



## Rectal neuroendocrine tumors: Update

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### Abstract

Rectal neuroendocrine tumors (NETs) are increasingly detected and are the most common gastrointestinal NET sites. Often discovered incidentally during endoscopy, most are small, well differentiated, and have an excellent prognosis. Local resection is typically considered curative. Several guidelines, namely the European Neuroendocrine Tumor Society guidelines 2023, National Comprehensive Cancer network 2025, and the Polish Network of Neuroendocrine Tumors (2017) emphasize the use of endoscopic and endoscopic ultrasound staging to select the appropriate therapy, ranging from resection to advanced techniques for larger or metastatic diseases, highlighting the need for an accurate initial assessment.

**Key Words:** Neuroendocrine; Rectum; Metastasis; Endoscopic ultrasound; Transanal

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**Core Tip:** This manuscript highlights that, although rare, rectal neuroendocrine tumors exhibit distinct prognostic and therapeutic profiles. Key innovations include the identification of metabolic syndrome components as risk factors, the prognostic value of vascular patterns and biomarkers such as chromogranin A as well as the refined endoscopic resection techniques showing efficacy for small tumors. Importantly, tumor grade and size are critical for predicting metastasis and survival, and local excision is often sufficient for smaller lesions.

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## INTRODUCTION

Neuroendocrine tumors (NETs) of the colorectum are rare and are classified by the World Health Organization (WHO) as malignant tumors. They account for 1%-2% of rectal tumors. Rectal NETs (RNETs) constitute 20 % of gastrointestinal NET's and up to 27% of all NET's. They differ in disease presentation, as they arise from the epithelium and differentiate into well- and poorly differentiated types. Often described as solitary, multiple (< 8 lesions), or numerous ( $\geq 8$  lesions), they carry different tumor behavior, invasion, and outcomes[1]. Rectal lesions have more favorable tumor-related survival outcomes than colonic lesions[2]. Furthermore, differentiation of the outcomes between rectosigmoid and RNETs is of paramount importance since survival differs; the 5-year survival significantly differed between the rectosigmoid junction *vs* RNET's [hazard ratio (HR) = 0.82, 95% confidence interval (95%CI): 0.70-0.95;  $P = 0.01$ ], better survival observed in men (HR = 0.69, 95%CI: 0.55-0.88;  $P < 0.01$ ) however , primary tumor surgery had no benefits ( $P = 0.56$ ) for patients with rectosigmoid junction NETs, It is observed that in RNET a tumor larger than 1 cm and invasion deeper than T1 could significantly increase the risk of regional lymph node metastases [all odds ratio (OR) > 5,  $P < 0.01$ ][3]. RNETs are rare and usually asymptomatic, as they are often diagnosed during colonoscopy. Large series detection has been reported in several countries. In a Polish series of 82005 colonoscopies, seven lesions were detected, with a mean age and polyp size of 52 years and 5 mm, respectively[4]. Other European studies have reported similar epidemiological findings. In Netherlands, the incidence of RNET with annual percentage changes was 6.2% (95%CI: 5.4%-7.1%), with a favorable survival and 5-year relative survival (RS): 72.4% (95%CI: 70.1%-74.7%)[5]. In Germany, with a series of 12602 neuroendocrine neoplasms cases, with 59% located in the rectum. 5-year RS was high for RNETs (95.9%, 95%CI: 94.6-97.1)[6]. In a study with a follow-up period of 30 years in Queensland, the Australia Gastrointestinal NET registry (4580 patients), higher and lower survival rates was noted for appendiceal and pancreatic NETs respectively. Men are at risk of death within 5 years of diagnosis at a rate of 40% (HR = 1.41, 95%CI: 1.20-1.65) especially over 40 years of age compared to a younger age population ( $P < 0.001$ ); this is explained based on better diagnostics and awareness[7].

### Risk factors

factors predictive of RNET diagnosis studied in a multivariable analysis showed that a positive history of malignancy (OR = 2.960, 95%CI: 1.673-5.237,  $P < 0.001$ ), high serum triglycerides (OR = 1.482, 95%CI: 1.046-2.100,  $P = 0.027$ ), high fasting glucose levels (OR = 1.008, 95%CI: 1.003-1.014,  $P = 0.001$ ) and elevated carcinoembryonic antigen marker levels (OR = 1.019, 95%CI: 1.003-1.035,  $P = 0.021$ ) were significant risk factors however, old age does not increase the risk (OR = 0.964, 95%CI: 0.951-0.977,  $P < 0.001$ )[8]. Furthermore, Presence of the metabolic syndrome (OR = 1.768, 95%CI: 1.071-2.918,  $P = 0.026$ ), high serum cholesterol (OR = 1.007, 95%CI: 1.001-1.013,  $P = 0.016$ ) high serum ferritin (OR = 1.502, 95%CI: 1.167-1.935,  $P = 0.002$ ), and a positive family history of cancer among first-degree relatives (OR = 1.664, 95%CI: 1.019-2.718,  $P = 0.042$ ) contribute to causation of RNET[9].

