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

Nowotwory neuroendokrynne jelita grubego — zasady postępowania (rekomendowane przez Polską Sieć Guzów Neuroendokrynnych)

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Abstract
Neuroendocrine neoplasms of the large intestine account for 20% of all neuroendocrine neoplasms (NENs) and are most commonly found in the rectum. The rate of detection of colorectal NENs is increasing, and this tendency will continue due to the widespread use of colonoscopy as a screening tool and the removal of all diagnosed lesions.
This paper provides updated guidelines for the management of patients with colorectal NENs. Recent data on epidemiology, clinical characteristics, biochemical, and pathomorphological diagnosis as well as useful imaging techniques are presented. We look in detail at novel methods of treatment including endoscopic and surgical management, pharmacological and radioisotope therapy. We summarise monitoring of the treatment. **(Endokrynol Pol 2013; 64 (6): 494–504)**

Key words: *colorectal neuroendocrine neoplasms; epidemiology; diagnosis; treatment; follow-up*

Streszczenie
Nowotwory neuroendokrynne (NENs) jelita grubego stanowią 20% wszystkich nowotworów neuroendokrynnych. Najczęstszą ich lokalizacją jest odbytnica. Nowotwory neuroendokrynne jelita grubego są wykrywane coraz częściej i liczba ta będzie wzrastać z uwagi na powszechność wykonywania kolonoskopii, w tym badań przesiewowych oraz usuwanie wykrytych zmian. W pracy przedstawiono aktualne zalecenia dotyczące diagnostyki i terapii NEN jelita grubego, z uwzględnieniem diagnostyki biochemicznej, patomorfologicznej, nowych technik obrazowania oraz leczenia endoskopowego, chirurgicznego, farmakologicznego i radioizotopowego. Omówiono także epidemiologię, charakterystykę kliniczną i monitorowanie leczenia. **(Endokrynol Pol 2013; 64 (6): 494–504)**

Słowa kluczowe: *nowotwory neuroendokrynne jelita grubego; epidemiologia; diagnostyka; leczenie; monitorowanie*

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1. Epidemiology

1.1. Introduction

The rate of detection of colorectal neuroendocrine neoplasms (NENs) is increasing, and this tendency will continue due to the widespread use of colonoscopy as a screening tool and the removal of all diagnosed lesions [1–5, 9, 12]. As the prognosis and management methods in colorectal NENs located in the colon differ from those for rectal NENs, they are discussed separately.

1.2. Epidemiology

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 of the disease is more frequent in females [2]. The average 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 [6]. They are detected by one in 1,000-2,000 endoscopic examinations [1, 5, 7–9].

According to Japanese authors, rectal NENs are slightly more common in the male population (M/F ratio — 1.5) [10], whereas American and Polish data demonstrates a similar prevalence of these neoplasms in both sexes [2, 5, 9]. The mean age of patients is 56 years. Current statistical data indicates 4.2 cases of rectal NENs in every 1,000,000 citizens [11].

2. Clinical characteristics

2.1. Clinical characteristics and symptomatology

Colorectal neuroendocrine neoplasms arise from two types of cells:

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

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

The symptoms associated with colonic neuroendocrine neoplasms are non-specific. They mainly include changes in bowel movement (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 the most common neoplasm affecting this area, adenocarcinoma. Despite the presence of serotonin-producing cells, carcinoid syndrome with its characteristic symptoms is rarely observed (< 5%) [3]. According to the largest database, SEER, 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, 11, 13]. The mean survival is 261 months for localised lesions, but becomes much shorter in the case of regional lymph nodes metastases or distant metastases (36 months and five months, respectively) [13].

Rectal NENs are most frequently detected accidentally during 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; distant metastases are rare, accounting for 2–8% of all cases [2, 13], which has a significant impact on the prognosis. The five-year survival rate is 75–88%, depending on the histological grade, proliferation index and clinical stage [2]. The mean survival in the case of locally advanced tumours is 290 months, but if the regional lymph nodes metastases or distant metastases occur, it is 90 months and 22 months, respectively [13].

