant neoplasms. At the early stage they create polyps, which macroscopically resemble adenomas. However, at the moment of diagnosis they are usually exophytic tumours, which in the microscopic assessment are diagnosed as neuroendocrine carcinomas or mixed neoplasms (MINENs). Most colonic NENs are highly malignant, and at diagnosis approximately 30% of cases present metastases to the lymph nodes, mesentery, peritoneum, and liver [8].

Rectal neuroendocrine neoplasms are a different group; they are usually polyps, 1 to 2 cm in diameter, with the morphology of well-differentiated neoplasms (NET G1, NET G2), infiltrating the mucosa and/or submucosa, whereas neuroendocrine cancers (NECs) of the rectum demonstrate an aggressive clinical course. At the moment of diagnosis, metastases to the lymph nodes are often found. Colorectal neuroendocrine carcinomas are highly malignant neoplasms. Carcinomas arising from the large cells account for approximately 75% of all colorectal NECs, and they are more frequently located in the right part of the colon. Sometimes they are associated with adenomas and adenocarcinomas. Their mitotic activity is high (median of 34/10 HPF), with a proliferative activity of more than 20%. Immunohistochemical examination sometimes indicates low chromogranin A expression and high expression of synaptophysin and CD 56. Small-cell carcinomas account for 25% of colorectal neuroendocrine carcinomas, and they are usually found in the distal section of the colon and rectum. They may be associated with squamous cell carcinoma or classic adenocarcinoma. They demonstrate the expression of chromogranin A and synaptophysin; some tumours are cdx2-positive and TTF1-positive. The Ki-67 proliferation index is above 50%, usually close to 100%. It should be emphasised that rectal NENs in 28 to 82% of cases express prostatic acid phosphatase, potentially resulting in a misdiagnosis of tumours arising in male patients [8]. Table I presents the pathogenesis of NENs of the colon and rectum

3.2.2. Diagnostic algorithm

In macroscopic assessment the following elements are considered:

— Length of that part of the intestine obtained for examination, with the description of the tumour

*evidence level according to OCEBM [68]

Table I. *The pathogenesis of colorectal NENs*

Enterochromaffin cell (EC)	EC cell NENs are neuroendocrine neoplasms of the midgut (midgut-type NEN), which: — occur mainly in the right part of the colon — produce serotonin — present histological and cytochemical characteristics similar to NENs in the ileocaecal area — form, morphologically, solid nests surrounded by a circumferential palisade of cells, sometimes with rosette or bulbous structures, very rarely solid fields — often have desmoplastic stroma — have a differentiation grade of G1 or G2 — have tumour diameter of approximately 4.9 cm — have positive cdx2 immunoexpression
L cell	L cell NENs are neoplasms of the hindgut (hindgut-type NEN), which: — are found in the distal section of the colon and rectum — produce glucagon-like peptides (GLP-1), PP/PYY, serotonin (30%), and somatostatin (20%) — usually form submucosal, single polyp-like nodules covered by the intestinal epithelium — are smaller than 1 cm in over 50% of the tumours — create trabecular structures in the microscopic image, rarely rosette or tubular structures — do not demonstrate immunoexpression of cdx2

location relative to the intestine resection margins (proximal, distal, and circumferential or radial margin, examined in the segments of the large intestine either unencased or incompletely encased by serosa, should be marked with ink);

— Tumour assessment: number, size in three dimensions, mutual relation of the tumours, cross-section appearance, considering extravasation and foci of necrosis, and the relation of the tumour to the intestinal wall layers;
— Condition of the mucosa at the tumour site (ulceration present/not present);
— Condition of the serosa at the tumour site;
— Presence and size of the lymph nodes;
— Presence of other tumours in the intestinal wall [8].

