Scholars LITERATURE

Neurological Sciences and Neurosurgery

Review Article

DOI: https://doi.org/10.47275/2692-093X-140
Volume 5 Issue 2

A Comprehensive Review on Recent Advances in Management, Presentation, and Pathophysiology of Rectal Neuroendocrine Tumors

CH Srinaini[1*], Harshitha Myneni[2*], Kasyap Kambhampati[3] and Saumya Lakshman Gaddalay[4]

[1]Kamineni Institute of Medical Science, Narketpalle, Telangana, India

[2]Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, Telangana, India

[3]NRI Medical College and General Hospital, Guntur, Andhra Pradesh, India

[4]Malla Reddy Medical College, Hyderabad, Telangana, India

Abstract

A rectal neuroendocrine neoplasm (r-NEN) is one of the most common digestive NENs, along with a small bowel NEN. Due to the widespread use of endoscopic screening for colorectal cancer and the advanced endoscopic procedures available today, their incidence has increased in the past few years. In view of their low risk of local or distant invasion, well-differentiated r-NENs smaller than 10 mm should be endoscopically removed. Because r-NENs larger than 20 mm may spread distantly and involve the muscularis propria, they should be surgically resected. Metastasis risk is intermediate for tumors between 10 and 20 mm, and endoscopic treatment can be challenging for these tumors. A possible algorithm is proposed here based on the limited and poorly codified indications for surveillance once a patient has been removed.

Keywords: Rectal neuroendocrine tumors, Systemic therapy, Endoscopy

[*]***Correspondence to:*** CH Srinaini, and Harshitha Myneni, Kamineni Institute of Medical Science, Narketpalle, Telangana, India, Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar, Telangana, India.

Citation: Srinaini CH, Myneni H, Kambhampati K, Gaddalay SL (2024) A Comprehensive Review on Recent Advances in Management, Presentation, and Pathophysiology of Rectal Neuroendocrine Tumors. Neurol Sci Neurosurg, Volume 5:2. 140. DOI: https://doi.org/10.47275/2692-093X-140

Received: August 01, 2024; **Accepted:** October 12, 2024; **Published:** October 16, 2024

Introduction

In most cases, NEN arise from the intestinal tract. In addition to indolent well-differentiated neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs) are very aggressive poorly differentiated NETs. It is possible for them to arise from practically any part of the human body [1, 2]. r-NENs represent 12% - 27% of all gastrointestinal NENs, after the small intestine. The proportion of NETs in rectal cancers, however, is 1% - 2%. The surveillance, epidemiology, and end results (SEER) database shows an increasing incidence of r-NENs over the past few years, and this trend was also confirmed by the German registry, as well as Asian register, even though the highest incidence rate (IR) was reported in the United States, where the rate was approximately 1.3 per 100,000 people and increased tenfold between 1970 and 2020 [3]. European IRs were lower than those reported in SEER, with Norway reporting the highest IR and Austria reporting the lowest. The lack of national registries may have caused an underreporting of the disease. As screening colonoscopies have become more popular, the incidence has increased. A polish screening colorectal cancer (CRC) program cohort of 50,148 participants reported a prevalence of r-NENs of between 0.05% and 0.07%, despite limited data on r-NENs diagnosed through CRC screening programs. NENs were identified in the English bowel cancer screening program 29 times for rectal cancer and 18 times for colon cancer, which represents a prevalence of 0.04% [4-7]. In Western countries, endoscopists are still not sufficiently recognizing r-NENs as neuroendocrine lesions, since a recent study revealed that only 18% of NETs were suspected to be neuroendocrine. The clinical significance of suspicion of r-NENs before their resection lies in the fact that it significantly influences how they are treated. It has been reported that patients diagnosed with r-NENs before resection showed a greater rate of complete resection than those whose tumors were resected as polyps before being diagnosed. The application of artificial intelligence to gastrointestinal endoscopy may be able to detect and diagnose r-NENs, thereby resulting in a greater incidence, but also more effective treatments [8-11].

Endoscopic appearance of r-NENs in clinical form

The majority of r-NENs are diagnosed incidentally during endoscopic evaluation for CRC screening or unrelated gastrointestinal symptoms. Anal discomfort, rectal bleeding, and changes in bowel habits may occur less frequently in r-NENs. A r-NEN appears as a small, round polypoid lesion derived from neuroendocrine epithelial cells, which has a smooth, normal-appearing mucosa, a round-shaped pit pattern, type I in Kudo classification, and invisible vessels, as described by Sano as type I. It is usually found on the frontal or lateral wall of the mid-rectum, about 4 to 10 cm above the dentate line [2, 12]. In up to 90% of r-NEN cases, at the time of diagnosis, the lesions are well differentiated epithelial lesions of less than 10 mm in size. They usually develop toward the submucosal layer, but without invading the muscularis propria. Atypical endoscopic findings (such as a semipedunculated appearance, hyperemia, central depression, erosion, and ulceration) have been reported for r-NEN exceeding 5 mm in diameter [13]. Further, virtual chromoendoscopy with NBI, showing large amorphous areas (Kudo V), may be useful in detecting invasive r-NENs. Unfortunately, the

macroscopic appearance of r-NENs resembles that of hyperplastic or adenomatous polyps, making the differentiation from other polypoid lesions challenging, and it is often determined after routine snare polypectomy or mucosectomy by pathological examination [14]. Artificial intelligence with computer-aided software may also aid in the detection and characterization of polypoid lesions, including r-NENs. In recent years, endoscopic ultrasound (EUS) has expanded the role of endoscopic evaluation of r-NENs, and it has proved helpful in defining the size, extent, and presence of pararectal nodal metastases. As seen on EUS, r-NETs generally appear as well-defined, hypoechoic lesions located in the second and third wall layers. Other EUS features such as lobulated forms, irregular margins, and echogenic foci may also indicate higher grades of cancer (Figure 1) [15-19].