MEN syndrome and other genetically conditioned syndromes are very rarely associated with colorectal NENs [12]. NENs in first-degree family members increase the risk of the disease by four times.

In 13% of patients with a colorectal NEN, another neoplasm develops [2, 4, 5]. The gastrointestinal tract, including intestines, is the most common site for synchronic tumours, while metachronous neoplasms affect the lungs, prostate gland and urinary tract. The detection of gastric GIST as a metachronous tumour in a patient with rectal NEN and hepatic and osseous metastases has recently been presented by Polish authors [59].

3. Diagnostics

3.1. Biochemical diagnostics

We do not have a specific marker for colorectal neuroendocrine neoplasms. Determination of serum chromogranin A (CgA) concentration is still the most valuable method of monitoring, therapy and anticipating the course of the disease. CgA concentration may be elevated and correlate with the severity

of the neoplastic disease, but frequently it is only slightly increased or remains normal [14–16, 61, 63] *(*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 [17, 18]. The human chorionic gonadotropin levels may also be increased [19] *(*evidence level 5)*.

In certain cases of tumours derived from the rectum, it can be helpful to determine the levels of the pancreatic polypeptide or enteroglucagon secreted by the neoplastic cells, but the usefulness of this type of tests has not been confirmed yet *(*evidence level 5).*

Minimal consensus on biochemical tests:
CgA assessment may be helpful.

3.2. Pathomorphological diagnostics

3.2.1. Pathogenesis

Colorectal NENs are divided into colonic NENs and rectal NENs, depending on their anatomical location. Their anatomical location is related to the prognosis and the diagnostic algorithm. Colonic tumours are most frequently found in its proximal section, i.e. in the caecum. Similarly to the above discussed NENs in different gastrointestinal locations, colorectal neuroendocrine neoplasms are divided into *well-differentiated* neuroendocrine neoplasms: NENs G1 and NENs G2, neuroendocrine carcinomas (NECs): large- or small-cell and mixed adenoneuroendocrine carcinomas (MANECs). Colonic NENs 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, in the microscopic assessment diagnosed as neuroendocrine carcinomas or mixed neoplasms (MANEC). Most colonic NENs are highly malignant, and at the diagnosis approximately 30% of cases present metastases to the lymph nodes, mesentery, peritoneum and liver. Rectal NENs are a different group; they are usually polyps of 1 to 2 cm in diameter, with the morphology of well-differentiated neoplasms (NEN G1, G2), infiltrating the mucosa and/or submucosa. However, rectal NENs demonstrate an aggressive clinical course. At the moment of diagnosis, metastases to the lymph nodes are often found. Colorectal NECs are highly malignant neoplasms. Carcinomas arising from the large cells amount for approximately 75% of all colorectal NECs, and 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), and proliferative activity is more than 20%. Immunohistochemical examination sometimes indicates a low CgA expression, and high expression of synaptophysin and CD 56. Small-cell carcinomas account for 25% of colorectal carcinomas, and 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% [62]. It should be emphasised that rectal NENs in 28 to 82% express prostatic acid phosphatase, a potential diagnostic pitfall for tumours arising in male patients (Table I).

Table I. ***The pathogenesis of colorectal NENs***
Tabela I. ***Patogeneza NEN okrężnicy i odbytnicy***

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

** evidence level according to CEBM [65]*

Table II. *TNM ENETS and UICC/AJCC classification of colorectal NENs*

Tabela II. *Klasyfikacja TNM UICC/AJCC, ENETS NEN okrężnicy i odbytnicy*

Feature T — primary tumour	Comment
pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour
pT1	Tumour invades mucosa and submucosa, size ≤ 2cm
pT1a	Tumour size < 1 cm in diameter
pT1b	Tumour size 1–2 cm in diameter
pT2	Tumour invades muscularis propria or size > 2 cm and invasion of mucosa or submucosa
pT3	Tumour penetrates muscularis propria and invades subserosa or the fat tissue of the sections unencased by peritoneum