Microscopic assessment is based on the assessment of the following parameters:

1. Histological type of the NEN according to the WHO 2017 classification [20], supplemented by Chapter 2.2 and Tables V and VI (p. 82–86).
2. Histological grade G according to ENETS/WHO 2017.
3. Pathomorphological pTNM staging according to ENETS and AJCC/UICC [19, 21]

Table II. *TNM AJCC 8, UICC 8 Edition 2017 classification of colorectal NENs [19, 21]*

Feature T — primary tumour x	Comments
pTX	Tumour has not been assessed
pT0	No evidence of a primary tumour
pT1	Tumour invades the mucosa or submucosa, size ≤ 2 cm
pT1a	Tumour size < 1 cm.
pT1b	Tumour size 1–2 cm
pT2	Tumour invades the muscularis propria or size > 2 cm and invades the mucosa or submucosa
pT3	Tumour penetrates the muscularis propria and invades the subserosal tissue, without invading the serosa
pT4	Tumour invades the peritoneum, other organs or adjacent structures

4. Assessment of immunohistochemical expression of neuroendocrine markers: chromogranin A and synaptophysin, as well the Ki-67/MIB1 proliferative activity (obligatory).
5. Immunohistochemical assessment of the markers: NSE, CD56, CDX2, and serotonin (conditional).
6. Assessment of surgical margins.

Regarding 1 and 2: histopathological WHO 2017 NEN classification and histological grading according to ENETS/WHO 2017 are presented in part one: "General guidelines for the management of gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours)" (*see* p. 79–110).

Regarding 3: pathological and clinical pTNM staging.

The staging of colorectal neuroendocrine neoplasms is verified using the TNM classification according to AJCC/UICC and ENETS. As for the location of this neoplasm, both classifications are consistent. It is important, however, that the European Neuroendocrine Tumour Society classification is also applied to neuroendocrine carcinomas. According to the AJCC/UICC classification, NECs are assessed by the same criteria as adenocarcinomas, not as neuroendocrine neoplasms. Table II gives the TNM classification according to the AJCC and ENETS criteria. Table III gives the assessment criteria for clinical staging of colorectal NENs.

3.2.3. Prognostic indicators in the histopathological report

The risk factors of colorectal NEN associated with metastases, include: tumour > 2 cm in diameter, invasion of the muscular layer of the colorectal wall,

*evidence level according to OCEBM [68]

vasoinvasion, and > 2 mitotic figures/10 HPF. It is recommended that any focal tumour necrosis is determined, which indicates a more aggressive tumour [8].

An important parameter in the histopathological report on a colorectal NEN is the assessment of the proximal, distal, and circumferential margin. The circumferential margin is assessed in segments of gastrointestinal tract either unencased or incompletely encased by serosa. It should be noted that it should be marked with ink during the macroscopic assessment of the surgical material. It is recommended that the distance is noted between the tumour foci with the deepest infiltrations and the circumferential margin line. A margin of > 1 mm indicates complete resection, whereas a margin of ≤ 1 mm is interpreted as incomplete [8].

Minimal consensus statement on pathomorphological examination:

Minimal histopathological report on colorectal NEN should include:

— *Histological type of the neoplasm according to WHO classification, considering the division into well-differentiated neuroendocrine neoplasms (NET G1 and NET G2) with Ki-67 index below 20%, and NET G3 and neuroendocrine carcinomas (NECs) with Ki-67 index above 20% or mixed neoplasms (MINENs);*
— *Histological G grading referring to well-differentiated neoplasms (NET G1, NET G2, NET G3) and NECs;*
— *pTNM histopathological staging according to ENETS and AJCC/UICC 8 (2017) classification systems;*
— *Assessment of surgical margins.*

*The histopathological diagnosis of NEN must be confirmed by immunohistochemical tests assessing expression of the neuroendocrine markers: synaptophysin and chromogranin A, as well as Ki-67 proliferative activity using the MIB1 antigen (*evidence level 3).*

3.3. Location diagnostics

3.3.1. Endoscopic diagnostics

The basic diagnostic method in colorectal NENs is colonoscopy with a biopsy for morphological assessment, supplemented by echoendoscopic examination (EUS). EUS is mainly performed in rectal lesions. In colonic tumours diagnosed as submucosal polyps/lesions, the colonoscopic assessment may be supplemented by USG mini-probe. The large intestine may also be examined using capsule endoscopy [8, 23].

