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Endoscopic, transanal, laparoscopic, and transabdominal management of rectal neuroendocrine tumors

Louis de Mestier, MD, Gastroenterologist and Research Fellow [a, b, c, *],
Diane Lorenzo, MD, Specialist Registrar in Gastroenterology [a, b],
Caroline Fine, MD, Specialist Registrar in Gastroenterology [d],
Jérôme Cros, MD, PhD, Assistant Professor of Pathology [b, c, e],
Olivia Hentic, MD, Gastroenterologist [a],
Thomas Walter, MD, PhD, Professor of Gastroenterology [d],
Yves Panis, MD, PhD, Professor and Head of Colorectal Surgery [b, f],
Anne Couvelard, MD, PhD, Professor and Head of Pathology [b, c, e],
Guillaume Cadiot, MD, PhD, Professor and Head of Gastroenterology [g],
Philippe Ruszniewski, MD, PhD, Professor of Gastroenterology and Dean of the Faculty of Medicine [a, b, c]

[a] *Department of Pancreatology and Gastroenterology, ENETS Centre of Excellence, AP-HP, Beaujon Hospital, Clichy, France*
[b] *Université de Paris, France*
[c] *INSERM UMR1149, Paris, France*
[d] *Department of Digestive Oncology, ENETS Centre of Excellence, Edouard Herriot University Hospital, Lyon, France*
[e] *Department of Pathology, ENETS Centre of Excellence, AP-HP, Bichat/Beaujon Hospital, Clichy, France*
[f] *Department of Colorectal Surgery, ENETS Centre of Excellence, AP-HP, Beaujon Hospital, Clichy, France*
[g] *Department of Hepato-Gastroenterology and Digestive Oncology, Robert Debré Hospital and Reims-Champagne-Ardennes University, Reims, France*

* Corresponding author. Department of Pancreatology and Gastroenterology, 100 boulevard du Général Leclerc, 92110, Clichy, France.
E-mail address: louis.demestier@aphp.fr (L. de Mestier).

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Rectal neuroendocrine tumors (RNET) are rare tumors but their prevalence is constantly increasing due to a prolonged survival and rising incidence related to a growing number of colonoscopies and improved knowledge. Their main prognostic determinant is tumor stage. While most RNET are localized, their management should be tailored depending on the presence or absence of the factors predictive of lymph-node metastases including tumor size, endoscopic aspect, T stage, grade and lymphovascular invasion. Endoscopic ultrasonography is the most relevant technique for locoregional assessment. Low-risk RNET can be treated using advanced endoscopic resection techniques or transanal endoscopic microsurgery, in expert centers because they require technicity and experience. Conversely, radical surgery with lymphadenectomy should be proposed in the presence of any pejorative factor. The long-term evolution of RNET remains to be specified, and prospective studies should be conducted in order to determine the relevance of the current management strategies.

Introduction

The objective of this review was to achieve a comprehensive appraisal of the management of patients with rectal neuroendocrine tumors (RNET), including the endoscopic, transanal, and surgical therapies. The management of RNET with distant metastases, and that of poorly-differentiated rectal carcinomas, are not specific of the rectum localization and were not tackled in this review.

Epidemiology

RNET account for approximately one-third of all digestive neuroendocrine neoplasms (NEN) [1–3]. The rectum is the first most common location of digestive NEN, with an incidence slightly higher than small-intestine NEN (approximately 1.2/100,000) [3,4]. However, their effective incidence may be underestimated, because all benign RNET may be not systematically reported in registries. The relative incidence of RNET may be higher in Asian countries (up to 50%) [5,6]. The annual incidence of RNET has been gradually rising over the last decades, from 0.15/100.000 in 1985 to 1.2/100.000 in 2012 [2,3,7]. This rise in incidence may be due to the increased number of screening colonoscopy performed, enhanced endoscopic detection, better clinical awareness and more systematic report in registries, as advocated by the increasing incidence of small localized RNET [8].

Significant risk factors of RNET are male gender (OR 1.37–1.92), personal history of previous malignancy (OR 2,96), alcohol consumption (OR 1.56), higher fasting plasma glucose levels (OR 1.08) and dyslipidemia (low high-density lipoprotein-cholesterol level [OR 1.85] and hypertriglyceridemia [OR 1.48]) [7,9]. Finally, RNET predominantly occur during the sixth decade of age, probably because it corresponds to the age at which screening colonoscopy programs start [4].

Circumstances of initial diagnosis

RNET are predominantly detected fortuitously at colonoscopy [10]. In two large Korean epidemiological studies, a RNET was detected in 0.17% and 0.98% of subjects who performed a screening colonoscopy [7,9]. RNET are generally diagnosed at an early, localized stage. Lymph node metastases (LNM) and distant metastases are uncommonly found at the time of initial diagnosis, accounting for 2%–8% each [2,8,9,11]. The rate of patients with symptoms at diagnosis is highly variable among series, up to 40% [12,13], but is most likely about 10–15% [10]. The most frequent symptoms present at

diagnosis include hematochezia (3%–33%) and change in bowel habits (5%–28%), likely unrelated to RNET [10,13,14].

The endoscopic aspect of RNET is usually typical of small submucosal neoplasms developing into the lower and intermediate portion of the rectum [12,13]. Most of them are polypoid with hemispherical bulging (65%–80%) [15]. They are classically described as having a yellowish coloration, which is in fact not so frequent (31% of cases in a series [15]) (Fig. 1). Half of RNET measure less that 5 mm, while lesions measuring 11–19 mm or >20 mm account for approximately 8% each [8,13]. A limited proportion (<10%) of RNET may present with a central depression or ulcer [10,16].

Pathological diagnosis

All pathologic samples should be examined by an expert pathologist. The pathologic diagnosis of RNET is not different from that of other NEN [17]. Synaptophysin is positive in almost 100% of cases, while chromogranin A staining is only positive in 28%–58% of cases, because RNET more frequently express chromogranin B [12,18]. In case of diagnostic issues, CD56 immunostaining can be useful [19].