Incidence, prevalence, progress and recurrence risk factors

Since these tumors are generally rare and there are few large epidemiological studies on rare cases, the risk factors associated with r-NENs are not fully understood. These neoplasms are not totally indolent, as they were traditionally thought, but they do exhibit a 3% to 60% risk of metastatic disease [20, 21]. For early detection and removal of r-NENs, identifying specific subgroups that are at increased risk of developing these tumors is of extreme relevance. High levels of cholesterol and ferritin, metabolic syndrome, and family history of cancer were associated with an increased prevalence of r-NENs, according to a large Asian retrospective study. r-NEN risk was significantly increased by higher fasting plasma glucose and hypertriglyceridemia, younger age, and previous malignancies. Study results revealed a significant association between male gender and low levels of high-density lipoprotein cholesterol with 101 cases of r-NENs found during screening colonoscopies [22-26].

Since metabolic syndrome appears to be a recognized risk factor for the development of r-NENs, the improvement in screening colonoscopy may partially explain this trend. There is still no clear explanation for the relationship between metabolic risk factors and r-NENs; however, insulin resistance may contribute to r-NEN pathogenesis, since insulin and insulin-like growth factors are associated with cell proliferation, differentiation, and apoptosis. It has been proposed that there are a number of predictors for metastases, progression, and recurrence of r-NENs; however, their relevance has not been clearly established, and current guidelines have not yet included clear-cut prognostic factors that could help manage these neoplasms [27]. There are a number of prognostic factors available. A lesion with a diameter of more than 20 mm is more likely to be metastatic in 60% - 80% of cases. The incidence of synchronous or metachronous metastases in patients with r-NENs measuring 10 - 19 mm is 4% - 20%. According to some large series, the optimal size cut-off for predicting the risk of metastases is 15 mm; in detail, it was observed that tumors larger than 15 mm were associated with an increased risk of distant metastasis in their study of 4893 r-NEN patients identified in the national cancer database [28]. However, one should keep in mind that metastases may also occur in lesions less than 15 mm, which suggests that tumor behavior is not influenced only by size. The size alone has limited accuracy since 26% of patients with stage IV neoplasms and 16% with G3 neoplasms have a primary tumor 10 mm in size; rather, staging and grading can accurately predict the prognosis of r-NEN patients. As a result of this study, the European neuroendocrine tumor society (ENETS) TNM staging accurately predicted prognosis in patients with r-NENs, with stage IV being associated with a worse outcome and progression-free survival (PFS) [29-31].

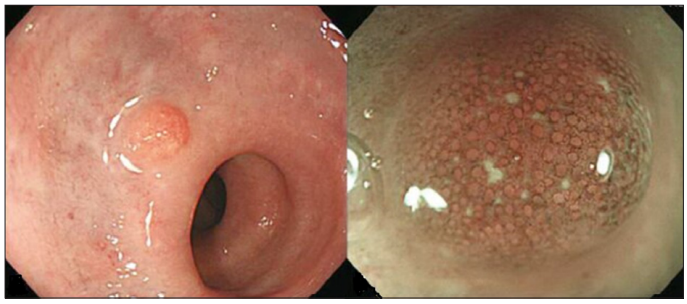

Figure 1: Endoscopic appearances of r-NETs [20].

A r-NEN can also be classified according to the World Health Organization classification of digestive system tumors, which differentiates NEN into NETs and NECs based on their molecular differences. Grading of NETs (mitotic count and proliferation index based on Ki67) is done according to proliferation index. NECs are classified according to their grade (NET G1, NET G2, and NET G3). The development of metastases may depend on both the primary neoplasms' diameter and their grade, according to growing evidence [32-36]. An analysis of 98 patients with r-NENs, characterized by 12% metastatic disease, showed that patients with G2 or G3 tumors, regardless of their size, were more likely to develop metastases; only G1 tumors were found to be associated with aggressive behavior based on their size (i.e., > 20 mm). Thus, small and diminutive r-NENs are highly susceptible to metastasis based on grade [37]. In r-NENs it was found that grade, besides stage, could predict prognosis, with G3 tumors having a worse overall survival (OS) and PFS. Among the important prognostic factors explored in the literature are: the depth of invasion (including involvement of the muscularis propria), lymphovascular and/or perineural invasion, the presence of regional nodal metastasis, atypical histology (including anaplasia, frequent mitotic cells, cellular pleomorphism, and mucin production), and mitotic rate, which are all likely to predict aggressive behavior, although there is little evidence to back them up. Currently, it remains unclear whether these factors are independent risk factors [38].

Current guidelines have always classified r-NENs as N0 vs N1 according to the presence or absence of metastatic lymph nodes. Using data from the national cancer database, a recent study found that patients with no positive lymph nodes (N0), one to four positive lymph nodes (N1), and five positive lymph nodes (N2) had significantly different survival rates, which suggests that a new nodal staging system can improve prognosis accuracy [39].

In addition, these findings suggest that a lymphadenectomy might be necessary in this setting, even if further research is needed to quantify the optimal number of lymph nodes to remove. As a final point, it should be noted that interobserver variations are often present in the assessment of lymphovascular invasion [40].

In a study involving 70 r-NENs, it was calculated a carcinoid of the rectum risk stratification score based on tumor size, depth of invasion, lymphovascular invasion, and mitotic rate. In addition, the score was associated with recurrence-free and disease-specific survival, and it was derived from histopathologic variables that might be assessed at biopsy and guide treatment [41]. In summary, according to the ENETS 2016 consensus guidelines and the union for international cancer control/ American joint committee on cancer (UICC/AJCC) indications, the size of the primary tumor, with a potential more updated cut-off of 15 mm, and the degree of differentiation with G2 and, indeed, G3 tumors, are considered to be the principal independent predictors of a dismal prognosis in r-NENs. A poor prognosis is also associated with the

number of positive nodes, taking 5 positive lymph nodes as a cut-off point, as well as the depth of invasion with invasion of the muscularis propria. It is necessary to conduct further studies in order to identify whether more aggressive surgical approaches or standardized follow-up protocols may be beneficial for this subgroup of neoplasms [42-44].