3.2.2. Diagnostic algorithm

In macroscopic assessment, the following elements are considered:

1. The length of the part of the intestine obtained for examination, with the description of the tumour location relative to the intestine resection margins (proximal, distal and circumferential or radial margin, examined in the segments of the large bowel either unencased or incompletely encased by peritoneum — should be marked with ink).
2. Tumour assessment: number, size in three dimensions, mutual relation of the tumours, cross-section appearance, considering extravasation and foci of necrosis, relation of the tumour to the intestinal wall layers.
3. Condition of the mucosa at the tumour site (ulceration present/not present).
4. Condition of the serosa at the tumour site.
5. Presence and size of the lymph nodes.
6. Presence of other tumours in the intestinal wall.

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

1. Histological type of the NEN according to the WHO 2010 classification.
2. The histological grade G according to ENETS/WHO 2010.
3. Pathomorphological pTNM staging according to ENETS and AJCC/UICC.
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.

Table III. *Colorectal GEP NENs staging*

Tabela III. *Ocena stopnia klinicznego zaawansowania NEN jelita grubego*

Stage	TNM feature
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

Regarding 1 and 2: Histopathological type of colorectal NENs according to the WHO 2010 classification and the histological grade of the NEN according to the integrated ENETS/WHO 2010 system are presented in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumors)" (*pp. 418–443*).

Regarding 3: Pathological pTNM and clinical staging.

The staging of colorectal neuroendocrine neoplasms is verified using the TNM classification according to AJCC/UICC and ENETS. As for this neoplasm location, 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 presents TNM classification according to UICC/AJCC and ENETS criteria. Table III presents the assessment criteria for clinical staging of colorectal NENs.

3.3. Prognostic indicators in the histopathological report

The risk factors of colorectal NEN associated with metastases include: tumour over 2 cm in diameter, invasion of the muscular layer of the colorectal wall, vasoinvasion, and more than two mitotic figures/10 HPF. It is recommended to determine the focal coagulative tumour necrosis, which indicates a more aggressive tumour.

An important parameter in the histopathological report on a colorectal NEN is the assessment of the proximal, distal and circumferential margin (radial or mesenteric). The circumferential margin is assessed in the segments of gastrointestinal tract either unencased or incompletely encased by peritoneum. It should be noted that during macroscopic assessment of the surgical material, it should be marked with ink. It is recommended to note the distance between the tumour foci with the deepest infiltrations and the circumferential (radial) margin line. A margin of

> 1 mm indicates complete resection, whereas a margin of ≤ 1 mm is interpreted as incomplete.

Minimal consensus on pathology:

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 (NEN) and neuroendocrine carcinomas (NEC) or mixed neoplasms (MANEC);*
- *histological G grading referring to well-differentiated neoplasms (NEN G1, NEN G2);*
- *pTNM histopathological staging according to ENET and AJCC/UICC classification systems (it is important to provide affiliation of the classification in each case);*
- *assessment of surgical margins.*

*Histopathological diagnosis of NEN must be necessarily confirmed by immunohistochemical tests assessing expression of the neuroendocrine markers: synaptophysin and chromogranin A, as well as the Ki-67 proliferative activity using the MIB1 antigen [62] (*evidence level 3).*

3.3. Location diagnostics

3.3.1. Endoscopic diagnostics

The basic diagnostic method in colorectal NENs is colonoscopy with 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 mini-probe USG.

Colonic NENs are most frequently lesions which macroscopically resemble cancer infiltration; diagnosed early, they are in the form of submucosal polyps/tumours.

Most rectal NENs (80%) demonstrate characteristic morphological features. They are nodules with a wide base, smooth at the surface, covered by a mucosa of normal appearance, or slightly yellow/white [5–9]. Atypical features (observed in 20%) include: semi-pedunculated shape, reddening of the mucosa, central depression, erosion or ulceration on the surface. Atypical features occur mostly in lesions larger than 1 cm. Ulceration of the surface is associated with a worse prognosis. Lesions are usually single. They are usually located in the middle part of the rectum.