The histo-prognostic grade is essential for the prognostic characterization and therapeutic decision-making [17] (Table 1). The 2017 WHO classification has subdivided the high-grade category (G3) into

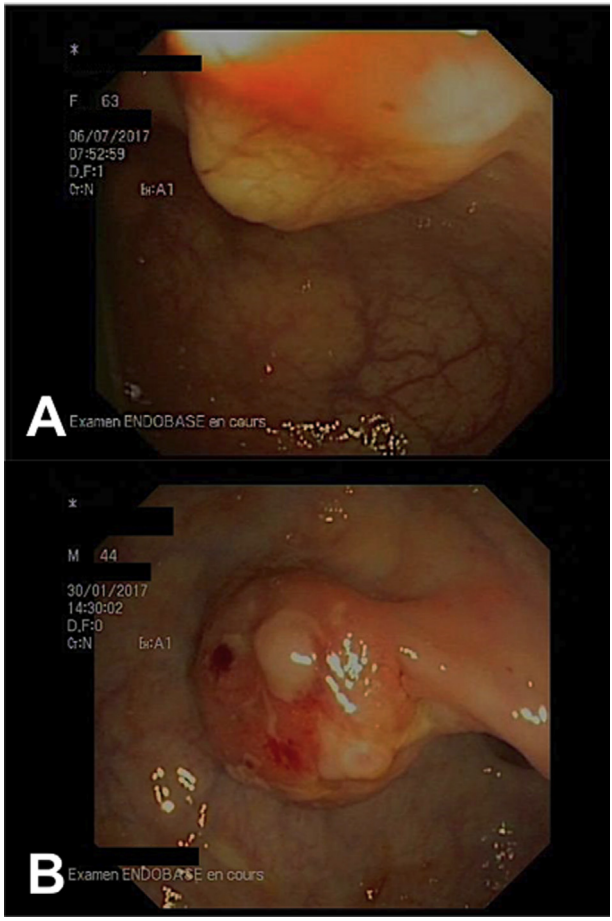

Fig. 1. Endoscopic findings of RNET. (A) Typical aspect: regular, yellowish, set-in-the-wall sessile lesion with smooth surface. (B) Atypical aspect with a pedunculated shape associated with erosions and hyperemia.

well-differentiated and poorly-differentiated NEN, the former having biological behavior closer to those of G2 NET. Well-differentiated G3 RNET are rare as it accounted for 12.5% of all rectal G3 NEN in a recent European collaboration [20]. Although the 2017 classification only concerned pancreatic NEN, it will be extended to all digestive organs within the next years, and is already used in routine practice for RNET [21].

Studies reported before 2015 generally assessed tumor grade based on the mitotic count rather than Ki67 [2]. Over the last years, several papers have shown Ki67 was reproducible and reliable and strongly correlated to that of resected specimen [22–24].

Prognostic characterization of RNET

Numerous studies have explored the risk factors for metastatic spreading. The essential prognostic factor of RNET is disease stage. In apparently localized tumors, the main factors associated with LNM and impaired prognosis are the invasion of the muscularis layer (stage T2) or beyond, tumor size, depression in or ulceration of the lesion, histoprognostic grade and lymphovascular invasion (LVI) [2,8,13,25–28]. Globally, all cases of RNET with LNM have at least one risk factor [19,29].

However, the reported studies were highly heterogeneous, which have limited the possibility of meta-analysis and determination of meaningful relative risks [2]. In particular, some studies have analyzed colonic and rectal NEN together, while other studies have analyzed NET and poorly-differentiated neuroendocrine carcinoma together, which have fundamentally different molecular landscape, clinical behavior and treatment.

Tumor stage

Tumor stage is the main prognostic factor of rectal NETs [2,28,30]. RNET must be classified according to the 8th edition of UICC Tumor-Nodes-Metastases classification (Table 2) [31], which only applies to well-differentiated RNET as poorly-differentiated carcinoma must be classified as for rectal adenocarcinoma. In a recent American epidemiological report, the 5-year disease-specific survival rate was 99.3%, 96.7% and 44.1%, for patients with local, regional and metastatic RNET, respectively [8].

The group of patients with regional LNM is heterogeneous and could be further divided depending on the number of invaded lymph nodes. Fields et al. [32] proposed to classify the regional LNM in operated patients as N0 (no positive lymph node), N1 (1–4 positive lymph nodes) or N2 (≥5 positive lymph nodes).

Most RNET are limited to submucosa, although 8%–19% of them may invade the muscularis propria (T2) [11,18,19,22]. T stage ≥2 is associated with an independent increase of the risk of LNM [6,11,13,33].

Table 1
2010 and 2017 WHO histoprognostic classifications of neuroendocrine neoplasms.

	Ki67 index	Mitotic count (number of mitoses per 10 high-power fields)
Grade 1 (G1)	<3% *	<2
Grade 2 (G2)	3%–20%	2–20
Grade 3 (G3)	>20%	>20

2010 classification			2017 classification		
	Grade	Differentiation		Grade	Differentiation
G1 NET	G1	Well differentiated	**G1 NET**	G1	Well differentiated
G2 NET	G2	Well differentiated	**G2 NET**	G2	Well differentiated
G3 NEC	G3	Poorly differentiated	**G3 NET**	G3	Well differentiated
			G3 NEC	G3	Poorly differentiated
MANEC	Mixed adeno-neuroendocrine carcinoma		**MiNEN**	Mixed neuroendocrine – non-neuroendocrine neoplasm	

NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; * ≤ 2% in 2010 classification.

Table 2
UICC Tumor-Node-Metastases classification of RNET, 8th edition.