### Clinical features

Rectal lesions are often missed when polyps are removed for several pathologies, in which NET represents a minority. Polyp size is rarely a direct symptom. Non-specific symptoms include non-specific abdominal pain, changes in bowel habits and rectal bleeding, and which are present in 50% of individuals; carcinoid syndrome symptoms may be a possible presentation as well. A manifestation of RNET with insulinoma secreting features has been described. Recently, a novel transcription factor with excellent sensitivity and specificity for neuroendocrine differentiation in various anatomic sites including RNET is identified which is insulinoma-associated protein 1. Metastatic disease in lymph nodes has shown to be associated with the presence of lymph vascular invasion (LVI), tumor size (> 10 mm) and but not with a positive Ki-67 proliferative index[10].

Atypical presentations of RNET are reported in the literature. One study reported RNETs diagnosed in 36-year-old monozygotic twins, which raised suspicion of an inherent tendency for RNET occurrence[11]; another case presented with symptomatic hypoglycemia in a patient with insulinoma and RNET[12]. Atypical metastatic sites have been detected in the skin with a poorly differentiated RNET[13]. A 60-year-old man was detected with a presacral pelvic mass as a part of Currarino syndrome, which is a rare, congenital, inherited disorder characterized by a triad of abnormalities: Anorectal malformation, a defect in the sacrum, and a presacral mass[14]. A patient with RNET undergoing treatment developed symptomatic and pathological metastasis to a basal skull meningioma[15]. Other bizarre metastatic locations, as reported in the first presentation of RNET, include the pancreas[16] and pelvic endometriosis[17]. Coexistence with other conditions in which the mucosa is pathologically abnormal, such as inflammatory bowel disease[18], adds further to the ambiguity; a case of hereditary non-polyposis colon cancer, an RNET, was diagnosed[19] and coexisted with celiac disease [20].

RNET is recognized during lower endoscopy and suspected lesions are removed with further precision using endoscopic ultrasound (EUS), which facilitates the diagnosis of small lesions that are not easily visualized using conventional white light endoscopy. The characteristics of RNET can be described using pathology, specific staining techniques, and molecular characterization. To estimate prognosis, a combination of tumor size measurements according to the WHO classification would help in planning management.

**Colonoscopy:** Lesions appear as hemispherical and hummocky submucosal protrusions. They have a smooth and complete mucosal surface and appear grossly normal or yellowish white in color[21]. Atypical features include lesions with ulceration/scar/central depression and hyperemia or flat-seating small polyps that are difficult to distinguish from hyperplastic polyps. Long term outcomes following use of biopsy forceps for the removal of small lesions investigated over a follow up period of 6.5 years (range 1.0-12.8 years) showed no overall or disease-related death. All recurrences were diagnosed > 5 years after the initial diagnosis and were successfully treated endoscopically[22]. Some clinicians

advocate against using biopsy forceps to sample lesions because of possible biopsy-induced fibrosis that alters further assessment and management. Relying on biopsy forceps removal is imprecise, Polyp size is an independent factor of residual disease with  $OR = 8.7 \pm 7.5$  each mm ( $P = 0.013$ ), characteristic findings of EUS accuracy ( $0.661 \pm 0.111$ ), grading ( $0.631 \pm 0.109$ ) and tumor size (3.1 mm as cut-off point) with area under the curves of  $0.821 \pm 0.109$ [23]. EUS is required to localize and resect lesions; hence, Park *et al*[24] reported that the size measured using endoscopy was not significantly different from that measured using EUS and histology ( $r = 0.914$  and  $0.727$ , respectively). Endoscopic vessel characteristics and vascular patterns are used to classify lesions into V1 and V2 types and validated to predict tumor grade and submucosal invasion in a study by Zheng *et al*[25]. Multivariate analysis demonstrated good association between vascular pattern and tumor grade ( $OR = 13.65$ , 95%CI: 2.06-90.58). Vascular pattern demonstrated perfect inter- and intra-observer agreements ( $k = 0.957$ ) with V1 exhibited sensitivity (94.5%), positive predictive value (97.7%), and accuracy (93.3%) for prediction of grade 1. A significantly deeper submucosal invasion for V2 lesions than for V1 lesions observed on histopathological analysis ( $P < 0.001$ ).

**EUS:** The EUS uses ultrasonic waves generated by linear, radial, or micro-probes. Therefore, hypoechoic submucosal lesions involving the mucosal, submucosal, and deeper layers[21] rarely present with a central hyperechogenic area and an acoustic shadow, indicating calcification[26]. Assessment and detection of incomplete resection and positive margins following endoscopic resection using endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) when examined by EUS detection ( $OR = 8.44$ , 95%CI: 1.18-41.35) *vs* visual detection ( $OR = 7.00$ , 95%CI: 1.50-47.48) were associated with residual lesion in patients with incompletely resected NET. EUS detection of residual lesions showed a sensitivity of 94%, positive predictive value of 88%, specificity of 71%, accuracy of 87% and negative predictive value of 83%[27].