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

EUS allows the ability to distinguish 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 choosing the optimal therapy (i.e. endoscopic or surgical treatment) [24, 25, 60]. Using EUS enables the ability to assess precisely the size of the lesion, determine the depth of infiltration, and describe the condition of lymph nodes. Sensitivity and specificity of this test in the assessment of the depth of infiltration is 87% and 93%, respectively [6]. Echoendoscopic features of colorectal NENs manifested as polyps include a well demarcated, iso- or hypoechogenic, homogenous lesion 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 up to 1 cm in diameter, some authors do not recommend EUS as a tool for assessment of the stage of disease advancement [26].

Classical colonoscopy is the basic examination in the diagnostics of colorectal tumours, including neuroendocrine lesions. Colorectal imaging is also possible with the use of video capsule endoscopy [27].

3.3.2. Other imaging examinations

As mentioned above, colonoscopy supplemented by EUS examination is of basic importance in the diagnostics of colorectal tumours. In the case of lesions closing the intestinal lumen, full colonoscopy is impossible. In such cases, CT/MR colonography is recommended [20, 21].

To assess the stage of advancement, USG, CT/MR and SRS may be used.

Abdominal ultrasound is a useful tool for the initial assessment of hepatic metastases and the possibility of fine-needle biopsy. Multiphase computed tomography or magnetic resonance is used to assess the lesions in the chest, abdominal cavity and pelvis. Scintigraphy of somatostatin receptors enables detection of lesions with increased SSTR expression, which is necessary to determine patient eligibility for the treatment with 'hot' somatostatin analogues.

In the case of negative SRS results, a PET/CT examination should be considered after the administration of 18 FDOPA, and for G2 and G3 NENs, PET/CT scan after the administration of 18 FDG [22, 23].

Minimal consensus on imaging:

- *Colonoscopy is the test of choice in the diagnostics of colorectal tumours;*
- *CT/MR/SRS are recommended for the assessment of the stage of tumour advancement and detecting metastases (*evidence level 3–4).*

** evidence level according to CEBM [65]*

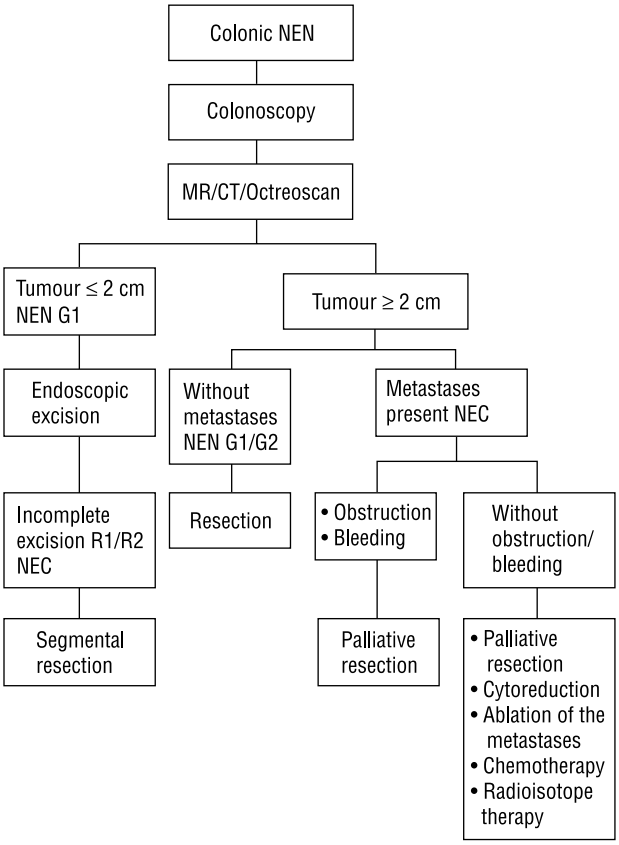

Figure 1. *Algorithm for the treatment of colonic neuroendocrine neoplasms (NEN) (according to Caplin M et al. [12]). MR — nuclear magnetic resonance; CT — computed tomography; NEC — neuroendocrine carcinoma; G1, G2 — neuroendocrine neoplasms carcinoma; R1 — microscopically incomplete resection; R2 — macroscopically incomplete resection*