TX	Primary tumor status cannot be assessed
T0	No evidence of primary tumor
T1a	Invades lamina propria or submucosa and size <1 cm
T1b	Invades lamina propria or submucosa and size 1–2 cm
T2	Invades lamina propria or submucosa and size >2 cm Or invades muscularis propria
T3	Invades the subserosal tissue without invading serosa
T4	Invades peritoneum or other organs
NX	Regional lymph-node status not evaluable
N0	No regional lymph-node metastasis
N1	Regional lymph-node metastases
Mx	Metastatic status not evaluable
M0	No distant metastasis
M1	Distant metastases
M1a	Hepatic metastasis only
M1b	Extrahepatic metastasis only
M1c	Hepatic and extrahepatic metastases

Tumor size

Between 70% and 85% of RNET have a size <10 mm [8,10,13,18,19,22,34]. The risk of metastases is very low (<3%) in RNET < 10 mm, and very high (30%–80%) in RNET ≥ 20 mm in size [2,6,8,11,35]. Between these two extremes, 4%–20% of patients with RNET measuring 10–19 mm have synchronous or metachronous metastases. In several large studies (n > 300), the optimal size cut-off to predict the risk of metastases was 15 mm [2,29,34]. However, LNM are possible in patients with RNET < 15 mm in size [29]. Hence, size alone is not sufficient to predict the risk of metastases with sufficient accuracy in RNET < 15 mm, but it should be considered along with the presence or absence of other predictive factors.

Atypical endoscopic features

Atypical endoscopic features (hyperemia, erosions, depression, ulcerations) have been reported in 6%–22% of RNET (Fig. 1) [10,15,35]. Although data in the literature are controversial, such atypia and especially tumor surface changes (erosions, depression, ulcerations) were associated with larger RNET size and an increased risk of LNM [35].

Histo-prognostic grade

The vast majority of RNET are G1 [13]. Between 2% and 13% of RNET are classified G2 or G3 and are associated with a significantly increased risk of metastases as compared to G1 RNET [18,19,22]. Sohn et al. [23] described that the rate of LNM was 6% and 75% in G1 and G2 RNET, respectively. As underlined above, whereas studies before 2015 mainly focused on grade defined by mitotic index, more recent works have confirmed that Ki67 had a significant prognostic impact in RNET [22,23,36].

Lymphovascular invasion

LVI has been frequently but inconstantly reported as a prognosis factor in RNET, because its evaluation suffers from inter-observer variations [23], and because two methodology exist. As routinely assessed using hematoxyllin-eosin coloration, LVI seems to be significantly associated with an increased risk of LNM [22,29], notably in RNET < 10 mm [37]. Alternatively, vascular or lymphatic invasion can be assessed by anti-CD31 immunostaining and elastica van Gieson staining or anti-podoplanin immunostaining, respectively, both combined to an anti-synaptophysin immunostaining to detect the RNET cells [19,38]. LVI was identified in 1%–20% and 30%–60% of RNET when assessed by hematoxylin-eosin alone or with double specific staining, respectively [19,36,38,39]. LVI evaluated by double specific staining was correlated with tumor size in several studies [19,36,39] although its

specificity may not be optimal to predict LNM [38,39]. Hence, double immunohistochemistry greatly increases the sensitivity of detection of LVI but its clinical relevance is not certain and this technique is difficult to apply routinely.

Status of resection margins

Resection margins of rectal NETs after endoscopic resection are sometimes positive at pathological examination. However resection margin positivity is not fully predictive of residual tumor nor recurrence, because the destruction of the neighboring tumor cells by cauterization during endoscopic resection could sterilize the resection site [2,29]. Indeed, in four series analyzed together, when full-thickness transanal endoscopic microsurgery (TEM) or radical surgery was performed after incomplete endoscopic resection, residual tumor was detected in 26/104 patients (25%) only [10,14,37,40,41]. Accordingly, in one large series the positive predictive value of pathological R0 was only 36%, while it was 94% for the endoscopic evaluation [29].

Hence, a pathologically-determined R1 status may result in unnecessary (and potentially morbid) surgical overtreatment. Nevertheless, R1 resection cannot be considered as curative, and salvage therapy must be further discussed [2]. The strategy consisting in performing biopsies of the resection area before considering further salvage therapy requires specific evaluation [2].

Initial management and diagnostic work-up

Initial management

The first step of the management of RNET is their recognition by the endoscopist during the initial colonoscopy [42]. The initial management of RNET may consist in two possible scenarios [2,28,29]. On the one hand, the endoscopic resection of an equivocal rectal polyp – unrecognized RNET – is commonly performed upfront by conventional polypectomy or mucosectomy, which may not achieve sufficient resection margins and frequently require salvage therapy. Therefore, the diagnosis is known afterwards. The factors predictive of LNM and local recurrence must then be assessed to decide if an additional treatment has to be discussed, and which is most appropriate. Otherwise, a rectal polyp suspicious of a RNET can be biopsied (ideally, perform superficial biopsies), photographed and marked for future resection. Marking can be performed by placing an endoscopic clip on the rectal wall opposite to the RNET, followed by an immediate (24–48 h) CT-scan, which will provide precise localization to facilitate future identification. Of note, future local salvage resection may be hampered by a clip (or tattoo) placed too close to the resection area, and by biopsies performed too deeply. Following pathological RNET confirmation, appropriate work-up can then be performed in order to assess the risk of metastases, and the most appropriate treatment can be achieved.

The recognition of RNET during initial endoscopy is thus of great importance, because it allows to prevent some inappropriate resections, and to make a plan for appropriate endoscopic resection at the first procedure, increasing the chances of curative resection [42]. In a large multicenter series, Moon et al. [10] reported that RNET were resected as polyps in 11% of cases, diagnosed by biopsies and then resected in 56% of cases, and suspected as RNET and resected upfront in 33% of cases. Importantly, RNET that were resected upfront as polyps had significantly less frequent R0 rate (23%) in comparison with other cases (69%, $p < 0.001$) [10].

Endorectal EUS

Endorectal endoscopic ultrasonography (EUS) has high diagnostic performances for RNET, including a positive and negative predictive values and a diagnostic accuracy of 81%, 92% and 85%, respectively [15]. At EUS, RNET generally have a round (51%) or nodular (32%) aspect. Their echo pattern can be hypoechoic (19%) or intermediate (78%) and is usually homogeneous. The accuracy of EUS for the determination of the depth of invasion, especially that of the muscularis propria, is above 90% [29,43]. Finally, EUS must evaluate the regional lymph nodes in order to identify signs of possible malignancy, although the penetration of the ultrasound may be too limited to examine the whole perirectal space [42,43].