Colonic NENs are most frequently lesions that macroscopically resemble cancer infiltration; diagnosed early, they take the form of submucosal polyps/tumours. Most rectal NENs (80%) demonstrate characteristic morphological features. They are nodular with a wide base, smooth on the surface, covered by a mucosa of normal appearance or slightly yellow/white [5–8]. Atypical features, observed in 20% of cases, include: semi-pedunculated shape, reddening of the mucosa, central depression, and erosion or ulceration on the surface. Atypical features occur mostly in lesions > 1 cm. Ulceration of the surface is associated with a worse prognosis. Lesions are usually single, and located in the middle part of the rectum.

Table III. ***Colorectal GEP NENs staging according to TNM AJCC 8, UICC. Edition 2017 [19, 20]***

Stage I	T1 N0 M0
Stage IIa	T2 N0 M0
Stage IIb	T3 N0 M0
Stage IIIa	T4 N0 M0
Stage IIIb	Any T N1 M0
Stage IV	Any T, any N M1

Contrary to other subepithelial lesions, in most patients (83%) with NEN, the biopsy results are positive [4]. This is because NENs arise from the muscular layer of the mucosa.

EUS allows the distinguishing of an epithelial polyp from a NEN (different echogenicity of lesions and different layer from which the lesion derives), determines the stage of local advancement, and helps in the choice of optimal therapy (i.e. endoscopic or surgical treatment) [8, 9, 24]. Using EUS enables precise assessment of the size of the lesion, and determination of the depth of infiltration, and description of the condition of lymph nodes. The sensitivity and specificity of this test in the assessment of the depth of infiltration is 87% and 93%, respectively [6]. In EUS, colorectal NENs manifested as polyps are well demarcated, iso- or hypoechogenic, homogenous lesions derived from the muscular layer of the mucosa. The lesion may infiltrate the submucosa; deeper layers are invaded less frequently.

In the case of neuroendocrine rectal lesions of < 1 cm diameter, some authors do not recommend EUS as a tool for the assessment of the stage of disease advancement [24]. However, the recent ENETS guidelines strongly recommend EUS in rectal NENs over 5 mm in diameter [9].

3.3.2. Other imaging examinations

As mentioned above, colonoscopy supplemented by EUS examination is essential in the diagnostics of colorectal tumours. In the case of lesions closing the intestinal lumen, full colonoscopy is impossible. In such cases, recommended are multiphase abdominal and pelvic CT (computed tomography)/MRI (magnetic resonance imaging), before and after the administration of the contrast medium, after filling the gastrointestinal tract with negative contrast, or CT colonography [8, 26].

*evidence level according to OCEBM [68]

To assess the stage of advancement, abdominal ultrasonography (US), CT/MRI, and somatostatin receptor imaging (SRI) may be used. Abdominal ultrasound is a useful tool for the initial assessment of hepatic metastases and for planning/performing a biopsy. To assess the lesions in the chest, abdominal cavity, and pelvis multiphase computed tomography or magnetic resonance (abdominal cavity and pelvis) is used. MRI of the pelvis is the method of choice to assess the local advancement of a rectal neoplasm. There are no separate data available for the sensitivity of SRI in the group of patients with colorectal NETs. SRI enables detection of lesions with increased somatostatin receptor (SSTR) expression, which is necessary to determine patient eligibility for treatment with somatostatin analogues or for radioisotope therapy based on these receptors (peptide receptor radionuclide therapy, PRRT) [8].

In the case of negative SRI results, a PET/CT examination should be considered after the administration of ^{18}F DOPA, for NECs and for quickly growing NENs, and PET/CT scan after the administration of ^{18}FDG [27, 28].