Rycina 1. *Algorytm leczenia nowotworów neuroendokrynnych (NEN) okrężnicy (wg Caplin M. i wsp. [12])*

4. Treatment

4.1. Surgical treatment

4.1.1. Surgical treatment of colonic NENs

In the surgical treatment of colonic NENs, it is recommended to follow general rules adapted for colorectal adenocarcinomas. If possible (in surgical patients with the possibility of ensuring tumour-free proximal, distal and radial margins), it is recommended to perform a radical resection appropriate for the part of the intestine, including the regional lymph nodes (**evidence level 1*). In NENs G1, G2 with distant metastases, mostly to the liver, a palliative resection with regional lymphadenectomy is recommended (**evidence level 1*), or, if it is technically possible, maximal tumour cytoreduction *(*evidence level 2)*, even if complete reduction is not achieved [47]. In the case of invasion of the adjacent organs, if possible from the technical point of view, a multi-organ 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)* [48].

Figure 1 presents the recommended algorithm for the treatment of colonic neuroendocrine neoplasms (NENs).

4.1.2. Surgical treatment of rectal NENs

Patients with rectal NENs are referred to surgical therapy if the lesion does not qualify for endoscopic treatment (invasion of muscularis propria, regional lymph nodes metastases) *(*evidence level 1*). If there are no metastases to the regional lymph nodes, the tumour requires transrectal resection, as the risk of dissemination of the disease is lower than after anterior resection *(*evidence level 1*) [49, 50]. In locally advanced tumours without distant metastases, resectional procedures are recommended, preferably saving the sphincters, as well as anterior resection with TME (total mesorectal excision), or, if necessary, abdominosacral amputation *(*evidence level 1)*. Radical surgery is performed for tumours larger than 2 cm or between 1 and 2 cm, if the muscular membrane is invaded. Surgery may be radical even in the case of lymph nodes invasion in T3 and T4 tumours, if no distant metastases are present [50–52]. The effect of radical resection on the development of distant metastases is not known. In locally and systemically advanced tumours with distant metastases, radical resection is not recommended (e.g. abdominosacral amputation of the rectum) due to an unfavourable prognosis. Survival is from six to a maximum of nine months after the diagnosis [53–56]. Only palliative anterior resection is accepted in the case of bleeding tumours, if local haemostasis is unsuccessful (e.g. argon plasma coagulator, APC) or if obstruction occurs *(*evidence level 1)*. In NENs G1, G2 with metastases limited to the liver, a radical local excision of the tumour with subsequent resection of the hepatic parenchyma (metastasectomy) *(*evidence level 1*), or in certain cases, liver transplantation *(*evidence level 4)* may be considered [57, 58, 60]. In small tumours with perirectal lymph nodes metastases, aggressive surgical treatment is recommended, particularly in younger patients [50, 53]. Some of these patients may require palliative resection of the rectum due to obstruction or bleeding, or reduction of the tumour mass. In the case of other than hepatic distant metastases, aggressive surgical management does not significantly influence the length of survival. Figure 2 presents the recommended algorithm for the treatment of rectal neuroendocrine neoplasms (NENs).