Treatment

r-NENs differ in their therapeutic approach depending on whether the patient has a localized, locally advanced, or advanced metastatic disease.

Standard polypectomy: The standard procedure for the removal of polyps is to use a snare, either hot or cold, to remove the polyps. In order to treat r-NENs, this type of polypectomy does not guarantee a sufficient resection rate of lesion margin [45].

Endoscopic mucosal resection (EMR): In traditional EMR, the lesion is re-snare resected, and then it is lifted by injecting a saline solution submucosally, reducing the risk of perforation and incomplete margin resection, particularly when the lesion is sessile. This is a safe, cost-effective, and technically easy procedure, but it results in a considerable rate of incomplete removal due to piecemeal resection. Conventional EMR reduces only 56% - 59% of R0 resections in 10 mm r-NENs, according to the most reliable evidence. In addition, submucosal fluid injections can paradoxically flatten or even depress loose connective tissue lesions, increase tissue tension, and even move the lesions to a less accessible site [46]. The underwater EMR technique (U-EMR) was inspired by the observation that the mucosa and submucosa separate from the muscular layer when colon air is removed from the lumen and replaced with water. Consequently, the colon lumen becomes less outstretched, a pseudopedicle forms, and a larger mucosal surface is captured. U-EMR is effective in removing en bloc > 20 mm lesions; a multicenter randomized controlled trial comparing conventionally injection-assisted and U-EMR in 219 colorectal laterally spreading tumors 15 - 70 mm demonstrated a significantly higher en bloc resection rate with U-EMR. In en bloc resections of r-NENs of less than 20 mm, no comparative studies have been conducted between conventional EMR and U-EMR. In the largest samples available to date, suction cap EMR has been shown to achieve 100% en bloc resection success rates and 93% histological complete resection rates for 10 mm r-NENs [47]. According to the circumferential incision (CI-EMR) m-EMR technique, which was first described in the literature for treating CRC, dots are marked around the lesion by argon plasma coagulation (APC) and only the mucosal layer is lifted with glycerin fructose and methylene blue, resulting in 97% en bloc resection and 94% complete resection rates, respectively. It is possible to achieve even greater complete resection if an elastic band is placed around the rectal lesion in addition to suction assisted by cap and lifting with injection. The majority of 77 patients in a Korean prospective study undergoing a ligation-assisted m-EMR (ligation-EMR (L-EMR)) of a r-NEN reached histologically complete resection en bloc [48]. The m-EMR technique performed with a double-channel gastroscope proved to be less effective in achieving complete resection rates, and it was also associated with higher adverse events. An analysis of data from 11 studies involving 811 patients who went through endoscopic treatment for r-NENs less than 10 mm in size in the mucosal layer following a systematic review and meta-analysis. Comparing m-EMR with conventional EMR, m-EMR demonstrated statistically significant higher rates of en bloc endoscopic and complete histological resection regardless of the procedure, the safety was the same [49-51]. It is, however, interesting to note that, based on a multivariate analysis of 277 r-NENs of any size treated with conventional EMR (243 of them), dual-channel EMR, and CI-EMR (for 44 m-EMRs), the histological complete resection rate was similar regardless of the endoscopic treatment modality, indicating that tumor size determines histological complete resections. Regardless of the EMR technique used, the EMR area should always be marked after the rectal lesion resection, in order to facilitate future salvage therapy in the case that the margins of the tumor are not completely removed [2].

In recent years, 90% - 100% of r-NENs have been detected with a diameter of > 10 mm due to greater awareness of these neoplasms, advancements in endoscopic technology, and better training for endoscopists. The lesions are usually intramucosal, and nearly every r-NEN that is more than 10 mm in diameter is a completely resected incidental tumor. The risk of lymphatic invasion and distant metastases for NENs smaller than 10 mm is nearly 0.7% and less than 2%, respectively. The use of EUS is highly recommended to exclude this distant occurrence, and to choose the type of endoscopic resection that is most efficient and feasible [52]. It is still the goal of therapy for these lesions to perform complete mini-invasive endoscopic en bloc resection, even if, to date, not all studies support a statistically significant increase in OS in patients with small r-NENs. Traditionally, r-NENs have been resected using a wide range of endoscopic procedures.

Endoscopic submucosal dissection: An endoscopic submucosal dissection involves using an electrocauterization knife to delineate a circumferential excision zone around the lesion, followed by injecting saline solution into the lesion to create a cushion beneath it. In order to accomplish this, a dilute solution of 0.4% sodium hyaluronate must be applied below the submucosal layer under direct visualization. This is a technically challenging procedure that requires endoscopists' specialized training and requires much practice [53]. Also, it takes longer to execute and has a higher peri-procedural adverse event rate compared to EMR (especially bleeding and perforation), but no significant difference was found between endoscopic submucosal dissection (ESD) and any m-EMR technique when it came to operating time for r-NENs. As a result of deep submucosal invasion of tumor cells, even ESD may cause incomplete resection and thus persistent positive vertical margins. In such cases, other endoscopic resection techniques may be used: the full thickness resection device (FTRD) Ovesco is an over-the-scope clip that combines a clip with a snare. The FTRD system allows for endoscopic full-thickness resection while closing a wall defect; it is particularly beneficial for subepithelial lesions [54].