### Pathology

The characteristic pathology shows cells with salt-and-pepper chromatin arranged in nests or sheets, and immunohistochemistry is positive for neuroendocrine markers such as chromogranin A (CgA) and synaptophysin. Biomarkers commonly used to predict survival include CgA, Ki-67 (a proliferative index used to estimate grading[28]) stains. Expression of CgA in RNETs was more commonly associated with male sex ( $P = 0.002$ ), older age ( $\geq 50$  years and older;  $P = 0.013$ ), large tumor size ( $\geq 1$  cm;  $P = 0.038$ ), radical resection ( $P = 0.003$ ), muscularis propria invasion ( $P = 0.002$ ), lymphovascular ( $P = 0.014$ ) and perineural ( $P < 0.001$ ) invasion, an involved resection margin ( $P = 0.028$ ), and lymph node metastasis (LNM;  $P = 0.003$ ). A higher plasma CgA levels ( $P = 0.023$ ) observed in patients with CgA expression than those without expression during the follow-up. Furthermore, in patients with RNETs with CgA expression the 10-year disease-free survival rate (91.5%) was significantly shorter than that in patients with negative expression (99.7%), in both multivariate ( $HR = 12.099$ , 95%CI: 2.044-71.608;  $P = 0.006$ ) and univariate ( $HR = 14.438$ , 95%CI: 2.911-71.598;  $P < 0.001$ ) analyses[29]. Ki-67 labeling index (LI) demonstrated characteristics features for Ki-67 LI in biopsy specimens for predicting grade 2 tumors with sensitivity, positive, negative predictive, specificity values of 53% (9/17), 100% (9/9), 87% (41/47) and 95% (41/43) respectively following endoscopic submucosal resection with a ligation device, trans-anal full-thickness surgical resection, or radical surgery with lymph node dissection[30].

### Medical imaging

Contrast-enhanced computed tomography (CT), used as an imaging histogram to predict the WHO grade to evaluate arterial and venous phases, could be an excellent indicator for predicting G1 and higher grades of RNET, as well as tumor size[31].

### Nuclear imaging

The best diagnostic accuracy using positron emission tomography (PET)-CT with 68Ga-labeled somatostatin analogs (68Ga-DOTATATE, 68Ga-DOTANOC, and 68Ga-DOTATOC) can be explained based on their high expression of somatostatin receptors on cell membranes. For detection of LNM in RNETs the use of 18F-FDG as a tracer taken up by G2 and G3 tumors use of 68Ga-DOTANOC PET-CT is a promising tool with high specificity and sensitivity and in visual and semiquantitative assessments, which is better than 8F-FDG PET-CT[32].

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## GRADING

Criteria of the European Neuroendocrine Tumors Society (ENETS) and the WHO be used interchangeably; in addition to tumor location, the 2010 WHO criteria are important independent prognostic parameters for colorectal NET (CRNET) in both univariate and multivariate analyses[33].

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## STAGING

Staging is estimated using the TNM classification system[34,35] which determines the treatment plan and outcomes. Overall, small tumors ( $< 10$  mm) that is well-differentiated without muscle layer invasion have a lower malignant propensity and can be endoscopically resected. Conversely, a higher malignant potential is expected for RNETs with size  $> 20$  mm have that is better surgically removed according to the Vienna consensus on the treatment of NET. While

grading is useful for determining the best treatment pathway, it also serves as a prognosticator, and the best size cut-offs for predicting overall survival (OS) and progression-free survival (PFS) are 10 mm and 12 mm, respectively. The 5-year OS and PFS were 79.5% and 65.2%. Stage IV and G3 were associated with worse OS (HR = 8.16,  $P = 0.002$ ; HR = 15.57,  $P = 0.0004$ ) and PFS (HR = 14.26,  $P < 0.0001$ ; HR = 6.42,  $P = 0.0007$ )[36].

## MANAGEMENT

Management modalities include endoscopic resection techniques such as ESD and EMR as well as surgical excision, supplemented by chemotherapy and/or radiotherapy. Several scientific bodies have proposed guidelines for the management of RNET; the updated guidelines of ENETS, National Comprehensive Cancer Network and Polish Network of Neuroendocrine Tumors summarized at Table 1. Decision of the management of RNETS depends on tumor size which are (less than 1 cm, between 1-2 cm and more than 2 cm).

### Surgical excision

Upon investigation of the outcomes related to delayed surgery and the incidence of pathologic upstaging for clinical stage 1 Colorectal Neuroendocrine Tumors (CRNET). Multivariable analysis demonstrated that male sex (HR = 3.16, 95%CI: 1.43-7.03,  $P = 0.005$ ), age (HR = 1.06, 95%CI: 1.03-1.10,  $P \leq 0.001$ ) and delayed surgery beyond 6 months (HR = 4.82, 95%CI: 1.13-20.55,  $P = 0.033$ ), associated with increased risk, while having a rectal primary (HR = 0.32, 95%CI: 0.15-0.68,  $P = 0.003$ ) was protective; however, delay beyond 6 months is significant with isolated rectal primary (HR = 4.5, 95%CI: 1-19.2,  $P = 0.044$ ). A 14 % incidence of tumor upstaging is noted when surgery is delayed more than 6 months ( $P = 0.0023$ ), however, active surveillance was associated with decreased OS (HR = 1.48, 95%CI: 1.02-2.13,  $P = 0.039$ ) compared with upfront resection. Nevertheless, when indicated clinically, surgical approaches depend on expertise, accurate localization, and the ability to remove lesions with margin free precision. A clinical Series that reported outcomes of local excision *vs* radical resection showed that radical resection resulted in tumors with higher stage and grade and larger in size. Higher rates of positive margins are noted with local excision (8.23% *vs* 0%,  $P = 0.04$ ). No 30-days mortality difference noted in either group; Furthermore, A longer median hospital stays (0 day *vs* 3 days,  $P < 0.01$ ) is noted in patients undergoing radical resection. After adjustment, no difference was seen in survival between the 2 patient groups (HR = 2.39, 95%CI: 0.85-6.70,  $P = 0.10$ )[37]. A large cohort from China compared laparoscopic surgery with the open approach; the laparoscopic approach had superior relapse-free survival ( $P = 0.048$ ) and fewer complications (14.5% *vs* 35.5%,  $P = 0.007$ ). Subgroup analysis revealed that the laparoscopic surgery group had superior relapse-free survival ( $P = 0.025$ ), fewer complications (10.9% *vs* 34.7%,  $P = 0.004$ ) and shorter postoperative hospital stays ( $9.56 \pm 5.21$  days *vs*  $12.31 \pm 8.61$  days,  $P = 0.049$ ) in RNET  $\leq 4$  cm[38]. G2 tumors investigated using a propensity score matching analysis found that a comparison between local excision and radical resection for grade 2 RNET with an optimal cutoff value of 1.5 cm predict cancer-specific survival (CSS).