** evidence level according to CEBM [65]*

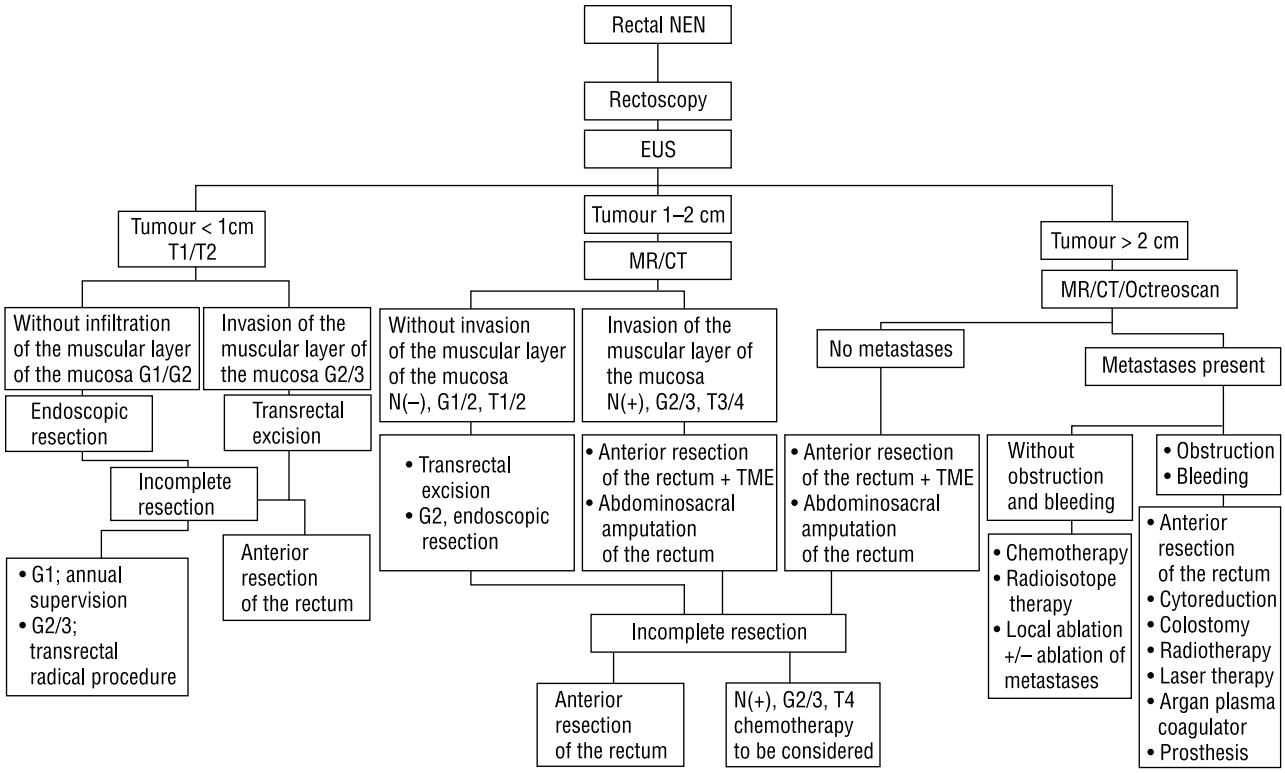

Figure 2. *Algorithm for the treatment of rectal neuroendocrine neoplasms (NENs) (modified according to Caplin M. et al. [12]). MR — nuclear magnetic resonance; CT — computed tomography; EUS — endoscopic ultrasonography; N(–) — non-invaded regional lymph nodes; N(+) — regional lymph nodes invaded with metastases; G1, G2 — neuroendocrine neoplasms; G3 — neuroendocrine carcinoma; TME — total mesorectal excision; T1 — infiltration does not transgress the submucosa; T2 — infiltration does not transgress the muscular membrane; T3 — infiltration does not transgress the serous membrane; T4 — infiltration penetrates the serosa; possible invasion of the adjacent organs*

Rycina 2. *Algorytm leczenia nowotworów neuroendokrynnych (NEN) odbytnicy (zmodyfikowano wg Caplin M. i wsp. [12])*

Minimal consensus on surgical treatment:

*Minimal scope of surgical treatment refers to endoscopic excision (polypectomy) or transrectal local excision, resection with the extent depending on the tumour location (with the intention to treat/palliative), and possible cytoreductive procedure (*evidence level 1).*

4.2. Endoscopic treatment of colorectal neuroendocrine neoplasms

Endoscopic treatment of colorectal NENs concerns mostly lesions in the rectum, because in colonic NENs surgical management is recommended due to the risk of regional lymph nodes metastases. The risk of lymph nodes metastases in colonic NENs is 4% for lesions ≤ 1cm, limited to the mucosa, and over 14% for the remaining lesions [28]. 80% of rectal NENs are ≤ 1 cm; they invade the submucosa and give no metastases, so they can be qualified for local endoscopic treatment. Larger lesions, up to 2 cm, may also be treated endoscopically. It is conditional upon lack of infiltration of the muscularis propria, non-invaded lymph nodes, covering mucosa without ulceration.