Based on a systematic review and meta-analysis of ten retrospective studies and 650 patients who underwent r-NEN resection, a significant increase in complete resection rates was found in the ESD group compared with the EMR group, but there was a similar rate of complete resection between the ESD and the m-EMR groups [55]. A comparison of 115 patients revealed no statistical significance between ESD and U-EMR in terms of R0 on 10 mm lesions not invading the muscularis. A bias in the definition of complete histological resection R0 can arise from the fact that EMR often suggests a piecemeal resection, whereas ESD guarantees an en bloc resection. The U-ESD technique has already been proposed as a promising modified ESD method. An additional systematic review and meta-analysis of 25 studies for 1094 patients found L-EMR and ESD to be the most effective endoscopic procedures for resecting ≤ 10 mm r-NENs (94.8% and 89.6% for L-EMR and ESD R0, respectively, compared to 59.1% and 72.4% for polypectomy/EMR and CI-EMR R0, respectively) [56-58]. In an additional meta-analysis of seven studies involving 386 patients, a study of L-EMR was found to have the highest R0 rate of 10 mm r-NENs as it achieved a higher R0 rate than ESD. As well as taking significantly less time to operate, it is associated with no significantly increased complication rate. The results

of a study comparing ESD with m-EMR found that ESD resulted in higher R0 resection rates (100% vs 70%) and lower recurrence rates (0% vs 17%). The ESD technique appears most appropriate for restraining > 10 mm r-NENs. Incomplete primary endoscopic resections, particularly those involving r-NENs of 10 mm or more, can also be salvaged using m-EMR or ESD. Endoscopic resection techniques are heterogeneous, and samples are limited, and follow-up time is limited, so it is important to consider the limitations of what has been revealed so far.

Transanal endoscopic microsurgery (TEM): TEM allows local excision of rectal lesions localized up to 20 cm from the anal verge without the need to perform segmental surgery. TEM is typically performed under general anesthesia in a lithotomy or clasp knife position, using anal retractors to dilate the anal sphincter and maintain exposure. A three-dimensional magnified rectoscope, combined with a multi-channel transanal device, is required [2]. With the device, the endoluminal pressure can be precisely controlled to delineate the schedule operating area by electrocautery dots. As a result of injecting saline solution into the submucosal plane, a visible submucosal cushion is created for the elevation of the lesion. An electrocautery or ultrasonic knife is then used to exorcise the tumor under direct vision, after which the wound is closed with absorbable sutures. The treatment of r-NENs with a diameter of 10 to 20 mm and no lymphatic invasion can either be achieved by an en bloc endoscopic resection through ESD or by a complete microsurgical excision through TEM. In prospective observational studies, neither ESD nor TEM have adequately compared ESD with m-EMR for > 10 mm r-NENS. TEM, according to single-center experiences, requires a longer operative time than ESD and has a higher incidence of anesthesia-related adverse events (such as acute retention of urine); additionally, anal dilation or retraction may result in higher postoperative morbidity. Meanwhile, TEM allows for deeper vertical margins during full-thickness resection [59]. The presence of fibrosis in the submucosa layer may also reduce the success rate of complete en bloc resections if local recurrence occurs. Due to its lower morbidity rate, short operating time, and, consequently, lower costs, ESD might be preferred over TEM in the case of a first incidental 10 - 19 mm r-NEN, whereas TEM might be the first choice for scar-embossed recurrent 10 - 19 mm r-NENs located within the first 20 cm of the rectum from the anal verge. As a whole, to date, robust superiority evidence is less important than team expertise in determining which of the two proposed techniques to perform. For the better definition of resectable 10 - 19 mm r-NEN treatment algorithms, prospective comparative studies must be conducted. TEM salvage was effective even for lesions larger than 10 mm. It is equivalent to TEM when r-NENs measuring 20 mm or less are localized within 6 cm of the anal verge by conventional transanal resection (Figure 2) [60].

With or without TME, low anterior resection (LAR) or intersphincteric resection

r-NENs with involvement of lymph nodes or those with involvement of the muscularis mucosae should be surgically resected, with or without TME. LAR and intersphincteric resection, with appropriate lymph node resection through TME, are the two most commonly performed laparoscopic techniques. There is often a temporary protective ileostomy associated with either laparoscopic LAR or intersphincteric resection. A significant improvement in quality of life can be achieved by anal preservation, if possible. In most cases, anal preservation is guaranteed due to the rare anal localization of r-NEN. An abdominoperineal resection with definitive colostomy is the most appropriate surgical procedure if anus is involved [2, 61-63].

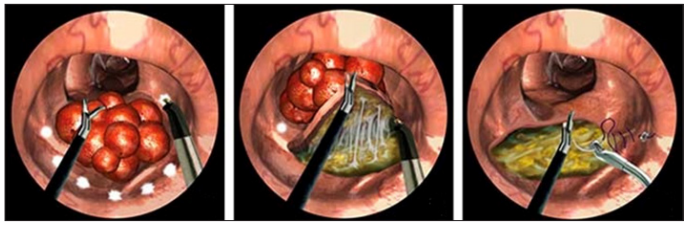

Figure 2: TEM [60].

Advanced disease treatment with systemic therapies

Approximately 10% of r-NENs measure > 10 mm at diagnosis, so a low number of cases are diagnosed as advanced metastatic disease. The management of r-NETs should be tailored based on the presence or absence of metastases-predicting factors, including tumor size, endoscopic aspects, T stages, grades, and lymphovascular invasion, as explained previously. Locoregional ultrasound is the most relevant technique for locoregional assessment. Furthermore, in all cases of high-risk r-NENs (i.e., those showing factors predicting aggressive disease, see above), magnetic resonance imaging (MRI) (or computed tomography (CT)) of the pelvis has been recommended as part of the initial workup to evaluate loco-regional spreading. A contrast-enhanced CT scan of the thorax, abdomen, and pelvis, liver MRI with diffusion-weighted sequences, somatostatin receptor isotopic imaging (scintigraphy or positron-emitting tomography) is recommended. Whenever a disease is advanced with distant metastases, a systemic approach represents the best treatment option. Systemic therapy is intended to alleviate symptoms and control disease. As a matter of fact, none of the current systemic treatments have provided a radical cure for r-NENs, but rather a disease stabilization with variable duration depending on prognostic factors. As r-NENs are usually nonfunctional, systemic therapies are usually used to reduce their proliferation rather than to alleviate their symptoms. Although studies examining specific response rates in r-NENs are limited, there are a number of systemic therapeutic options for advanced r-NENs. Furthermore, palliative surgery is still controversial, whether it is used for primary tumor removal or debulking surgery [64-65].

Chemotherapy: NECs with G3 characteristics are more likely to be poorly differentiated r-NECs, whereas r-NETs with G3 characteristics are rarer. Unlike other r-NENs, r-NECs have a highly aggressive biological behavior and poor prognosis (small and large cell carcinomas). A metastatic low-differentiated G3 NEC is mostly treated with chemotherapy, in accordance with the current ESMO guidelines, which highly recommend chemotherapy for this entity.