However, other grade 2 RNET  $\leq 1.5$  cm size showed no significant differences in relapse-free and CSS rates between local excision and radical resection groups ( $P > 0.05$ ). Conversely, in patients with grade 2 RNETs ( $> 1.5$  cm), relapse-free survival was significantly lower in the local excision group than in the radical resection group ( $P = 0.04$ )[39].

In addition to the use of surgery as a primary modality of resection, it is also used to salvage a previous unresected lesion, incompletely resected lesion or recurrence (mainly grades 1 and 2) performed endoscopically or surgically to cover more depth-margin-free removal[40,41] using full-thickness transanal endoscopic surgery (TEM).

### Impact of resection following surgery

For patients with RNETs of 10-20 mm, there was no survival benefit for local excision compared with radical resection; multivariate analysis of CSS, tumor size 14-20 mm ( $P = 0.011$ ), M1 stage ( $P < 0.001$ ) and age  $> 60$  years ( $P = 0.005$ ) were identified as independent prognostic factors for worse CSS.

In the multivariate analysis of OS, male sex ( $P = 0.007$ ), black ethnicity ( $P = 0.016$ ), age  $> 60$  years ( $P < 0.001$ ), and T2/T3/T4 stage ( $P = 0.007$ ) were significantly associated with worse OS. Nodal (N) stage was not independent predictive factor for CSS or OS, suggesting that local excision may be an adequate treatment for these patients[42].

Based on several guidelines for RNET with size  $> 2$  cm, a comparison between local excision and radical surgery for pN0 and pN1 in selected patients with RNETs  $> 2$  cm local excision is a viable alternative to radical surgery. Tumor grade and nodal status independently predict survival and should be factored in the selection of surgical intervention. It is shown that a similar survival between the pN0 and pN1 groups among the higher risk groups would benefit from radical surgery[43].

Endoscopic excision: Used for excision of small and large RNET.

R0 (*i.e.*, resection with margin free) resection rate is achieved with success using TEM (97.6%-100%). EMR is recommended for small ( $< 10$  mm) lesions, in conjunction with modified techniques which are (cap, ligation band, anchoring tip)[44]. EMR with suction when used for small lesions could achieve a higher complete resection rate than ESD (OR = 4.08, 95%CI: 2.42-6.88,  $P < 0.00001$ ) with shorter procedure time than in the ESD group (standard mean difference: -1.59, 95%CI: -2.27 to -0.90,  $P < 0.00001$ ) without significant difference in overall complication rate (OR = 0.56, 95%CI: 0.28-1.14,  $P = 0.11$ ) and better overall recurrence rate (OR = 0.76, 95%CI: 0.11-5.07,  $P = 48\%$ ) between both groups[45]. Comparing the outcomes of EMR and ESD, especially in high-volume centers, 304 patients [ESD = 126, modified EMR (m-EMR) = 178] were included, with 218 patients in the matched groups [modified ESD (ESDM) = 109, m-EMR = 109]. The R0 resection rate was not significantly different between the two groups (90.0% *vs* 82.3%,  $P = 0.221$ ). However, a significantly shorter procedural time was observed at the m-EMR group than in the ESD group (6 minutes *vs* 26 minutes,