Hence, EUS should be part of the initial work-up of all RNET, with the exception of those measuring <5 mm without any pathological factor predictive of LNM – and resected in totality if endoscopic removal was performed upfront [2,28,42]. Finally, total colonoscopy is mandatory for all patients with RNET to exclude concomitant colonic cancer and other colorectal NEN, which can occur in up to 8% of cases [44,45].

Pelvic cross-sectional imaging (MRI, CT-scan)

The aims of pelvic magnetic resonance imaging (MRI) are to assess T stage, perirectal extension and regional lymph-node involvement. However, the criteria of mesorectal lymph-node suspiciousness are ill-defined. Two studies [46,47] recently reported that the size of lymph nodes determined by morphological imaging was significantly greater in case of metastatic involvement. A size threshold around 3 mm was associated with an area under the ROC curve of approximately 0.8, but clinical relevance may be limited because the positive predictive value was <15%.

Overall, MRI is clinically relevant for the evaluation of parietal extension, especially in case of RNET > T1, and to suspect LNM in case of lymph-node enlargement [48] (Fig. 2). Hence, it is recommended to perform pelvic MRI (otherwise, CT-scan) as part of the initial work-up of all RNET ≥ 10 mm [2,28]. Nevertheless, in the absence of lymph-node enlargement, LNM cannot be ruled out and therapeutic decision-making must take into account the other factors predictive of LNM.

Distant work-up: conventional morphologic and isotopic imaging

Additional explorations are justified in all RNET ≥ 20 mm in size, and otherwise in case of LNM or high-risk factors of LNM [2,42]. It should include contrast-enhanced thoracic-abdominal-pelvic CT-scan, liver MRI and somatostatin-receptor isotopic imaging (scintigraphy or positron-emitting tomography).

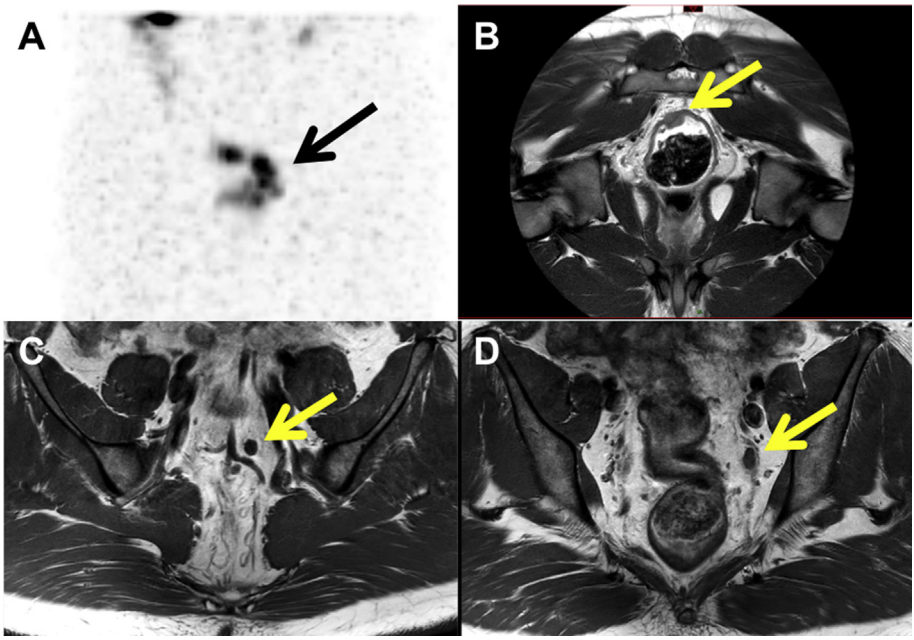

Fig. 2. Imaging work-up of a RNET diagnosed at colonoscopy performed for rectal bleeding in a 44-year old man. A, somatostatin receptor scintigraphy showing multiple focal positivity in the rectum and the mesorectum (arrows), evocative of RNET and associated lymph-node metastases. B, sagittal T2-weighted pelvic MRI showing a 20 × 11 × 14 mm tumor (arrow) localized at 11 cm from anal verge, invading the muscularis propria and the mesorectum. C-D, axial T1-weighted pelvic MRI showing two enlarged (8 mm of small axis) lymph nodes suspect of metastatic spreading.

Because of their typically hypervascular aspect, RNET-associated metastases usually enhance after contrast injection at the arterial phase, with wash-out at the portal phase [49]. MRI – especially diffusion-weighted sequences – has better sensitivity than CT-scan and somatostatin-receptor scintigraphy for the detection of distant lesions, especially liver metastases [50].

Most RNET express somatostatin receptors and are thus suitable for somatostatin-receptor scintigraphy (Octreoscan®) (Fig. 2) or ^{68}Gallium positron-emitting tomography (Fig. 3). The latter should be preferred as it has increased affinity and spatial resolution, requires shorter time and exposes the patient to less radiation. Somatostatin-receptor imaging enables to identify distant metastases with excellent sensitivity.

Techniques of endoscopic resection of RNET

Standard polypectomy and mucosectomy

Polypectomy and mucosectomy (endoscopic mucosal resection [EMR] or strip biopsy) consist in the snare resection of RNET, performed without or with initial saline injection into the submucosa (which aims at reducing the risks of perforation and incomplete vertical resection margins) respectively (Fig. 4) [51]. However, they expose to a risk of piece-meal rather than en-bloc resection, which limits the quality of the pathological examination and increases the risk of incomplete resection. We previously reported that those standard resection techniques yielded only a 59% R0 rate in RNET $\leq$ 10 mm [2].

