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ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms: Colorectal Neuroendocrine Neoplasms

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Introduction

The last ENETS guidelines on colorectal (hindgut) NETs were published in 2008 [1], however, there has been new relevant data related to epidemiology and staging including the new WHO classification. These guidelines therefore include these new changes as well as update management and in addition we propose an algorithm of management.

Classification and Epidemiology

Classification can be by primary site and the two natural categories are colon and rectum since these tumours have a different natural history. It is no longer appropriate to classify the colonic tumours as hindgut and midgut, since there is no evidence that caecal tumours are different from those arising from the remainder of the colon.

Colon Tumours

Colonic neuroendocrine tumours (NETs) total approximately 7.5% of all NETs in US series [2–4], 4–7% in European series [5–7] and 8% in Asian series [8]. Their documented incidence in the US SEER database has risen from approximately 0.02 to approximately 0.2 per 100,000 from 1973 to 2004. In Europe the reported incidence is in the region of 0.06 per 100,000 population and this may represent a less sophisticated dataset. Non-appendiceal colonic NETs have a slight preponderance for a Black ethnic background in the USA [4]. These tumours are generally synaptophysin-positive and may also have scattered serotonin and somatostatin-positive cells. Many more of these tumours will have metastases at the time of diagnosis (approx. 30–40%), possibly because of the later presentation due to the absence of early symptoms. Metastases are frequently found in the liver, lymph nodes, mesentery

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or peritoneum and patients have a 5-year survival rate of about 43–50% [4–6]. The mean age of diagnosis is approximately 55–65 years.

Rectal Tumours

NETs of the rectum have been increasing in incidence. The latest SEER report (SEER 17) documented an increase from 0.2 per 100,000 in 1973 to 0.86 per 100,000 in 2004. At this point, their proportion of all NETs was 18% of all NETs and 27% of all gastrointestinal NETs [4]. The proportion of rectal NETs reported in Europe is somewhat less at 5–14% of all NETs [5–7]. There may still be an underestimation of true numbers since there is no complete reporting of colorectal NETs of benign behaviour to the SEER and European databases. In Asia, rectal carcinoids in the Japanese studies accounted for 60–89% of all gastrointestinal carcinoids [8]. The overall apparent increase is probably genuine but may, in part, be due to increased awareness and increased reporting of small polypoid NET lesions removed at endoscopy. In Japan the periodic screening rates are high including colonoscopies although it would appear that there is a definite ethnic association with rectal carcinoids [8, 9]. Rectal NETs have a higher incidence in the Black and Asian population in the USA [2, 4] with the population-corrected Black versus White and Asian versus non-Asian ratios being 2.3 and 4.99, respectively. Rectal NETs are diagnosed in relatively young patients, with a mean age at diagnosis of 56.2 years [2, 4]. Rectal tumours are usually small, polypoid lesions located between 4 and 20 cm above the dentate line on the anterior or lateral rectal wall and are mainly discovered incidentally on routine sigmoidoscopy. Rectal NETs usually contain glucagon and glicentin instead of serotonin and they rarely cause the NET syndrome [10]. Small rectal NETs (those <2 cm) rarely metastasise and endoscopic or other transanal excision is curative. Larger tumours carry a higher malignant potential with subsequent metastases to bone, lymph nodes and liver [11]. Overall, distant metastates from rectal NETs occur in only 2.3% from the SEER database, however, the Spanish and Japanese dataset report higher figures and from the Japanese dataset this was dependent on features of lymphovascular invasion in the resected polyp [6, 8].

The incidence of functioning tumours in the colon and rectum is extremely low. Soga [12] in his statistical evaluation of 1,271 rectal NETs showed an infrequent (13%) association but this was higher than other series. Three patients out of 38 had carcinoid syndrome in the Shebani series [10], Federspiel et al. [13] showed 45% serotonin immunostaining but normal plasma levels, and 1 of 36 patients in the Alberta series secreted serotonin [14]. Overall, no particular hormone preponderance has been described.

The incidence of multicentric NETs of the colon is low, but adenocarcinoma of the colon is a common occurrence as part of a family cancer trait in patients with NET in any part of the gastrointestinal tract, especially over the age of 40 years [15].

Minimal Consensus Statement on Classification and Epidemiology

There has been a genuine increased incidence of rectal NETs.