Classical polypectomy cannot be performed in the treatment of colorectal neuroendocrine neoplasms, as these lesions derive from the second layer of the gastrointestinal wall 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 mucosal dissection (ESD) [29–32]. The latter is considered the method of choice. ESD, compared to EMR, provides a higher ratio of en-bloc and R0 resections (100% *v.* 89% and 82–91% *v.* 65–70%).

The EMR method consists in submucosal administration of certain substances, most often saline solution with adrenalin, and subsequent removal of the lesion with a diathermic loop. This method has a few variants. The most popular ones include: strip biopsy and cap assisted endoscopic mucosal resection (EMR-C). The strip biopsy technique requires using a two-channel

** evidence level according to CEBM [65]*

endoscope. One channel is used to introduce forceps elevating the lesion after the initial injection, and the other to introduce the cutting loop.

EMR-C is performed with the use of a classical endoscope. A plastic cap is placed at the end of the endoscope. After injecting the submucosa, the loop is placed on the edge of the cap, the lesion is aspirated into the cap, and then cut off with the loop. The basic limitation for the EMR techniques is the size of the lesion. Any neoplastic lesion that may be removed in one piece must be of 1–1.5 cm in diameter. Removing larger lesions is possible only via piecemeal resection, and is associated with a high risk of local recurrence (up to 5%).

ESD enables removing the tumour in one piece (en-bloc), within the healthy tissue, regardless of the size of the lesion, fibrosis or ulceration. Application of this method became possible after the Olympus Tokyo company had introduced a special knife (insulation tip-IT knife) which reduces the risk of perforation due to a porcelain ball-shaped tip. The procedure starts with 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 in order 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 distant results [30].

ESD procedures are performed in Poland in the following centres: General, Gastroenterological and Gastrointestinal Neoplasms Surgical Teaching Hospital, Medical University of Lublin; Endotherapy Non-public Health Care Facility in Warsaw, and the Department of Gastroenterology, Pomeranian Medical University in Szczecin. Szczecin has seen the largest number of procedures performed [15].

Minimal consensus on endoscopic treatment:

Endoscopic treatment of colorectal NENs concerns mostly lesions in the rectum.

*With lesions of up to 1 cm — endoscopic mucosal resection and endoscopic submucosal dissection (*evidence level 3).*

4.3. Medical treatment

4.3.1. Biotherapy

Somatostatin analogues (SSA), m-TOR inhibitors:

Carcinoid syndrome is extremely rare in colorectal neuroendocrine neoplasms. If it is present, the primary tumour probably arises from the initial section of the large intestine. In the case of disseminated neoplastic process with the symptoms of excessive serotonin secretion, using SSA is the treatment of choice (evidence level 1). In non-functional neuroendocrine neoplasms (NF-NENs), there is no conclusive evidence of anti-neoplastic effectiveness of somatostatin analogues [12], but their effectiveness may not be excluded, due to the recently published results of the CLARINET, RADIANT-2 study and Polish observations [33, 59, 64].

A detailed analysis of the RADIANT-2 subgroups, including only the patients with advanced G1/G2 colorectal NENs (39 cases, mostly with primary tumours located in the colon) has demonstrated that, statistically, the progression-free survival of the patients who received everolimus plus octreotide LAR (19 patients, including 14 with histological grade G1) was significantly longer (median PFS 29.9 months) than in the patients receiving placebo plus octreotide LAR (20 patients, including 12 with the histological grade G1) (median PFS 6.6 months; the hazard ratio was HR: 0.34; 95% CI:0.13-0.89; p = 0.011, which resulted in a 66% relative reduction in the risk of progression in patients treated with everolimus. Tumour regression (not meeting the CR and PR RECIST criteria) was observed in the everolimus arm in 67% of patients, and in the placebo arm in 37%. Assessment of the role of somatostatin analogues in the treatment of colorectal G1/G2 NENs is difficult due to the lack of a referential arm, in which only placebo would be administered; however, everolimus seems to be active in these cases *(*evidence level 3*).