Patients with advanced GEP-NECs could benefit from chemotherapy regimens combining cisplatin or carboplatin with etoposide. Irinotecan can be used in similar cases to etoposide. A combination of streptozocin and 5-fluorouracil (5-FU) as well as doxorubicin is the most used treatment for advanced G1/2 r-NEN, even though clinical and radiological response rates are low. A three-drug regimen (5-FU, dacarbazine, and epirubicin), used historically since the 1990s, has been associated with a response rate of 30% [2, 66].

Treatment of high-grade r-NECS with combined radiation and chemotherapy: High-grade r-NECs treated with combined radiation therapy (RT) and chemotherapy: an interesting study examined the efficacy of chemotherapy combined with radiotherapy for poorly differentiated, aggressive high-grade G3 r-NECs, defined as having a Ki67 index of 20% and a mitotic index ≥ 20/10 at high power.

As a result of a preliminary retrospective univariate and multivariate analysis, RT significantly improved survival in patients with G3 r-NECs

who were treated with surgery and RT.

As a result of a multicenter American multidisciplinary study, chemotherapy (based on platinum, etoposide, and fluoropyrimidine) with or without radiotherapy and surgery had similar results in terms of PFS and OS (49.1 mo vs 39.2 mo, p = 0.42). RT, when combined with chemotherapy, leads to similar outcomes as surgery when it comes to r-NEC prognosis. An overview of the most common systemic therapies [67-71].

Surveillance

Literature indicates that r-NENs need to be followed up. Furthermore, most of the indications found in the consensus guidelines are based on expert opinion rather than evidence. It has been documented that grade is more heavily prognostic than r-NEN size in the main guidelines. According to the ENETS guidelines, follow-up should take place in a specialized NEN center or at least at a hospital that works closely with a specialized NEN center [72]. Following up is recommended based on tumor size, grade, and operative outcome (if curatively resected). Upon curative resection of G1/2 r-NENs within < 10 mm, only one endoscopic check should be performed at 12 months after the resection. Further investigation is not required. A follow-up endoscopic examination is recommended for G1/2 lesions 10 - 20 mm in size. Furthermore, both CT and MRI are recommended for conventional radiological imaging [2, 73]. It is also recommended to perform somatostatin receptor imaging (SRI) every 12 - 24 months. Both curatively and non-curatively resected G1/2 lesions > 20 mm should receive close follow-up (every 3 - 12 mo), consisting of endoscopy every 6 - 12 mo, CT or MRI every 3 - 12 mo, and SRI every 12 - 24 mo. A 3 month follow-up is recommended, by performing CT or MRI; an endoscopy is recommended every 6 - 12 months; nuclear medicine imaging (both SRI and fluorodeoxyglucose-positron emission tomography) is advised every 12 months. It may nonetheless be necessary to obtain an EUS examination if there is a suspicion of recurrence or progression [74-77].

Conclusion

Combined with small bowel NENs, r-NENs are among the most common digestive NENs. Their incidence has increased dramatically over the last few years likely as a result of endoscopic screening for CRC and improvements in endoscopic techniques. A recognition of metabolic syndrome as a risk factor for the development of r-NENs might have contributed to the increasing incidence of these cancers. As endoscopists often don't recognize these neoplasms, the incidence and prevalence of these neoplasms are underestimated. Artificial intelligence may help detect and treat r-NENs by applying it to gastrointestinal endoscopy in an increasingly vast realm of artificial intelligence. One of the most important predictors of metastases, progression, and/or recurrence of r-NENs has been the diameter and grade of the primary neoplasm, although they are not clearly related. Small r-NENs with a low metastatic risk are usually removed endoscopically; larger r-NENs with a high metastatic risk are usually surgically resected. In contrast, metastatic spread and a dismal prognosis are mainly predicted by a more updated cut-off size of 15 mm and differentiation with G2 and G3 tumors. Furthermore, the number of positive nodes (≥ 5 as a cut-off) and depth of invasion (invasion of the muscularis propria) are associated with poor prognoses.

Locally advanced r-NENs with a lateral spreading diameter ≥ 10 mm, but still T1N0, should be treated endoscopically; lesions that invade the muscularis propria or local lymph nodes should be treated surgically. For scar-embedded recurrent resectable lesion, TEM is the treatment of choice. Surveillance guidelines are based primarily on experts' opinions and not evidence. The follow-up depends on the size, grade, and outcome of the tumor, according to the ENETS guidelines. Rather than relying solely on retrospective studies, it would be advantageous to encourage large prospective studies that define standardized guidelines for r-NENs and define clear-cut prognostic factors and scores that might assist in their management.

Acknowledgements

None.

Conflict of Interest

None.