Pathology and Genetics

Neuroendocrine neoplasms of the colon and rectum are classified and graded according to WHO 2010 [16]. The following categories are recognized: neuroendocrine tumour (NET), neuroendocrine carcinoma (NEC) and mixed adenoneuroendocrine carcinoma (MANEC). Tumours are graded into three levels based on tumour cell proliferation: G1: mitotic count <2 per 10 high-power fields (HPF) and/or Ki67 ≤2%; G2: mitotic count 2–20 per 10 HPF and/or Ki67 3–20%; G3: mitotic count >20 per 10 HPF and/or Ki67 >20%. Mitotic counting is performed on at least 50 HPF (1 HPF = 2 mm^2) and the Ki67 index is calculated as the percentage of positive tumour cell nuclei in 'hot spots' (500–2,000 cells) using the MIB1 monoclonal antibody. When grade assessed by mitotic count and Ki67 differ, the higher grade is assumed. There is evidence to support the grading system in the stomach, duodenum and pancreas, as well as in the large intestine [Jann et al.: Cancer 2011]. The WHO classification implies that neuroendocrine neoplasms as a category are malignant and consequently should be staged according to a site-specific staging system (TNM) [17, 18].

NET is a well-differentiated neuroendocrine neoplasm composed of tumour cells expressing neuroendocrine markers (chromogranin A, synpatophysin) and hormones. The cellular atypia and the proliferative activity are low. NETs are by definition grade G1 or G2 tumours. This category includes tumours previously classified as 'carcinoid tumours'. NETs of the colon and rectum are either of enterochromaffin (EC) cell type or L cell type. *EC cell NETs* occur mainly in the right colon and are characterised by serotonin production. Tumour cells grow as solid nests with peripheral palisading, sometimes with formation of rosettes and cribriform

patterns. Cytologically, tumour cells are uniform, with round to oval nuclei, coarse chromatin and indistinct nucleoli. A prominent desmoplastic stroma frequently surrounds tumour cell nests, while tumour necroses are rare. The mitotic count and Ki67 index is low, usually corresponding to grade G1. EC cell NETs are immunoreactive for low molecular weight keratins, chromogranin A, synaptophysin and serotonin. *L cell NETs* occur predominantly in the distal colon and rectum and are characterised by production of glucagon-like peptide and PP/PYY. These tumours usually grow in a trabecular pattern, sometimes with rosettes and tubular structures. The cytological features include round to oval nuclei, granular chromatin and indistinct nucleoli. The stromal reaction is minimal and tumour necroses are infrequent. Ki67 index and mitotic count are usually low, and most tumours belong to grade G1. The majority of L cell NETs stain for low molecular weight keratins, chromogranin A, synpatophysin, GLP, and PP/PYY. A majority of rectal NETs also stain positive for prostatic acid phosphatase [1, 6].

NEC is a poorly differentiated, high-grade malignant neoplasm composed of tumour cells expressing neuroendocrine markers (chromogranin A, synpatophysin) and showing marked cellular atypia, frequent necroses and high proliferative activity. NECs are by definition grade G3 tumours. This category includes tumours previously classified as small cell carcinoma, large cell NEC and poorly differentiated endocrine carcinoma.

Two categories of NEC are now recognized: large cell NEC and small cell NEC. Large cell NECs occur predominantly in the right colon and account for 75% of all colorectal NECs. Tumours are frequently associated with an adjacent adenoma or adenocarcinomas. The growth pattern is solid or undifferentiated, with areas of necrosis. Organoid growth patterns may also be encountered. Tumours are composed of medium-sized to large cells, with highly atypical, vesicular nuclei and prominent nucleoli. The mitotic count is high (median 34/10 HPF) and by definition the mitotic count should be >20/10 HPF (median 34), and Ki67 >20%, corresponding to grade G3. Immunohistochemical staining for chromogranin A, synpatophysin and CD56 is positive in a majority of tumours, and is required to establish the neuroendocrine differentiation. Specific hormone production, however, is lacking. *Small cell NECs* represent 25% of all colorectal NECs and occur mainly in the distal colon and rectum. Tumours are often associated with a squamous cell carcinoma or adenocarcinoma. The growth pattern is diffuse or organoid, with frequent necroses. Tumour cells are by definition small to medium-sized, with scant cytoplasm and round to ovoid nuclei with coarse chromatin and inconspicuous nucleoli. Nuclear moulding may be present. The proliferative activity is always high, with mitotic counts usually in the range 30–145 (median 65) per 10 HPFs and Ki67 index 50–100%. Tumour cells are immunoreactive for low molecular weight keratins (often globular pattern), chromogranin A, synpatophysin and CD56. Aberrant p53 and Rb expression are common events in the pathogenesis of small cell NECs.