4.3.2. Systemic chemotherapy

Systemic chemotherapy is primarily dedicated to neuroendocrine carcinomas (NECs). Detailed recommendations are presented in the section on general recommendations in GEP NENs (*see pp. 418–443*).

In the case of progression of advanced non-small cell NEC, after the treatment with cisplatin and etoposide, a second-line chemotherapy may be considered, including temozolomide + bevacizumab (± kapecitabin) or irinotecan plus 5-FU [34, 35] *(*evidence level 4).*

If we can immunohistochemically determine the expression of O^6-methylguanine-DNA-methyl transferase (MGMT), which is a DNA repair enzyme responsible for the removal of methyl groups from guanine in the O^6 position, then in the absence of staining the neoplastic cells for MGMT, a temizolomide-based chemotherapy regimen may be introduced in the treatment of colorectal NEN *(*evidence level 4).*

Patients with MANEC of the large intestine should be treated following the standards of the oncological management dedicated to classical colorectal carcinomas [34].

** evidence level according to CEBM [65]*

Table IV. ***Risk assessment system for rectal NENs — CaRRS (according to Fahy et al. [4])***

Tabela IV. ***System oceny ryzyka dla NEN odbytnicy — CaRRS (wg Fahy i wsp. [4])***

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	–	–	–

Minimal consensus statement on medical therapy:

Advanced non-functional G1/G2 NEN — somatostatin analogues with or without everolimus may be considered; in the case of progression, systemic chemotherapy based on 5-fluorouracil (e.g. 5-FU + doxorubicin + streptozocin).

*The basic treatment of NEC is chemotherapy based on platinum derivatives (*evidence level 3).*

4.4. Radioisotope treatment

There is no separate data concerning the effectiveness of targeted therapy with radioisotope labelled somatostatin analogues (PRRT) in the group of patients with colorectal NENs. Eligibility for the treatment is in accordance with the principles described in the general section.

Taking into account the high degree of effectiveness of PRRT in other GEP NENs, PRRT should be considered in patients with disseminated or non-surgical NENs G1, G2, with increased somatostatin receptor expression confirmed in the scintigraphic examination, if other available treatment methods prove ineffective [36–46].

Minimal consensus statement on isotope treatment:

*PRRT should be considered in patients with disseminated or non-surgical G1 and G2 NENs, with increased somatostatin receptor expression demonstrated in SRS, if other available treatment methods prove ineffective (*evidence level 4).*

4.5. Follow-up

After a complete endoscopic or surgical removal of the colorectal neuroendocrine neoplasm, the following follow-up is recommended [12]:

— G1, G2 tumours up to 1 cm, without the lymph nodes 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 year;
— tumours larger than 2 cm: obligatory follow-up examinations;
— G1/G2: 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.

Follow-up imaging examinations:

— For lesions in the rectum: EUS, colonoscopy, MR
— For lesions in the colon: CT, colonoscopy
— Liver assessment: contrast-enhanced MR, multidetector CT
— It is recommended to determine serum CgA 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 [6]. Each parameter can be awarded 0–2 points (Table IV). Zero points means a low-risk patient, 1–2 points – a patient of medium risk, 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%).

Risk assessment: 0 points — low risk, 1–2 points — medium risk, ≥ 3 points — high risk.

Minimal consensus statement on follow-up:

— *For lesions in the rectum: EUS, colonoscopy, MR*
— *For lesions in the colon: CT, colonoscopy*
— *Liver assessment: contrast-enhanced MR, multidetector 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 CEBM [65]*

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