References

1. Habal N, Sims C, Bilchik AJ (2000) Gastrointestinal carcinoid tumors and second primary malignancies. J Surg Oncol 75: 310-316. https://doi.org/10.1002/1096-9098(200012)75:4<306::AID-JSO14>3.0.CO;2-3
2. Gallo C, Rossi RE, Cavalcoli F, Barbaro F, Boškoski I, et al. (2022) Rectal neuroendocrine tumors: current advances in management, treatment, and surveillance. World J Gastroenterol 28: 1123-1138. https://doi.org/10.3748/wjg.v28.i11.1123
3. Park SS, Han N, Lee J, Chang HJ, Oh JH, et al. (2018) Multiple small, rectal neuroendocrine tumors with numerous micronests. J Dig Dis 19: 572-575. https://doi.org/10.1111/1751-2980.12645
4. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, et al. (2008) Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 9: 61-72. https://doi.org/10.1016/s1470-2045(07)70410-2
5. Park CS, Lee SH, Kim SB, Kim KO, Jang BI (2014) Multiple rectal neuroendocrine tumors: report of five cases. Korean J Gastroenterol 64: 103-109. https://doi.org/10.4166/kjg.2014.64.2.103
6. Manhal K, Christophe R, Radu B, Daniel L, Jeremy S, et al. (2022) Case report of multiple rectal neuroendocrine tumors in a context of ulcerative colitis. Int J Surg Case Rep 91: 106760. https://doi.org/10.1016/j.ijscr.2022.106760
7. Sasou S, Suto T, Satoh T, Tamura G, Kudara N (2012) Multiple carcinoid tumors of the rectum: report of two cases suggesting the origin of carcinoid tumors. Pathol Int 62: 699-703. https://doi.org/10.1111/j.1440-1827.2012.02852.x
8. Xie R, Fu KI, Chen SM, Tuo BG, Wu HC (2018) Neurofibromatosis type 1-associated multiple rectal neuroendocrine tumors: a case report and review of the literature. World J Gastroenterol 24: 3806-3812. https://doi.org/10.3748/wjg.v24.i33.3806
9. Ghassemi KA, Ou H, Roth BE (2010) Multiple rectal carcinoids in a patient with neurofibromatosis. Gastrointest Endosc 71: 216-218. https://doi.org/10.1016/j.gie.2009.06.026
10. Saxe DH (1953) Multiple carcinoid of the rectum; case report. Am J Surg 86: 553-555. https://doi.org/10.1016/0002-9610(53)90355-9
11. Maruyama M, Fukayama M, Koike M (1988) Case of multiple carcinoid tumors of the rectum with extraglandular endocrine cell proliferation. Cancer 61: 131-136. https://doi.org/10.1002/1097-0142(19880101)61:1%3C131::aid-cncr2820610123%3E3.0.co;2-g
12. Rigdon RH, Fletcher DE (1946) Multiple argentaffin tumors (Carcinoids) of the rectum. Am J Surg 71: 822-824. https://doi.org/10.1016/0002-9610(46)90231-0
13. Maeda K, Koide Y, Katsuno H, Matsuoka H (2020) Malignant potential of multiple rectal carcinoid tumors measuring ≤10 mm. Asian J Surg 43: 1033-1034. https://doi.org/10.1016/j.asjsur.2020.06.008
14. Doi M, Ikawa O, Taniguchi H, Kawamura T, Katsura K (2016) Multiple rectal carcinoid tumors in monozygotic twins. Clin J Gastroenterol 9: 215-221. https://doi.org/10.1007/s12328-016-0662-7
15. Haraguchi M, Kinoshita H, Koori M, Tsuneoka N, Kosaka T, et al. (2007) Multiple rectal carcinoids with diffuse ganglioneuromatosis. World J Surg Oncol 5: 1-5. https://doi.org/10.1186/1477-7819-5-19
16. Zhou JL, Lin GL, Zhao DC, Zhong GX, Qiu HZ (2015) Resection of multiple rectal carcinoids with transanal endoscopic microsurgery: case report. World J Gastroenterol 21: 2220-2224. https://doi.org/10.3748/wjg.v21.i7.2220

17. Colbert PM (1976) Primary carcinoids of the ileum and rectum. A simultaneous occurrence. JAMA 236: 2201-2203. https://doi.org/10.1001/JAMA.1976.03270200039028

18. McNeely B, Owen DA, Pezim M (1992) Multiple microcarcinoids arising in chronic ulcerative colitis. Am J Clin Pathol 98: 112-116. https://doi.org/10.1093/ajcp/98.1.112

19. Zhu Y, Wang M (2006) A case of double primary carcinoma of the rectum. Chinese J Pathol. Zhonghua Bing Li Xue Za Zhi 35: 1-431. https://doi.org/10.3760/J.ISSN:0529-5807.2006.07.016

20. Okamoto Y, Fujii M, Tateiwa S, Sakai T, Ochi F, (2004) Treatment of multiple rectal carcinoids by endoscopic mucosal resection using a device for esophageal variceal ligation. Endoscopy 36: 469-470. https://doi.org/10.1055/s-2004-814386

21. Kanter M, Lechago J (1987) Multiple malignant rectal carcinoid tumors with immunocytochemical demonstration of multiple hormonal substances. Cancer 60: 1782-1786. https://doi.org/10.1002/1097-0142(19871015)60:8<1782::AID-CNCR2820600819>3.0.CO;2-T

22. Modlin IM, Sandor A (1997) An analysis of 8305 cases of carcinoid tumors. Cancer 79: 813-829. https://doi.org/10.1002/(SICI)1097-0142(19970215)79:4<813::AID-CNCR19>3.0.CO;2-2

23. Hassan MM, Phan A, Li D, Dagohoy CG, Leary C, et al. (2008) Risk factors associated with neuroendocrine tumors: a U.S.-based case-control study. Int J Cancer 123: 867-873. https://doi.org/10.1002/ijc.23529

24. Li Y, Wu ZQ, Xu Q, Goyal H, Xu HG (2021) Development and validation of novel nomograms using serum tumor markers for the prediction of preoperative histologic grades in gastroenteropancreatic neuroendocrine tumors. Front Oncol 11: 1-9. https://doi.org/10.3389/fonc.2021.681149

25. Plöckinger U, Rindi G, Arnold R, Eriksson B, Krenning EP, et al. (2004) Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European neuroendocrine tumour society (ENETS). Neuroendocrinology 80: 394-424. https://doi.org/10.1159/000085237

26. Edge SB, Compton CC (2010) The American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17: 1471-1474. https://doi.org/10.1245/s10434-010-0985-4

27. Jackson AS, Rosenthal A, Cattoni M, Bograd AJ, Farivar AS, et al. (2020) Staging system for neuroendocrine tumors of the lung needs to incorporate histologic grade. Ann Thorac Surg 109: 1009-1018. https://doi.org/10.1016/j.athoracsur.2019.09.053

28. Takimoto CH (2008) Commentary: tumor growth, patient survival, and the search for the optimal phase II efficacy endpoint. Oncologist 13: 1043-1045. https://doi.org/10.1634/theoncologist.2008-0180