Minimal consensus on imaging examinations:

— *Colonoscopy is the test of choice in the diagnostics of colorectal tumours.*
— *EUS is recommended in rectal NENs ≥ 5 mm.*
— *CT/MRI/SRI is recommended for assessing the stage of tumour advancement and detecting metastases (*evidence level 2/3).*
— *SRI is required to determine a patient's eligibility for antiproliferative treatment with SSA and PRRT (*evidence level 2/3).*
— *^{18}FDG PET/CT examination is indicated in patients with NECs, with rapidly growing NETs, and in patients qualified for radioisotope therapy (*evidence level 3).*

4. Treatment

4.1. Surgical treatment

4.1.1. Surgical treatment of colonic NENs

Recommendations regarding surgical treatment of colonic NENs are analogous to those regarding the treatment of colonic adenocarcinoma [8]. Resection (performed by open or laparoscopic access) with lymphadenectomy is indicated in patients with tumours without distant metastases *(*evidence level 1)*. In the case of NENs G1 and G2 with distant metastases (usually to the liver), a palliative resection with regional lymphadenectomy is recommended *(*evidence level 1)* or, if possible, maximal cytoreduction of the tumour *(*evidence level 2)*, even if complete reduction is not achieved.

In the case of invasion of the adjacent organs, if possible from the technical point of view, a multiorgan excision with left- or right-sided hemicolectomy is suggested, or extensive resections of the transverse colon, considering the extent of the lymphatic drainage *(*evidence level 1)* [8].

4.1.2. Surgical treatment of rectal NENs

If the lesion does not qualify for endoscopic treatment (ESD), surgical therapy is the method of choice. Classical surgical techniques include low anterior resection or abdominosacral/perineal amputation of the rectum, whereas minimally invasive methods include transanal endoscopic microsurgery (TEM) or laparoscopic resectional procedures.

Figure 1 gives the recommended algorithm for the treatment of rectal neuroendocrine neoplasms [8].

Indications for local resection of rectal NEN (TEM, ESD) include tumour size < 1 cm, absence of lymph node invasion, and good tumour differentiation [7]. Local treatment of larger lesions, up to 2 cm, is possible. The treatment is considered sufficient if the pathomorphological examination does not reveal any adverse prognostic factors [7–9].

Local excision using the TEM technique is a promising therapeutic option because it enables transanal transmural excision of the lesion. Literature data reveals the superiority of TEM over classical local excision through the open anus because the method demonstrates high efficacy and safety in groups of carefully selected patients [29].

In a study by Kim et al. (2012), in 97% of patients undergoing the TEM procedure free margins were obtained in the histopathological examination [30].

In another study, Wu et al. demonstrated a higher rate of free margins obtained after using the TEM technique (100%) compared to ESD and EMR (82.6% and 65.5%, respectively) [31].

Tumours > 2 cm in diameter (according to some authors, even those > 1.5 cm) are frequently associated with infiltration of the muscle membrane. In such cases resectional procedures are recommended, preferably saving the sphincters. Anterior resection of the rectum with total excision of the mesorectum (TME, total mesorectal excision) is the procedure of choice, possibly including construction of protective stomy [8, 32].

Radical resection is also recommended in the presence of other risk factors for the regional lymph nodes, such as: high tumour mitotic index (G2, G3, Ki-67 > 2%), invasion of lymphatic and blood vessels, or positive expression of HES77 [33, 34].

In the case of T3 and T4 tumours with invasion to the local lymph nodes, oncological radicality can be achieved, provided there are no distant metastases.

If the tumour is located low in the rectum, or if it invades the sphincter, then abdominosacral or abdominop-

*evidence level according to OCEBM [68]