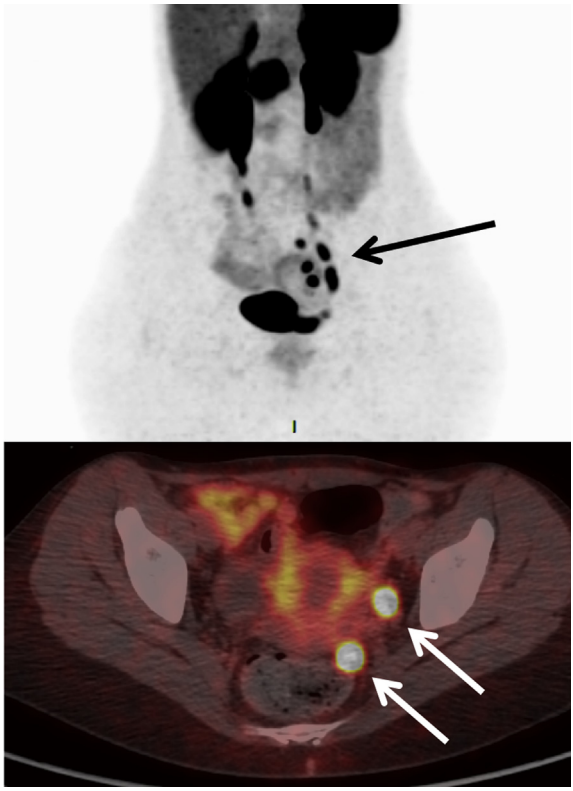

Fig. 3. ^{68}Ga-DOTATOC PET performed for the follow-up of a 63 years old female patient. Endoscopic mucosal resection was performed 6 years before for a RNET of the low rectum measuring 12 mm, G2 (Ki67 4%), with lymphovascular invasion, without adjunctive therapy. PET showing multiple foci of somatostatin receptor expression, corresponding to suspicious lymph nodes at CT-scan, evocative of RNET regional recurrence.

More recently, some studies reported EMR using a circumferential incision around the lesion performed by a stiff snare tip or a dissection knife, enabling to perform a snare resection inside the peripheral incision. It may enable to achieve higher (69–74%) but still insufficient R0 resection rates [52,53].

Hence, as underlined above the polypectomy/EMR area should be marked after the resection to facilitate future localization and salvage therapy in case the margins are positive [2,28,40]. If marking was not performed during polypectomy and the margins are found to be invaded, then the patients should be recalled urgently in order to mark the site prior to healing from the resection attempt, which usually occurs rapidly.

Advanced endoscopic resection techniques

In order to improve the efficacy of endoscopic removal, advanced modified EMR techniques have been developed, such as endoscopic mucosal resection using a cap (EMR-C) (Fig. 5) [54,55] and ligation-assisted endoscopic submucosal resection (ESMR-L) (Fig. 6) [56,57].

More recently, the use of endoscopic submucosal dissection (ESD) has been increasingly reported for RNET (Fig. 7) [43,58]. It carries a higher risk of perforation and rectal bleeding than other techniques [2,59]. Interestingly, Chen et al. the rates of incomplete resection and complications were reported to decrease by 71% and 78% respectively, over a 5-year period [58]. Hence, ESD requires specific skill, experience, longer operative time and should only be carried out in expert centers.

Comparison of the endoscopic resection techniques

Comparisons between endoscopic resection techniques are limited, because studies are few, heterogeneous, nearly all retrospective and with limited follow-up. In a previous analysis of 25 studies including 1094 patients, we reported that ESMR-L and ESD were the most effective techniques, with respective mean R0 rates of 94.8% and 89.6% (vs. 59.1% and 72.4% for polypectomy/EMR and EMR-C, respectively) and very low recurrence rates, but with limited follow-up (<5 years) [2]. Similarly, in a meta-analysis of 14 comparative studies (782 patients), He et al. [60] reported that modified EMR (EMR-C or ESMR-L) and ESD both achieved significantly higher complete resection than simple EMR, but with no difference between them.

Regarding RNET $\leq$ 10 mm, most recent studies reported similar efficacy of ESD and ESMR-L [16,59]. However, a meta-analysis regrouping 7 studies (386 patients) reported that ESMR-L achieved a higher R0 rate than ESD (96.1% vs. 83%) for RNET $\leq$ 10 mm [61]. Additionally, ESD took significantly longer operative time and tended to cause more complications ($p = 0.11$). Hence, ESMR-L may be the most appropriate technique of endoscopic resection of RNET $\leq$ 10 mm.

Data are more limited regarding RNET measuring >10 mm. Modified EMR requires cap aspiration, which may be more difficult in this setting. Conversely, the R0 rate and tolerance of ESD were demonstrated not to be impaired in patients with RNET > 10 mm compared to $\leq$10 mm [16,58]. Furthermore, one study reported that ESD, in comparison to modified EMR-C, achieved higher R0 resection rate (100% vs. 70%) and lower recurrence (0% vs. 17%) in 55 patients with RNET < 16 mm (median size, 12.3 ± 3.7 mm, vs. 10.4 ± 3 mm, respectively) [62]. Hence, ESD appears as the most appropriate technique for the endoscopic resection of RNET sized >10 mm, whenever it is indicated.

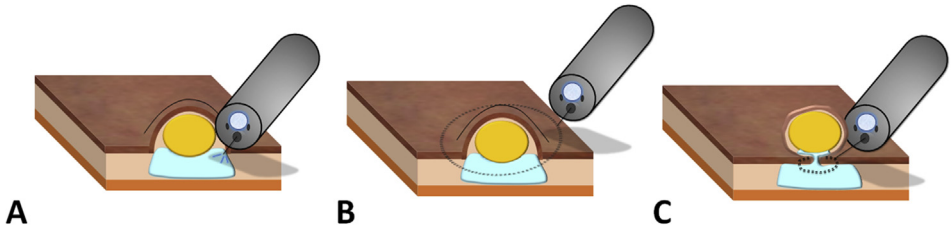

Fig. 4. Technique of endoscopic mucosal resection (EMR). A, submucosal saline injection. B, position of a snare around the lesion. C, tightening of the snare at the basis of the lesion and resection using blended electrosurgical current.