**Table 1 International guidelines for management of rectal neuroendocrine tumors**

| Guidelines                                             | Treatment recommendations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| European Neuroendocrine Tumor Society, 2023[76]        | <p>For lesions <math>\leq 10</math> mm: Endoscopic resection such as mEMR, ESD, and eFTR is recommended and recurrence rates are low</p> <p>For lesions <math>\geq 20</math> mm: Initial assessment is performed using EUS and pelvic MRI for local staging. Distant metastases staging is done using chest and abdominal CT/MRI and 68Gallium SSA-PET-CT. For positive lesions Surgical resection using LAR or APR is recommended (after exclusion of unresectable distant metastases)</p> <p>For lesions 10-20 mm: Initial assessment is performed using EUS and pelvic MRI for local staging. Distant metastases staging is done using chest and abdominal CT/MRI and 68Gallium SSA-PET-CT. For positive lesions, either endoscopic or definitive surgical therapy is decided through multidisciplinary team discussions</p>                                                                                                                                                                                                                                                                                                                                                                       |
| National Cancer Comprehensive Cancer Network, 2025[77] | <p>Very small (<math>&lt; 1</math> cm)</p> <p>Negative margin: No further follow-up</p> <p>Indeterminate margin: Classification into low grade (G1) that requires endoscopy follow up (6-12 months) and referral to the pathway below (all other tumor sizes) if positive or intermediate grade (G2)</p> <p>All other tumor sizes</p> <p>T1 stage: Resection (endoscopic or transanal)</p> <p>Lesions less than 1 cm with no follow up</p> <p>Lesions follow up every 6-12 months</p> <p>Management depends on the size for T2-T4 stages: Comprehensive assessment by colonoscopy, multiphasic imaging CT scan/MRI, Chest CT scan, SSRT PET-CT or SSRT PET-MRI and biochemical evaluation as clinically indicated</p> <p>Size <math>\leq 2</math> cm: Resection by endoscopy or transanal surgery; if size <math>&lt; 1</math> cm, no further follow up is needed; if 1-2 cm, frequent (6-12 months) follow up by endoscopy or MRI</p> <p>Size <math>&gt; 2</math> cm or presence of positive lymph nodes: Low anterior resection, abdominoperineal resection, or Neoadjuvant or definitive chemoradiation. Aim for cytoreduction</p> <p>Metastatic lesions: Management with aim of cytoreduction</p> |
| Polish Network of Neuroendocrine Tumors, 2022[78]      | <p>Size <math>&lt; 1</math> cm with no risk factors: Endoscopic resection</p> <p>Size 1-2 cm with no risk factors: Endoscopic resection</p> <p>Size 1-2 cm with risk factors: Surgical treatment using: (1) Transanal approach with either Transanal endoscopic microsurgery or through the open rectum access; (2) Laparoscopic approach with either abdominoperineal amputation of the rectum or anterior resection of the rectum; and (3) Through open access with either abdominoperineal amputation of the rectum or anterior resection of the rectum</p> <p>Risk factors to consider include: Infiltration of the muscular membrane proper, involvement of regional lymph nodes, infiltration of lymphatic and/or blood vessels, and a proliferation index above 2%</p>                                                                                                                                                                                                                                                                                                                                                                                                                         |

T1 means tumor invades the lamina propria or submucosa; T2 means tumor invades the muscular layer or is 2 cm in size; T3 means tumor invades into subserosal tissue; T4 means tumor invades serosa and/or adjacent organs (American Joint Committee on Cancer (AJCC) 8<sup>th</sup> edition)[79]. mEMR: Modified endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; eFTR: Endoscopic full-thickness resection; MRI: Magnetic resonance imaging; CT: Computed tomography; SSA: Somatostatin analogues; EUS: Endoscopic ultrasound; PET: Positron emission tomography; LAR: Low anterior resection; APR: Abdominoperineal resection; SSRT: Somatostatin receptor.

$P < 0.001$ ). Adverse events are not significant between the two groups (perforation rate: 0.9% *vs* 0.9%,  $P = 1.00$ , post-procedural bleeding rate: 5.5% *vs* 2.8%,  $P = 0.335$ ). Performance skills to achieve R0 resection rate significantly higher in the m-EMR group than in the ESD group (87.9% *vs* 64.5%,  $P = 0.017$ ) among the trainees as shown on Subgroup analysis [46]. Use of water submersion and resection are employed for small RNETs with no adverse events and high R0 resection and *en bloc* rates[47] as well as underwater ESD[48]. Use of ESD would be an alternative method for the use of a ligation band[49-51], Furthermore incorporating myectomy with ESD for RNETs  $< 16$  mm in diameter without metastasis will overcome vertical margin residual disease and achieves a higher histological complete resection rate with ESD with myectomy; however, the complication rate and operative time are comparable[52]. A recent network meta-analysis reported that EMR with ligation (EMRL), EMR with a cap (EMRC), ESD, ESDM, and TEM showed higher resectability than EMR in terms of achieving histologically complete resection. ESD requires a higher operative time compared to EMR, EMRC, EMRL, endoscopic mucosal resection with pre-cutting, endoscopic mucosal resection with dual-channel endoscope, and endoscopic mucosal resection under water, EMR, ESDM, EMRC and TEM are associated with a lower risk than ESD[53].

### Impact of resection following endoscopic techniques

Risk factors of residual tumor following salvage local resection (SLR) after incomplete resection are the use of cold forceps biopsy for primary resection (OR = 3.60, 95%CI: 1.02-14.52,  $P = 0.043$ ) and suspected remnant tumors before SLR (OR = 15.56, 95%CI: 2.94-82.35,  $P = 0.002$ ) which are associated with residual tumor[54].

Positive (OR = 75.993,  $P < 0.001$ ), or indeterminate (OR = 13.203,  $P = 0.001$ ) resection margins and presence of LVI (OR = 61.971,  $P < 0.001$ ) were more likely to undergo additional treatment[55]. A global trend toward R1 resection with a rate of 75% following the initial resection[56], hence, resection with the aim of R0 (free margin) is desired. However, it is arguable that considering the location, patient condition, and comorbidity taken into account when further interventions to be considered for aim of R1 results post-resection[57].