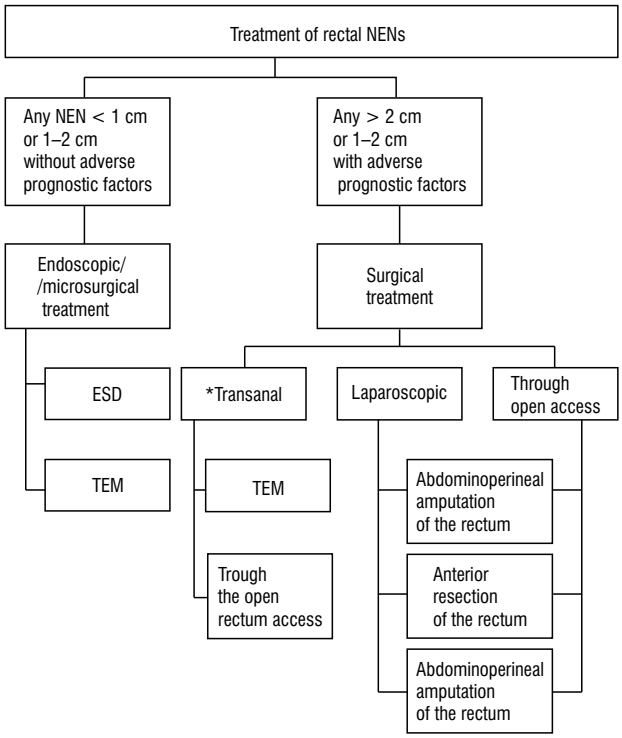

Figure 1. *Algorithm for the treatment of neuroendocrine rectal neoplasms (according to Starzyńska et al. [8]); *in individual cases*

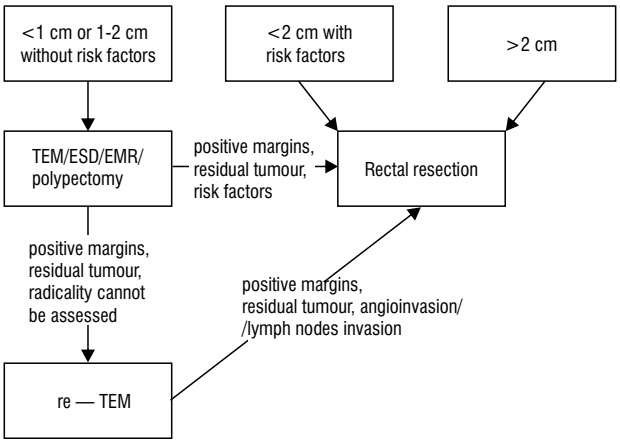

Figure 2. *Algorithm of management in case of incomplete TEM or endoscopic treatment (according to Hyoung RK et al. [39])*

erineal amputation are recommended *(*evidence level 1)*. The most recent data also question the established limit diameter. Some authors suggest that tumour size over 15 mm is the cut-off point between local excision and abdominoperineal rectal amputation because in this group the risk of distant metastases is very high. In such cases ESD resection is burdened with a high risk of oncological failure. In special cases, especially if the patient does not consent to a radical procedure, using the TEM technique can be an optimal solution. However, the patient must be informed that in the case of unfavourable results of the histopathological examination of the tumour removed via TEM, a radical rectal resection may be necessary.

In a series of cases described by Gleeson et al., no metastases were found if the lesion size did not exceed 9 mm [35]. Local resection was considered safe in lesions of 10 to 16 mm in diameter in the study by McDermott et al. (however, it was a collective analysis, in which the quality of data was evaluated as low or moderate for all the cases included in the series) [36]. One study questioned the superiority of a radical resection over a local excision procedure in the case of rectal NENs of 10 to 20 mm in diameter, with or without lymph node invasion, because the radical resection may adversely affect quality of life [37].

In locally and systemically advanced tumours with distant metastases, radical resections are not recommended because in this group of patients survival is 6–9 months following the diagnosis [8, 9].

Palliative surgery is indicated in the case of a bleeding tumour if local haemostasis is ineffective (e.g. argon plasma coagulator, APC), or gastrointestinal obstruction *(*evidence level 1)*. In NETs of G1 and G2 with metastases limited to the liver a radical local excision of the tumour with subsequent resection of hepatic parenchyma (metastasectomy) *(*evidence level 1)* or, in certain cases, a liver transplant *(*evidence level 4)* [8]. However, it should be emphasised that the available literature presents only the results of treatment of individual series of patients with colorectal NENs with hepatic metastases [38].

In the case of incomplete excision of a rectal tumour during an endoscopic procedure, it is recommended that salvage surgery is performed. Analysis of the literature does not allow the unambiguous establishment of whether salvage treatment is necessary, and if it is, the data does not indicate clearly which option is the best. Therefore, each case should be treated individually, based on the patient's risk factors and the clinical experience of the physician and the centre. Following incomplete resection with endoscopic techniques or after procedures performed with other techniques, the patient should be referred to centres specialising in the treatment of NENs (Fig. 2).