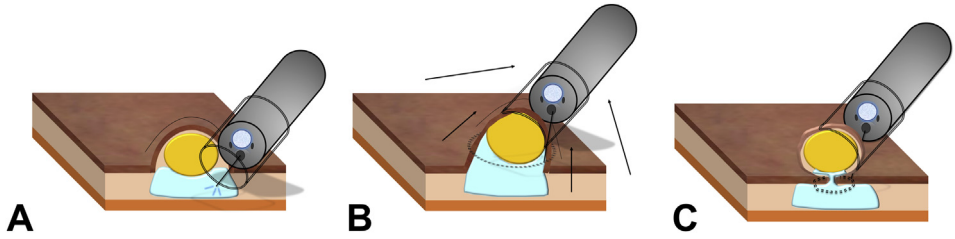

Fig. 5. Technique of endoscopic mucosal resection using a cap (EMR-C). A. position of a cap at the top of the endoscope and submucosal saline injection. B, insertion of an asymmetric snare into the inner rim of the cap, and position around the lesion. Aspiration of the lesion into the cap. C, tightening of the asymmetric snare at the basis of the lesion and resection using blended electrosurgical current.

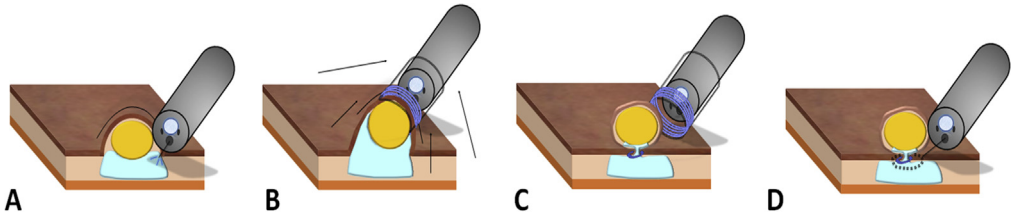

Fig. 6. Technique of ligation-assisted endoscopic submucosal resection (ESMR-L). A, submucosal saline injection. B, position of a band ligation system at the top of the endoscope (similar to that used for the ligation of esophageal varices) and aspiration of the lesion into the cap. C, deployment of an elastic band beneath the lesion. D, snare resection at the basis of the lesion using blended electrosurgical current.

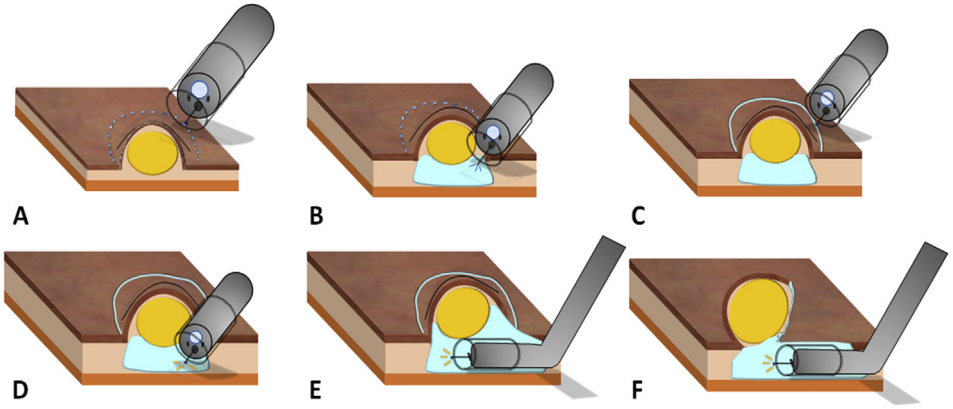

Fig. 7. Technique of endoscopic submucosal dissection (ESD). A, delimitation of the minimal external circumference of the excision zone around the lesion by marking electrocautery dots using an ESD knife. B, submucosal saline injection. C, circumferential incision around the surface delimitated by the dots. D-F, dissection beneath the lesion, along the submucosal plane, using the ESD knife under direct visualization.

Salvage endoscopic therapy following incomplete polypectomy

Endoscopic resection induces tissue fibrosis and hardening, which can make future salvage EMR more difficult and less successful [2]. Adjunctive EMR-C achieved 100% of clear resection margins in several series regrouping 43 small RNET incompletely resected by polypectomy/EMR [10,63]. While ESD was less comprehensively evaluated in this indication, it seems feasible, although complete resection rates are approximately 80% [10,64,65]. Of note, endoscopic salvage therapies increase the

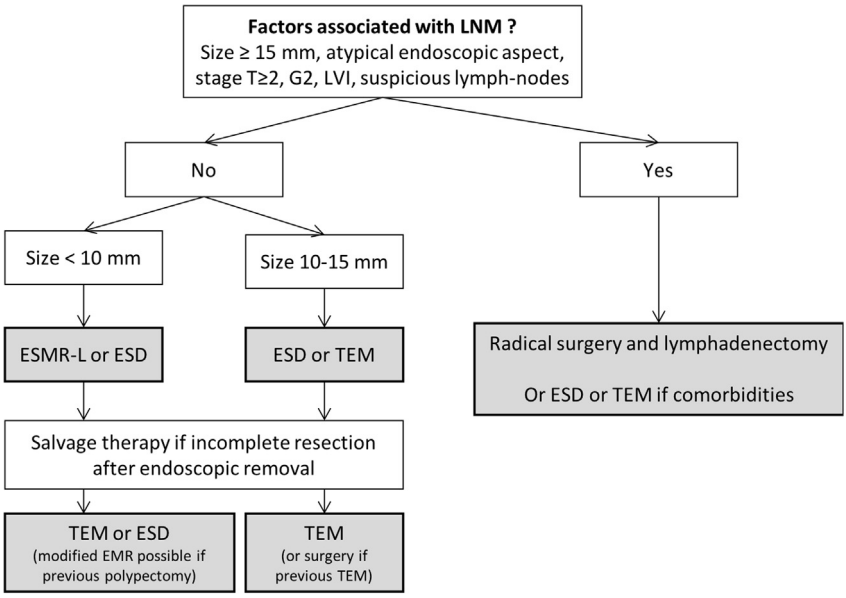

Fig. 8. Proposed algorithm of treatment of non-metastatic rectal NETs according to tumor size and the presence or not of factors predictive of lymph-nodes metastases.

risk of bleeding, which may occur in up to 23% of patients [63,64]. Overall, modified EMR-C and ESD are feasible for adjunctive treatment following incomplete primary endoscopic resection, especially for RNET < 10 mm. Nevertheless, confirmatory studies are required to confirm their efficacy. In addition, ESD has not been properly compared to transanal endoscopic microsurgery (TEM) in the setting of salvage therapy. The latter could achieve better results, especially for RNET ≥ 10 mm (see 8.2).