29. McCormick D (2002) Carcinoid tumors and syndrome. Gastroenterol Nurs 25: 105-111. https://doi.org/10.1097/00001610-200205000-00004

30. Tempfer CB, Tischoff I, Dogan A, Hilal Z, Schultheis B, et al. (2018) Neuroendocrine carcinoma of the cervix: a systematic review of the literature. BMC Cancer 18: 1-16. https://doi.org/10.1186/s12885-018-4447-x

31. Belák J, Kudlác M, Zak V, Cavarga I, Kocan P, et al. (2010) Surgical management of bronchopulmonary carcinoid tumors: experience over 8 years and review of the literature. Tumori J 96: 84-89. https://doi.org/10.1177/030089161009600114

32. Hung YP (2019) Neuroendocrine tumors of the lung: updates and diagnostic pitfalls. Surg Pathol Clin 12: 1055-1071. https://doi.org/10.1016/j.path.2019.08.012

33. Gridelli C, Rossi A, Airoma G, Bianco R, Costanzo R, et al. (2013) Treatment of pulmonary neuroendocrine tumours: state of the art and future developments. Cancer Treat Rev 39: 466-472. https://doi.org/10.1016/j.ctrv.2012.06.012

34. Zacharias J, Nicholson AG, Ladas GP, Goldstraw P (2003) Large cell neuroendocrine carcinoma and large cell carcinomas with neuroendocrine morphology of the lung: prognosis after complete resection and systematic nodal dissection. Ann Thorac Surg 75: 348-352. https://doi.org/10.1016/s0003-4975(02)04118-8

35. Gustafsson BI, Kidd M, Chan A, Malfertheiner MV, Modlin IM (2008) Bronchopulmonary neuroendocrine tumors. Cancer 113: 5-21. https://doi.org/10.1002/cncr.23542

36. Detterbeck FC (2010) Management of carcinoid tumors. Ann Thorac Surg 89: 998-1005. https://doi.org/10.1016/j.athoracsur.2009.07.097

37. Tabaksblat EM, Langer SW, Knigge U, Grønbæk H, Mortensen J, et al. (2016) Diagnosis and treatment of bronchopulmonary neuroendocrine tumours: state of the art. Acta Oncol 55: 3-14. https://doi.org/10.3109/0284186x.2015.1067715

38. Kim JY, Hong SM (2016) Recent updates on neuroendocrine tumors from the gastrointestinal and pancreatobiliary tracts. Arch Pathol Lab Med 140: 437-448. https://doi.org/10.5858/arpa.2015-0314-ra

39. Kwaan MR, Goldberg JE, Bleday R (2008) Rectal carcinoid tumors: review of results after endoscopic and surgical therapy. Arch Surg 143: 471-475. https://doi.org/10.1001/archsurg.143.5.471

40. Witzigmann H, Loracher C, Geissler F, Wagner T, Tannapfel A, et al. (2002) Neuroendocrine tumours of the duodenum. Langenbecks Arch Surg 386: 525-533. https://doi.org/10.1007/s00423-001-0260-z

41. Hoffmann KM, Furukawa M, Jensen RT (2005) Duodenal neuroendocrine tumors: classification, functional syndromes, diagnosis and medical treatment. Best Pract Res Clin Gastroenterol 19: 675-697. https://doi.org/10.1016/j.bpg.2005.05.009

42. Sahani DV, Bonaffini PA, Castillo CFD, Blake MA (2013) Gastroenteropancreatic neuroendocrine tumors: role of imaging in diagnosis and management. Radiology 266: 38-61. https://doi.org/10.1148/radiol.12112512

43. Thavaraputta S, Graham S, Mejia AMR, Lado-Abeal J (2019) Duodenal somatostatinoma presenting as obstructive jaundice with the coexistence of a gastrointestinal stromal tumour in neurofibromatosis type 1: a case with review of the literature. BMJ Case Rep 12. https://doi.org/10.1136/bcr-2018-226702

44. Cives M, Strosberg J (2017) Radionuclide therapy for neuroendocrine tumors. Curr Oncol Rep 19: 1-9. https://doi.org/10.1007/s11912-017-0567-8

45. Massironi S, Campana D, Partelli S, Panzuto F, Rossi RE, et al. (2018) Heterogeneity of duodenal neuroendocrine tumors: an Italian multi-center experience. Ann Surg Oncol 25: 3200-3206. https://doi.org/10.1245/s10434-018-6673-5

46. Bonds M, Rocha FG (2020) Neuroendocrine tumors of the pancreatobiliary and gastrointestinal tracts. Surg Clin North Am 100: 635-648. https://doi.org/10.1016/j.suc.2020.02.010

47. Stinner B, Rothmund M (2005) Neuroendocrine tumours (carcinoids) of the appendix. Best Pract Res Clin Gastroenterol 19: 729-738. https://doi.org/10.1016/j.bpg.2005.06.003

48. Robertson RG, Geiger WJ, Davis NB (2006) Carcinoid tumors. Am Fam Physician 74: 429-434.

49. Goto K, Kodama T, Matsuno Y, Yokose T, Asamura H, et al. (2001) Clinicopathologic and DNA cytometric analysis of carcinoid tumors of the thymus. Mod Pathol 14: 985-994. https://doi.org/10.1038/modpathol.3880423

50. Wang AY, Ahmad NA (2006) Rectal carcinoids. Curr Opin Gastroenterol 22: 529-535. https://doi.org/10.1097/01.mog.0000239868.27328.1d

51. Yangong H, Shi C, Shahbaz M, Zhengchuan N, Wang J, et al. (2014) Diagnosis and treatment experience of rectal carcinoid (a report of 312 cases). Int J Surg 12: 408-411. https://doi.org/10.1016/j.ijsu.2014.03.002

52. Northrop JA, Lee JH (2007) Large bowel carcinoid tumors. Curr Opin Gastroenterol 23: 74-78. https://doi.org/10.1097/mog.0b013e328011752a

53. McDermott FD, Heeney A, Courtney D, Mohan H, Winter D (2014) Rectal carcinoids: a systematic review. Surg Endosc 28: 2020-2026. https://doi.org/10.1007/s00464-014-3430-0