Minimal consensus statement on surgical treatment:

— *Colonic NENs mostly require surgical treatment.*
— *Rectal NENs associated with adverse prognostic factors (regardless of the size)*
— *and tumours of 2 cm or more in diameter should be treated surgically.*

4.2. Endoscopic treatment of colorectal neuroendocrine neoplasms

For endoscopic treatment of colorectal NENs, eligible patients should be those who are at almost no risk of metastases to regional lymph nodes or of distant me-

*evidence level according to OCEBM [68]

tastases. Endoscopic mucosal dissection (ESD) is the optimal treatment method because it is associated with the highest R0 resection rate [40–44].

In colonic NENs, due to the high risk of metastases to regional lymph nodes, surgical treatment is recommended. In a study based on a large group of patients with colonic NENs treated surgically (923 patients), Al. Natour et al. analysed the relationship between the size of lesion, depth of invasion, and occurrence of metastases. The authors demonstrated that in the case of early detected lesions, smaller than 1 cm, and limited to the mucosa, the risk of metastases to the regional lymph nodes was 4%, and for other lesions it was ≥ 14% [45].

Approximately 80% of rectal NENs qualify for endoscopic local therapy. It has been documented that in rectal NENs the size of the tumour is a sensitive indicator of the risk of the metastases to the regional lymph nodes and disease progression [36]. It has also been demonstrated that only in patients with neoplasms of < 10 mm the risk of metastases is low and prognosis good. In this group, the ratio of patients with regional lymph node invasion is 3%, and with distant metastases it is 1.6%. With tumours of 11–19 mm, the risk of metastases increased to 66%, and 50% for regional lymph nodes and distant metastases. In the case of lesions > 20 mm, in 73% of patients metastatic lesions were found in the lymph nodes at the diagnosis, while in all of the patients (100%) distant metastases occurred.

Established prognostic factors include depth of invasion, vascular status, and proliferation index. Bad prognostic markers/risk factors include invasion of the muscularis propria, lymph node invasion or/and angioinvasion, and proliferation index > 2%.

According to McDermott et al., rectal NENs of up to 10 mm, without any risk factors, are eligible for endoscopic treatment [37]. In the group of lesions 10–20 mm in diameter the neoplasm may be removed endoscopically, and after assessment of the preparation/ /risk factors, further management can be determined. Rectal NENs > 20 mm, and those with bad prognostic markers, should undergo radical surgical treatment, including resection of the mesorectum.

Classical polypectomy cannot be performed in the treatment of colorectal neuroendocrine neoplasms because these lesions derive from the second layer of the gastrointestinal wall (muscularis mucosae) and grow towards the submucosa. In most cases, with small lesions (up to 1 cm), endoscopic mucosal resection (EMR) is conducted, in different versions, as well as endoscopic submucosal dissection (ESD) [40–44]. The latter has been proven to be the method of choice. ESD, in comparison to EMR, provides a higher ratio of en bloc and R0 resections (100% *vs.* 89% and 82–91% *vs.* 65–70%), while the frequency of complications is similar. Most complications (delayed bleeding, perforation) may be treated endoscopically. No fatal complications have been reported.

ESD enables removal of the tumour in one piece (en bloc), within the healthy tissue, regardless of the size of the lesion or the presence of fibrosis. Application of this method became possible after the Olympus Tokyo company introduced a special knife (insulation tip-IT knife), which reduced the risk of perforation due to a porcelain ball-shaped tip. The procedure starts by marking the borders of the lesion, allowing for a healthy tissue margin. Saline solution with diluted adrenalin and indigo carmine is injected into the submucosa to elevate it and increase its volume. When a small incision is made, the next steps include performing a round incision and dissection of the lesion within the submucosa. Endoscopic treatment is associated with very good longterm results [41].