## CHEMOTHERAPY

With improved resection techniques, the use of neoadjuvant chemotherapy has become limited. Factors such as male sex, age  $\geq 60$  years and distant metastases were associated with worse survival, whereas administration of chemotherapy and surgical resection were associated with a reduced risk of death. For non-metastatic tumors treated with surgical resection, administration of chemotherapy conferred protection, while the presence of positive lymph node ratio  $\geq 42\%$  (median value) was associated with an increased risk of death[58]. Gefen *et al*[59] reported United States National Cancer Database data. Among clinical T4 tumors, lesions more than 20 mm in size, poorly differentiated histology, and metastatic disease were independent predictors of worse OS and defined as high-risk groups. No significant survival benefit in any of the high-risk groups with use of neoadjuvant chemotherapy, except for high-grade RNETs where neoadjuvant therapy improved OS to a mean duration of 30.9 months compared with 15.9 months when neoadjuvant therapy was not administered ( $P = 0.006$ )[59]. Peptide receptor radionuclide therapy for metastatic RNET has high efficacy and morphological responses with minimal toxicity and encouraging survival results[60]. The chemotherapeutic agent pembrolizumab was used for previously treated advanced well-differentiated NET, including RNET[61]. Future genomic predictions would help improve responsiveness of the tumor by profiling CRNETs, revealing strong evidence that BRAF (V600E) is an oncogenic driver that is responsive to BRAF-MEK combination therapy[62].

## RADIATION THERAPY

Neoadjuvant treatment has been successfully used in metastatic RNET mainly with yttrium peptide receptor radionuclide [63], Lu-DOTATATE, Y-DOTATATE and sequential duo-peptide receptor radionuclide therapy[64,65].

## PROGNOSIS

Prediction of outcome depends on several factors, importantly is the presence of LNM. Table 2 present studies analyzing factors associated with LNM based on initial presentation and prior to intervention, following endoscopic resection, following both endoscopic resection and curative surgery and following curative surgery.

Risk scores were developed to predict prognosis and a nomogram (consisting of age, sex, tumor size, grade, and TNM stage) validated by Feng *et al*[66] showed excellent discrimination (C-index: 0.648 *vs* 0.583,  $P < 0.001$  and 0.648 *vs* 0.603,  $P = 0.016$ , respectively, compared with G grade and TNM classification). Similarly, the GATIS score was developed at multiple centers in China based on tumor grade, T stage, tumor size, age, and the prognostic nutritional index used for prediction, with superior predictive power for OS and PFS[67,68]. Tumor grade remains an important predictive factor for different RNET sizes even in small or diminutive lesions[69].

Management of CRNET is advocated in highly specialized and high volume (HV) center is associated with better survival outcomes; While, those who treat fewer than one patients with CRNETs every 3 years on average had worse outcomes, with low volume (LV) patients having a 14 months median OS (95%CI: 10-19) compared to HV centers had a median OS of 33 months (95%CI: 25-49). In multivariable analysis, Mortality following resection at a LV center was associated with increased risk of mortality [1.42 (95%CI: 1.01-2.00),  $P = 0.04$ ] in multivariate analysis[70].

LVI is a prognostic factor in several RNET. Kwon *et al*[71] reported that LVI was associated with tumor grade 2 ( $P = 0.006$ ) and large tumor size ( $> 5$  mm,  $P = 0.007$ ). Specifically, the only independent predictive factor for the presence of LVI is tumor grade 2 (HR = 4.195, 95%CI: 1.321-12.692,  $P = 0.015$ ). No recurrence was observed over 28.8 months regardless of the presence of LVI. There was no difference between the use of conventional hematoxylin and eosin staining or immunohistochemistry[71]. Regarding LVI after EMR, an excellent long-term prognosis was observed, confirming that EMR is a valid treatment option for small [5 mm (range 2 mm-13 mm)] RNET[72].

The risk of recurrence following endoscopic resection needs to be considered, risk factors are LVI, muscularis propria or deeper invasion, size  $\geq 10$  mm, positive resection margins, or mitotic count  $\geq 2/10$ . In a multicenter study in Korea, the risk of extracolonic recurrence was significantly higher in the high-risk group than in the other groups[73]. Furthermore, LNM following polyp resection, endoscopic resection, or surgery are important determinants. Predictive high-risk features for LNM are resection margin invasion (+; OR = 2.897, 95%CI: 1.057-7.936,  $P = 0.039$ ), pathologic size (OR = 1.208, 95%CI: 1.062-1.374,  $P = 0.001$ ), and angiolymphatic invasion (OR = 22.155, 95%CI: 7.563-64.904,  $P = 0.001$ )[74]. While, post-surgical resection, LNM only was associated with depth of invasion ( $P = 0.003$ ) and tumor diameter ( $P = 0.006$ )[75].