Transanal endoscopic microsurgery (TEM)

Principles of TEM

TEM is a minimally-invasive surgical technique requiring specific equipment, consisting in a disposable multi-channel port positioned trans-anally, steadily controlling rectal endoluminal pressure and allowing the combined used of a rigid rectoscope with magnified tridimensional vision and single-use endosurgical instruments. Following the marking of the scheduled resection area by electro-cautery dots, RNET resection generally consists in a full-thickness resection, down to the outer fatty tissue. The median operating time reported in the literature varies from 45 to 80 min. The rectal defect is usually closed by a running suture secured with clips, as it was shown to decrease postoperative morbidity [66], although this was contradictory with another series that reported similar morbidity [67]. The advantage of TEM over endoscopic techniques is the full-thickness resection of large lesions, hence yielding a theoretical 100% complete resection rate. It is particularly relevant for lesions from the low or intermediate portions of the rectum, where it can avoid the need for segmental resection surgery and its associated morbidities for lesions amenable to local excision [40]. TEM has become the resection technique of reference for T1 (sm1-2) malignant rectal lesions, as an alternative to ESD [68].

Results of TEM in RNET

Specific studies on the outcomes of TEM in RNET are limited and heterogeneous. Three series reported altogether 107 RNET treated by TEM, which achieved a 100% R0 rate [40,41,69], while two other

series reported R1 margins in 3/16 and 2/23 patients, respectively [14,70]. The recurrence rate was very limited, although follow-up duration was frequently short. Mean hospital stay is usually 2–3 days and the most frequent adverse events are acute urine retention (up to 20% [71]), postoperative anal pain and occasional bleeding [41,69,70].

Comparisons between TEM and endoscopic techniques, especially ESD, are very few in the literature, retrospective, limited by selection bias and mostly included RNET $\leq$ 10 mm. While TEM may achieve similar or slightly higher complete resection rate than ESD for RNET $\leq$ 10 mm (82% vs. 72% in one series [51], and 100% vs. 97% in another [71]), the morbidity rate might be slightly higher.

Regarding RNET > 10 mm, the efficacy of TEM has not been specifically studied, and even less compared to that of ESD. Still, larger RNET size may not influence its efficacy, which was 100% in one series of RNET sized 27 mm on average [69]. Hence, TEM appears as a reference technique for the resection of RNET measuring 10–15 mm, as an alternative to ESD, depending on the local expertise. Prospective comparative studies should be conducted to better define their respective place within the treatment algorithm of such lesions.

TEM seems very appropriate for salvage resection following incomplete endoscopic excision, with results as favorable as for primary resection. Indeed, four series reported a 100% R0 resection rate in 68 patients in total, in which TEM was performed after incomplete polypectomy, with no remarkable morbidity [10,14,40,41].

TEM requires experience although the related learning curve may be relatively short, with one study estimating that a minimum of 10 cases are required for a surgeon to be proficient with this technique [70]. Still, TEM is not widely applicable and should be reserved to expert centers. Overall, TEM appears effective and safe for RNET < 20 mm with typical features, avoiding the need for extensive surgical resections.

Radical surgery, including laparoscopic and transabdominal approach

Principles of radical surgery for RNET

Rectal radical surgery with lymphadenectomy should be discussed in all cases of RNET with suspected LNM or with a high risk of LNM. For these patients, it is recommended to perform a formal oncologic low anterior resection (LAR) with total mesorectal excision (TME) [28]. By analogy with rectal cancer, laparoscopic surgery has become the standard surgical approach because it achieves better short- and longer-term outcomes compared with transabdominal surgery. The intervention must begin with the exploration of the peritoneal cavity and liver. The segmental rectal resection generally consists in LAR but can be very low anterior resection or intersphincteric resection, depending on the localization of the RNET, and is systematically temporary protected by an ileostomy. A distal digestive resection margin of $\geq$10 mm must be performed [37]. Anal preservation is an important outcome of radical rectal surgery because permanent stoma has a negative effect on quality of life. That is particularly true in the setting of RNET, because post-surgical survival can be very prolonged, even in the rare cases of recurrence. In patients with RNET, the possibility of anal preservation may be facilitated by the frequent limitation of tumor invasion to submucosa, small tumor size and short distal resection margins.

Appropriate lymph-node resection primary relies on TME, but the precise extent of optimal lymphadenectomy during RNET surgery is ill-defined. High ligation of inferior mesenteric artery is not mandatory to achieve appropriate lymphadenectomy [37]. Lateral pelvic lymphadenectomy can be associated if lateral pelvic lymph nodes are suspicious on preoperative imaging (>7 mm). Besides, RNET usually develop LNM in the mesorectum but can develop alternative lymphatic passages outside the mesorectum, such as obturator canal LNM, which existed in 27% of patients operated by LAR in one series [72]. These unusual LNM might contribute explaining why some patients who underwent RNET R0 surgical resection may develop metachronous distant metastases. Although it is unknown whether

systematic pelvis sidewall lymphadenectomy may improve overall survival, this highlights the importance of performing accurate preoperative work-up such as ^{68}Gallium-PET.

Results of radical surgery for RNET

The outcomes of laparoscopic surgery for RNET were scarcely described due to their rarity and the even rarer indications of radical surgery. In addition, comparisons with endoscopic resection are missing and would be challenging since their respective indications are opposite by nature.