ESD procedures are performed in Poland in the following centres Department General, Gastroenterological and Gastrointestinal Neoplasms Surgery Teaching Hospital, Medical University of Lublin; Endotherapy Non-public Health Care Facility in Warsaw; Department Gastroenterology, CMKP, Warsaw; Oncology Centre, Bydgoszcz; Department of Gastroenterology, Medical University in Białystok; and the Department of Gastroenterology, Pomeranian Medical University in Szczecin. The largest number of procedures were performed in Szczecin.

Minimal consensus statement on endoscopic treatment:

— *Endoscopic treatment of colorectal NENs concerns mostly lesions in the rectum.*
— *ESD is the treatment of choice among endoscopic techniques.*
— *Rectal NENs of up to 1 cm in diameter is an optimal indication for endoscopic treatment.*
— *Rectal NENs of 10–20 mm in diameter may be removed endoscopically (ESD), and after the assessment of the preparation/risk factors, further management can be determined.*

4.3. Pharmacological treatment

4.3.1. Biotherapy

Somatostatin analogues (SSA)

Carcinoid syndrome is very rare in colorectal neuroendocrine tumours. In the case of a disseminated neoplastic process with the symptoms of excessive serotonin secretion, using somatostatin analogues is the treatment of choice *(*evidence level 1)* [46]. In non-functional neuroendocrine neoplasms (NF-NENs), there is no conclusive evidence of the anti-neoplastic effectiveness of SSA, but their effectiveness may not be excluded, due to the results of the CLARINET and RADIANT-2 studies [47,48].

*evidence level according to OCEBM [68]

Targeted therapy — m-TOR inhibitors (everolimus)
An analysis of the RADIANT-2 subgroups, including only those patients with advanced G1/G2 colorectal NENs, has demonstrated that, statistically, the progression-free survival of the patients who received everolimus plus octreotide LAR (median PFS 29.9 months, n = 19) was significantly longer than in those patients receiving placebo plus octreotide LAR (median PFS 6.6 months, n = 20). Using both drugs (everolimus + SSA) in combination may be justified in the case of G1/G2 neoplasms, but further verification is required [48]. The CLARINET study did not demonstrate any clear advantages of using lanreotide; however, the data regarding neuroendocrine neoplasms of the large intestine in this subgroup was too limited to draw any conclusions.

Everolimus is recommended in non-resectable, locally advanced and/or metastatic colorectal NENs (G1 and G2) as a second-line therapy, if SSA treatment is ineffective, or as a third-line therapy, if SAA and/or interferon alpha (INF-α) (currently unavailable in Poland) and PRRT therapy is unsuccessful [46, 49].

4.3.2. Chemotherapy
Chemotherapy is indicated primarily in the treatment of patients diagnosed with neuroendocrine carcinomas (NEC). In the case of poorly-differentiated NECs, standard management should involve chemotherapy using platin derivatives [46, 50, 51]. Detailed recommendations are presented in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms" (*see* p. 79–110). Second-line therapy in patients with NECs should be considered individually, exclusively in patients with good function (*evidence level 4).

Regimens based on oxiplatin (FOLFOX, XELOX), irinotecan (FOLFIRI, IP), or temozolomide are recommended (*evidence level 4) [52–56].

Chemotherapy involving platin derivatives may be repeated in patients who demonstrate good response to first-line treatment that persists for over three months, and if no side effects of the therapy are observed.

In patients with NETs chemotherapy is not recommended, except for NET G2 with Ki-67 > 15%, and aggressive course (RECIST progression within 3-6 months), or without SSTR expression, if other therapeutic methods are unsuccessful, i.e. the disease progresses despite the treatment with everolimus (presently not refunded for this indication in Poland) or INF-α (presently unavailable in Poland) [45]. Chemotherapy is based on temozolomide and/or capecitabine and/or capecitabine with bevacizumab (bevacizumab is not refunded in this indication in Poland) [57, 58].

Patients with MINEN of the large intestine should be treated following the standards of the oncological management intended for classical colorectal carcinomas.