Table 2 Studies of factors related to lymph nodes metastasis in rectal neuroendocrine tumors

| Level of assessment                                                                 | Ref.                            | Country        | Study type    | Cohort                                                                                                                                                                                           | Stage         | Risk factors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------------------------------------------------------------|---------------------------------|----------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Studies that assess lymph nodes metastasis at baseline, prior to tumor intervention | Hyun <i>et al</i> [80], 2015    | South Korea    | Retrospective | 247 patients; at baseline prior to excisional intervention                                                                                                                                       | Not mentioned | Univariate analysis: Tumor size ( $P < 0.001$ ), shape ( $P < 0.001$ ), color ( $P < 0.001$ ) and surface changes ( $P < 0.001$ ) were significantly associated with LNM<br><br>Multivariate analysis: Tumor size (OR = 11.53, 95%CI: 2.51-52.93, $P = 0.002$ ) and atypical surface (OR = 27.44, 95%CI: 5.96-126.34, $P < 0.001$ ) changes were independent risk factors for LNM<br><br>Atypical endoscopic features were associated with LNM in RNETs $< 10$ mm ( $P = 0.005$ ) and 10-19 mm ( $P = 0.041$ ) in diameter                                                                                                                                        |
|                                                                                     | Wang <i>et al</i> [81], 2021    | China          | Retrospective | 223 patients; the incidence of LNM was 10.8%                                                                                                                                                     |               | Univariate and multivariate regression analyses: Tumor size, grade A, and depth of tumor invasion were independent risk factors for LNM ( $P < 0.05$ ); AUC = 0.948 (95%CI: 0.890-1.000)                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|                                                                                     | O'Neill <i>et al</i> [82], 2021 | United Kingdom | Retrospective | 32 patients had small lymph nodes ( $\leq 10$ mm)<br><br>81% ( $n = 26$ ) are grade 1 with Ki67 $< 3\%$<br><br>At baseline with no management intervention                                       |               | Radiological staging confirmed nodal involvement in 25% (8/32)<br><br>Two cases had distant metastatic disease<br><br>LVI in 3% (1/32) of patients but none demonstrated peri-neural invasion                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                                                                                     | Wei <i>et al</i> [83], 2018     | China          | Retrospective | 419 patients; at baseline, prior to interventions                                                                                                                                                |               | Univariate and multivariate regression: Tumor size, G grade and the depth of tumor invasion were independent risk factors for LNM ( $P < 0.05$ )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                                                     | Kojima <i>et al</i> [84], 2019  | Japan          | Retrospective | 79 patients; at baseline prior to interventions; LNM in 12.7%, recurrences in 3.8%, and multiple cancers in 30.4% of the subjects                                                                |               | LOH of PHLDA3 and MEN1 tumor suppressor genes at Lymph nodes of RNET<br><br>LOH PHLDA3 (60%) and MEN1 (66.7%)<br><br>Lymphatic invasion and WHO classification were found to be independent risks for LNM                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                     | Concors <i>et al</i> [85], 2018 | United States  | Retrospective | 3880 (79.3%) had well-differentiated tumors, 540 (11.0%) had moderately differentiated tumors, 473 (9.7%) had poorly differentiated tumors                                                       |               | The association between tumor size and distant metastatic disease was stronger for well-differentiated and moderately differentiated tumors (OR = 1.4, $P < 0.001$ for both) than for poorly differentiated tumors (OR = 1.1, $P = 0.010$ ). For well-differentiated tumors, the optimal cut point for distant metastatic disease was 1.15 cm (AUC = 0.88, 88% sensitive and 88% specific). Tumors $\geq 1.15$ cm in diameter were associated with a substantially increased incidence of distant metastatic disease [72/449 (13.8%)]. For moderately differentiated tumors, the optimal cut point was also 1.15 cm (AUC = 0.87, 100% sensitive and 75% specific) |
| Study that assesses LNM after endoscopic resection                                  | Tie <i>et al</i> [86], 2024     | China          | Retrospective | 128 patients; 92 patients underwent ESD; 19 patients underwent EMR; no significant difference between the two groups regarding the positive rates of basal tumor margin and lateral tumor margin |               | Tumor size and age at diagnosis were predictors for LNM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Studies that assess LNM following endoscopic resection and curative surgery         | Sohn <i>et al</i> [87], 2017    | Korea          | Retrospective | 28 (43.8%) patients underwent transanal excision, EMR or ESD was performed in 15 (23.4%) patients, and radical resection in 21 (31.8%) patients                                                  |               | Multivariable analyses: Tumor size ( $\geq 2$ cm, $P = 0.003$ ) and tumor grade (G2, $P < 0.001$ ; G3, $P = 0.008$ ). Tumor $< 2$ cm, the risk factors for LNM include: Tumor grade, mitosis count, and Ki-67 index<br><br>Significant prognostic factors for survival include: Tumor size, T stage, LNM, and tumor grade                                                                                                                                                                                                                                                                                                                                         |