54. Nesti C, Bräutigam K, Benavent M, Bernal L, Boharoon H, et al. (2023) Hemicolectomy versus appendectomy for patients with appendiceal neuroendocrine tumours 1-2 cm in size: a retrospective, Europe-wide, pooled cohort study. Lancet Oncol 24: 187-194. https://doi.org/10.1016/s1470-2045(22)00750-1

55. Murray SE, Lloyd RV, Sippel RS, Chen H (2013) Clinicopathologic characteristics of colonic carcinoid tumors. J Surg Res 184: 183-188. https://doi.org/10.1016/j.jss.2013.05.107

56. Shehabeldin AN, Ro JY (2019) Neuroendocrine tumors of genitourinary tract: recent advances. Ann Diagn Pathol 42: 48-58. https://doi.org/10.1016/j.anndiagpath.2019.06.009

57. Fine SW (2007) Neuroendocrine lesions of the genitourinary tract. Adv Anat Pathol 14: 286-296. https://doi.org/10.1097/pap.0b013e3180ca8a89

58. Teegavarapu PS, Rao P, Matrana MR, Cauley DH, Wood CG, et al. (2014) Neuroendocrine tumors of the kidney: a single institution experience. Clin Genitourin Cancer 12: 422-427. https://doi.org/10.1016/j.clgc.2014.06.008

59. Howitt BE, Kelly P, McCluggage WG (2017) Pathology of neuroendocrine tumours of the female genital tract. Curr Oncol Rep 19: 1-13. https://doi.org/10.1007/s11912-017-0617-2

60. Conner MG, Richter H, Moran CA, Hameed A, Albores-Saavedra J (2002) Small cell carcinoma of the cervix: a clinicopathologic and immunohistochemical study

of 23 cases. Ann Diagn Pathol 6: 345-348. https://doi.org/10.1053/adpa.2002.36661

61. Transanal Endoscopic Microsurgery.
62. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD (2005) Current status of gastrointestinal carcinoids. Gastroenterology 128: 1717-1751. https://doi.org/10.1053/j.gastro.2005.03.038
63. Maione F, Chini A, Milone M, Gennarelli N, Manigrasso M, et al. (2021) Diagnosis and management of rectal neuroendocrine tumors (NETs). Diagnostics 11: 771-783.
64. Basuroy R, Haji A, Ramage JK, Quaglia A, Srirajaskanthan R (2016) Review article: the investigation and management of rectal neuroendocrine tumours. Aliment Pharmacol Ther 44: 332-345. https://doi.org/10.1111/apt.13697
65. Sumida T, Nagata S, Ougoshi H, Ishida Y, Kuwahara T, et al. (2005) Multiple rectal carcinoid tumors treated by endoscopic mucosal resection-report of a case. Gastroenterol Endosc 47: 1419-1424. https://doi.org/10.11280/GEE1973B.47.1419
66. Nishikawa Y, Chino A, Ide D, Saito S, Igarashi M, et al. (2019) Clinicopathological characteristics and frequency of multiple rectal neuroendocrine tumors: a single-center retrospective study. Int J Colorectal Dis 34: 1887-1894. https://doi.org/10.1007/s00384-019-03405-z
67. Kasuga A, Chino A, Uragami N, Kishihara T, Igarashi M, et al. (2012) Treatment strategy for rectal carcinoids: a clinicopathological analysis of 229 cases at a single cancer institution. J Gastroenterol Hepatol 27: 1801-1807. https://doi.org/10.1111/j.1440-1746.2012.07218.x
68. Takatsu Y, Fukunaga Y, Nagasaki T, Akiyoshi T, Konishi T, et al. (2017) Short- and long-term outcomes of laparoscopic total mesenteric excision for neuroendocrine tumors of the rectum. Dis Colon Rectum 60: 284-289. https://doi.org/10.1097/dcr.0000000000000745
69. Al Natour RH, Saund MS, Sanchez VM, Whang EE, Sharma AM, et al. (2012) Tumor size and depth predict rate of lymph node metastasis in colon carcinoids and can be used to select patients for endoscopic resection. J Gastrointest Surg 16: 595-602. https://doi.org/10.1007/s11605-011-1786-1
70. Shin S, Maeng YI, Jung S, Yang CS (2022) A small, low-grade rectal neuroendocrine tumor with lateral pelvic lymph node metastasis: a case report. Ann Coloproctol 38: 327-331. https://doi.org/10.3393/ac.2021.00899.0128
71. Ramage JK, De Herder WW, Fave GD, Ferolla P, Ferone D, et al. (2016) ENETS consensus guidelines update for colorectal neuroendocrine neoplasms. Neuroendocrinology 103: 139-143. https://doi.org/10.1159/000443166
72. Ricci AD, Pusceddu S, Panzuto F, Gelsomino F, Massironi S, et al. (2022) Assessment of the risk of nodal involvement in rectal neuroendocrine neoplasms: the Novara score, a multicentre retrospective study. J Clin Med 11: 713-722. https://doi.org/10.3390/jcm11030713
73. Tanaka H (2003) Multiple rectal carcinoid tumors with 31 lesions, report of a case. Stomach Intestine 38: 1193-1199.
74. Shah MH, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, et al. (2021) Neuroendocrine and adrenal tumors, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 19: 839-868. https://doi.org/10.6004/jnccn.2021.0032
75. Copur MS, Manapuram S (2019) Multiple primary tumors over a lifetime. Oncol Williston Park 33: 629384.
76. Cohen-Mekelburg S, Schneider Y, Gold S, Scherl E, Steinlauf A (2017) Advances in the diagnosis and management of colonic dysplasia in patients with inflammatory bowel disease. Gastroenterol Hepatol NY 13: 357-362.
77. Greenstein AJ, Balasubramanian S, Harpaz N, Rizwan M, Sachar DB (1997) Carcinoid tumor and inflammatory bowel disease: a study of eleven cases and review of the literature. Am J Gastroenterol 92: 682-685