Minimal consensus for pharmacological treatment:
— *In patients with colorectal NETs with carcinoid syndrome symptoms, SSA therapy is a treatment of choice.*
— *In patients with non-surgical, locally advanced, and/or metastatic colorectal NETs G1 and G2 without SSTR expression, SAA should be considered as the first-line antiproliferative therapy; in case of progression, everolimus or PRRT is recommended.*
— *In patients with Ki-67 > 15%, if the disease still progresses rapidly, temozolomide and/or capecitabine-based chemotherapy is recommended.*
— *In patients with NECs, the treatment of choice involves chemotherapy with the use of platin derivatives.*

4.4. Peptide Receptor Radionuclide Therapy with radioisotope-labelled somatostatin analogues (PRRT)
Presently, there is very limited data concerning the effectiveness of targeted therapy with radioisotope-labelled somatostatin analogues in the group of patients with colorectal NENs. The observed survival following PRRT is shorter than in midgut tumours [59]. However, there are no randomised data in this group of patients. Qualification and treatment should follow the principles described in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours)" (*see* p. 79–110).

PRRT in hindgut tumours should be considered in patients with diffused or non-resectable NETs, demonstrating high overexpression of somatostatin receptors, confirmed by SRI examination [59–68].

Minimal consensus statement on radioisotope treatment:

*PRRT should be considered in patients with diffused or non-resectable hindgut NETs, if the tumour presents high overexpression of somatostatin receptors in the SRI examination (*evidence level 3/4).*

4.5. Follow-up
After a complete endoscopic or surgical removal of the colorectal neuroendocrine neoplasm, the following follow-up is recommended [7, 8, 22]:
— G1, G2 tumours up to 1 cm, without lymph node metastases, without invasion of the muscularis propria – regular monitoring of patients is not recommended;
— G3 tumours smaller than 1 cm and G1–3 tumours of 1–2 cm: colonoscopy every 12 months;
— tumours larger than 2 cm: obligatory follow-up examinations: G1/G2 tumours: colonoscopy/imaging examination/CgA in the first year; for G3 tumours, the same examinations every 4–6 months in the first year, then once a year.

*evidence level according to OCEBM [68]

Table IV. *Risk assessment system for rectal NENs — CaRRS (according to Fahy et al. [21])*

No. of points	Tumour size	Depth of invasion	Angioinvasion	Mitotic index
0	< 1 cm	Mucosa/ submucosa	Absent	< 2/50 HPF
1	1–1.9 cm	Muscularis propria or deeper	Present	≥ 2/50 HPF
2	≥ 2 cm	–	–	–

Risk assessment 0 points — low risk, 1–2 points — indirect risk, ≥ 3 points — high risk

Follow-up imaging examinations:

— for lesions in the rectum: EUS, colonoscopy, MRI;
— for lesions in the colon: CT, colonoscopy;
— liver assessment: contrast-enhanced MRI, multi-detector CT.

It is recommended that serum CgA is determined for ten years.

A precise system of risk assessment for rectal NENs has been developed, including a combination of four features: size, depth of invasion, vascular invasion, and mitotic index [8, 21]. Each parameter can be awarded 0–2 points (Table IV). Zero points means a low-risk patient, 1–2 points — a medium risk patient, and 3 or more points — a high-risk patient. Low-risk patients (lesion < 1 cm, limited to the mucosa/submucosa, without vascular invasion, mitotic index < 2/50 HPF) do not require imaging tests for the assessment of the stage of the disease, and do not need monitoring. In medium-risk patients imaging examinations should be considered and follow-up tests performed. High-risk patients require imaging examinations before the planned treatment, and frequent follow-up examinations, due to a high risk of distant metastases (47%) and local recurrence (31%).

Minimal consensus statement on follow-up:

Minimal consensus on follow-up examinations in colorectal NENs:

— *for lesions in the rectum: EUS, colonoscopy, MRI;*
— *for lesions in the colon: CT, colonoscopy;*
— *liver assessment: contrast-enhanced MRI, multi-detector CT;*
— *all lesions larger than 2 cm will require follow-up; smaller tumours should be followed up in the presence of poor prognostic factors (*evidence level 3).*

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*evidence level according to OCEBM [68]

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