The safety and short-term outcomes seem similar to those for rectal adenocarcinoma. In two series combining 105 patients who underwent laparoscopic LAR for RNET, 23% underwent very low anterior resection and 13% underwent intersphincteric resection [37,73]. Only one patient required conversion to open surgery, anal preservation was achieved in all patients and a temporary ileostomy was set in 58% of cases. In these series, the median length of hospital stay was approximately 14 days. The most frequent adverse events were anastomotic leakage (8%), surgical site infection (8%) and ileus (3%) [37,73].

Selecting the patients for surgery based on the proposed above-mentioned criteria seems appropriate as it may identify adequately the patients with LNM, with a N+ rate of 15–50% [37,73,74]. The long-term outcomes were favorable, with a 100% R0 rate in non-metastatic patients and very a low recurrence rate (3%–10% after a follow-up of 42–68 months). Radical laparoscopic surgery does not seem less effective nor more technically difficult in case of previous incomplete endoscopic resection, hence it is an appropriate salvage therapy procedure [10,37,73].

Synthesis: indications of resection techniques in patients with RNET (Fig. 8)

RNET without factors predictive of LNM

RNET < 15 mm in size with no pejorative feature are associated with a very low risk of LNM and can be adequately resected by local excision. Polypectomy or standard EMR should not be performed if a RNET is suspected, or must be associated with marking of the resection area.

If tumor size is < 10 mm, modified EMR (EMR-C, ESMR-L) appear as the most appropriate endoscopic resection techniques and especially ESMR-L, which achieves complete resection rates in more than 95% of cases [2,60,61]. While ESD appears more effective than polypectomy/EMR, it may be similarly or less efficient than ESMR-L in RNET < 10 mm in size. TEM remains an option but does not seem justified for these lesions with low malignancy potential, notably because of its greater technicity requirement, slower recovery and possibly higher morbidity rate.

Regarding RNET measuring 10–15 mm, the two most relevant techniques appear to be ESD and TEM, which may each be superior to modified EMR, although they were not appropriately compared between them [16,58,62,69]. In the absence of prospective comparison, both can be performed in this indication, depending on local expertise.

In case of incomplete resection following initial endoscopic resection, it is currently unclear whether salvage therapy is necessary, but if so, TEM and ESD appear as the most appropriate techniques, with TEM probably being preferable in case of tumor size ≥10 mm and/or incomplete vertical margins [28,42].

RNET associated with factors predictive of LNM

RNET ≥ 15 mm in size, and/or those with pejorative features, are good candidates for radical surgery with lymphadenectomy [2,28]. However, in patients with comorbidities, the risks associated with radical surgery may overcome its benefits. In this setting ESD or TEM can be considered, although it does not allow the acknowledgment of lymph-node status, hence follow-up should be adapted with shortened intervals.

Surveillance

The follow-up of RNET is not well codified and does not rely on clinical evidence. No specific surveillance is recommended for completely resected RNET < 10 mm that are not associated with factors predictive of LNM [2,28].

By analogy with rectal cancer, RNET ≥ 10 mm treated by local or radical R0 resection could undergo surveillance rectoscopy at 1 year, 3 years then every 5 years [68]. In case of endoscopic resection while having pejorative features, or R1 resection without salvage therapy, one rectoscopy/EUS examination every 6–12 months for at least 5 years could be performed [14,28,29]. Systematic biopsies of the resection area – if detectable – could be relevant during endoscopic follow-up to detect early local relapse, but this has not been evaluated. As recommended by ENETS, yearly abdominal-pelvic MRI should be performed to detect perirectal and/or distant (liver) recurrence. Somatostatin receptor imaging could be performed alternatively, although never evaluated in this indication (Fig. 3). The duration of follow-up remains unknown, as data on long-term monitoring of rectal NETs are scarce. Total colonoscopy should be performed every 5 years.

Conclusions

RNET are rare neoplasms, but with a constantly increasing prevalence. Their management should be tailored depending on the presence or absence of the features associated with LNM, including T stage, tumor size, atypical endoscopic aspect, grade, and LVI. Low-risk RNET can be treated locally, probably at best using ESMR-L for lesions ≤10 mm and ESD or TEM for lesions sized 10–15 mm, in expert centers because they require technicity and experience. These techniques may also be relevant as salvage therapy of incompletely resected low-risk RNET. Conversely, radical surgery with lymphadenectomy should be proposed in the presence of any pejorative factor. The long-term evolution of rectal NETs remains to be specified, and prospective studies should be conducted in order to determine the relevance of these management strategies.

Practice points

- The recognition of RNET during the initial endoscopy is of paramount importance for appropriate management decision-making. If a RNET is suspected, standard polypectomy/EMR should not be performed, or associated with marking of the resection area.
- The main factors associated with the risk of lymph-nodes metastases in RNET are invasion of the muscularis propria (T2), tumor size ≥ 15 mm, atypical endoscopic aspect, G2 and LVI. Their identification relies on expert histopathological analysis, EUS and pelvic MRI.
- Patients with RNET at low risk for LNM are good candidates for local resection. The most appropriate resection techniques may be ESMR-L or ESD for RNET < 10 mm, and ESD or TEM for RNET measuring 10–15 mm, depending on local expertise.
- Salvage resection of low-risk RNET that are R1 following primary endoscopic resection can be adequately performed using TEM or ESD.
- RNET with any factor associated with increased risk of LNM should be considered for surgical resection with lymphadenectomy.
- Completely resected RNET < 10 mm with no pejorative factor may not require follow-up. Otherwise, follow-up relies on regular endoscopic examination and abdominal/pelvic MRI (or somatostatin receptor imaging).
- Total colonoscopy is mandatory for all patients with RNET to exclude concomitant colonic cancer and other colorectal NEN, which can occur in up to 8% of cases.

Research agenda

- Endoscopic training programs should include RNET recognition module.
- Large cohorts with prolonged follow-up should be conducted in order to better understand the natural history of RNET, and to validate the impact of the prognostic factors currently used.
- The algorithm for most appropriate therapies should be defined, especially for 10–20 mm RNET. Prospective comparative trials of the different resection techniques are needed.
- Long-term follow-up of RNET that are R1 following endoscopic resection should be further investigated.

Conflicts of interest

The authors declare no conflict of interest that could influence the content of this article.

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