|                                                    |                                  |                       |               |                                                                                                                                                                                                                                                                                        |                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------------------------|----------------------------------|-----------------------|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                    | Storino <i>et al</i> [88], 2021  | United States         | Retrospective | Local excision in 93.4% of cases with polypectomy in 52 (42.6%), EMR in 48 (39.3%), and transanal excision in 14 (11.5%). The 3 patients (2.5%) underwent abdominoperineal resection or low anterior resection and 5 patients (4.1%) received adjuvant chemotherapy                    | LNM 4 (3.3%) and distant metastasis 4 (3.3%)                                                  | Overall, 5-year survival for patients with localized disease was 98.2% (95%CI: 93-99.5)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                    | Sugimoto <i>et al</i> [89], 2016 | Japan                 | Retrospective | 55 patients metastatic (11 lesions) and non-metastatic (46 lesions) endoscopic submucosal resection with a ligation device, transanal full-thickness surgical resection, or radical surgery                                                                                            |                                                                                               | Univariate analysis: Ki-67 labeling index > 3.0% (OR = 120, $P < 0.001$ ); positive lymphatic or venous permeation (OR = 67.6, $P < 0.001$ ); WHO grading classification G2 (OR = 58.7, $P < 0.001$ ); tumor size > 10 mm (OR = 9.8, $P = 0.0037$ ); submucosal invasion > 4000 $\mu\text{m}$ (OR = 6.8, $P = 0.012$ ); central depression (OR = 5.7, $P = 0.018$ )<br><br>Multivariate logistic regression analyses vascular permeation (OR = 111; $P = 0.006$ ) and Ki-67 labeling index > 3.0% (OR = 88; $P = 0.012$ ) were independent risk factors for metastasis                                     |
|                                                    | Tsang <i>et al</i> [90], 2018    | Canada; United States | Retrospective | 91 RNET: Local ablation ( $n = 5$ ); local excision ( $n = 79$ ); surgical resection ( $n = 4$ ); pelvic radiation ( $n = 1$ ; T3N1 tumor)                                                                                                                                             | G1 and G2 tumors with a Ki-67 $\leq 20\%$ and/or mitotic count $\leq 20$ per high-power field | Univariate analysis: Association between local relapses and; Ki-67, mitotic count, grade, and LVI ( $P < 0.01$ ) was found. Larger tumor size was associated with decreased disease-free survival                                                                                                                                                                                                                                                                                                                                                                                                          |
| Studies that assess LNM following curative surgery | Kim <i>et al</i> [91], 2016      | Korea                 | Retrospective | 40 patients had 1052 lymph nodes removed Following curative surgery                                                                                                                                                                                                                    | Not mentioned                                                                                 | Metastasis-positive lymph nodes had significantly greater long and short diameters ( $P < 0.001$ ) than metastasis-negative lymph nodes                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                    | Takaoka <i>et al</i> [92], 2025  | Japan                 | Retrospective | 28 patients had post rectal resection with total mesorectal excision. LNM was found in 20 patients (39.2%), with lateral LNM occurring in 4 (7.8%) patients                                                                                                                            |                                                                                               | No significant association was found between LNM and 5-year relapse-free survival (90%) for metastasis-negative patients <i>vs</i> 58.1% for metastasis-positive patients ( $P = 0.094$ )                                                                                                                                                                                                                                                                                                                                                                                                                  |
|                                                    | Ushigome <i>et al</i> [93], 2019 | Japan                 | Retrospective | From 102 patients 1169 lymph nodes in the mesorectum were retrieved from all specimens, with 78 (6.7%) lymph nodes showing metastasis. Post-rectal resection with total mesenteric excision or tumor-specific mesenteric excision with or without lateral pelvic lymph node dissection |                                                                                               | Mean length (long-axis diameter) of metastatic lymph nodes in the mesorectum was significantly larger than that of non-metastatic lymph nodes (4.31 mm <i>vs</i> 2.39 mm, $P < 0.01$ )<br><br>The optimal cut-off of major axis length for predicting mesorectal LNM was 3 mm<br><br>Prediction of the small size of lymph nodes preoperatively is limited with CT scan of the abdomen and requires more precise imaging or EUS                                                                                                                                                                            |
|                                                    | Wang <i>et al</i> [94], 2021     | China                 | Prospective   | 58 patients post radical surgical treatment                                                                                                                                                                                                                                            |                                                                                               | At 1 year and 3 years postoperative, disease-free survival rates were 64.5% and 48.8%, respectively; while OS rates were 90.5% and 75.4%, respectively<br><br>Univariate analysis: Tumor differentiation ( $P = 0.002$ ), gross morphology ( $P = 0.009$ ), T stage ( $P = 0.024$ ), and extramural vascular invasion ( $P = 0.009$ ) were associated with OS<br><br>Multivariate analysis: Tumor differentiation (HR = 6.002, 95%CI: 1.210-29.767, $P = 0.028$ ) and gross morphology (HR = 3.438, 95%CI: 1.038-11.382, $P = 0.043$ ) were independent prognostic factors affecting the clinical outcomes |

Grade A: According to World Health Organization grading of neuroendocrine tumor. LNM: Lymph node metastasis; OR: Odds ratio; 95%CI: 95% confidence interval; RNET: Rectal neuroendocrine tumor; AUC: Area under the curve; LVI: Lymph vascular invasion; LOH: Loss of heterozygosity; WHO: World Health Organization; ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection; CT: Computed tomography; EUS: Endoscopic

ultrasound; OS: Overall survival; HR: Hazard ratio.

## CONCLUSION

RNETs are rare malignancies with diverse clinical features. Prognosis is strongly influenced by tumor size, grade, lymphovascular invasion, and metastatic spread. Although small, well-differentiated tumors ( $\leq 10$  mm) can often be managed effectively with endoscopic resection, larger- or higher-grade lesions may require surgical intervention. Advanced imaging and biomarker analyses can aid in accurate staging and risk stratification. Multimodal treatments, including peptide receptor radionuclide therapy, show promise for metastatic diseases. Centralized high-volume care is associated with improved outcomes. Individualized management based on tumor characteristics and patient factors is essential to optimize survival and minimize recurrence.

## FOOTNOTES

**Author contributions:** Khayyat M performed literature review, collection and Khayyat YM performed initial drafting and final review of the manuscript.

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