Minimal Consensus Statement on Histopathology and Genetics

Histological classification is according to WHO criteria. The minimum immunocytochemistry includes chromogranin, synaptophysin and Ki67. In the absence of known genetic background there is no indication to perform genetic counselling, germline or somatic DNA testing.

Hereditary Tumour Syndromes

Multiple endocrine neoplasia syndrome and other hereditary syndromes are not normally associated with colorectal NETs, although a few reports of familial colorectal NETs are described [19] with a standardized incidence ratio for offspring of 4.65.

Minimal Consensus Statement on Manifestation of Hereditary Tumour Syndromes

Hereditary tumour syndromes are very rare in colorectal NETs.

Clinical Presentation and Prognosis

Colon Tumours

Colonic NETs usually present late, as large tumours, often with extensive metastatic disease when the diagnosis is made. The commonest symptoms are diarrhoea, abdominal pain, gastrointestinal blood loss or weight loss [2]. Clinically, anaemia, hepatomegaly or a palpable abdominal mass may be present. Bowel obstruction, bleeding and pain are possible presentations, similar to adenocarcinoma. Usually the presumptive diagnosis of colonic adenocarcinoma is made until histology distinguishes the neuroendocrine nature. A tissue diagnosis is often made on colonoscopic biopsy. A frequent presentation is

of liver metastases at routine ultrasound of the liver. Overall the most frequent presentation of all the cases is finding at a routine endoscopy performed for other reasons and the next frequent is rectal bleeding. Forty-five percent of colonic tumours are localised at diagnosis in the latest SEER subset [4], although in the smaller Spanish registry only 22.5% were localized [6]. In the Japanese series 65% of colonic tumours were localized at diagnosis [8].

It is common for isolated neuroendocrine cell 'nests' to be present in random colonic biopsies performed for other reasons, and these can be collocated with inflammation from inflammatory bowel disease [20]. This may be an incidental finding or may be a response to inflammation and these are not usually tumours. In addition, small polyps containing small NETs can be found and removed routinely at colonoscopy [21]. Such small polyps (<1.0 cm) which are completely removed at endoscopy do not metastasise [22].

Colon NETs have the worst overall 5-year prognosis of any gastrointestinal tract NET, between 40 and 70% depending on the specific site and stage [2, 4, 23]. Survival for localized, regional and distant disease was 261, 36 and 5 months respectively from the 2004 SEER data [4]. Survival for sigmoid and other distal colonic NETs is better, probably due to earlier diagnosis and treatment with easier access to high-quality endoscopy.

Rectal Tumours

They may present as an incidental finding on sigmoidoscopy or colonoscopy (approx. 40%), with change in bowel habit, blood per rectum, anorectal symptoms (e.g. tenesmus, discomfort or pain) and weight loss [10]. It is very rare for rectal tumours present with features of carcinoid syndrome, as EC tumours with serotonin production are rare. Malignant metastatic disease may present with right upper quadrant abdominal pain and hepatomegaly, lethargy, wasting, anorexia or generalized symptoms of carcinomatosis. Bowel obstruction from rectal tumours is rare, but may occur with rectosigmoid or sigmoid lesions, or advanced intra-abdominal disease. The majority of rectal NETs are localised at diagnosis (75–85%). Distant metastases at diagnosis are uncommon, between 2 and 8% [2, 4]. In the late SEER data 1973–2004, 4% had regional metastases and 5% distant metastases. In the Japanese registry 30% had regional metastases and 8% distant metastases [8].

Rectal NETs in the SEER database have an overall 5-year survival rate of 75.2–88.3% [2]. Survival for localized, regional and distant disease was 290, 90 and 22 months, respectively [4]. The vast majority therefore have a survival expectancy in excess of 75% at 5 years, comparing favourably with the overall survival for all gastrointestinal NETs. Factors influencing survival are tumour size and histology, including lymphovascular invasion and proliferation index.

Minimal Consensus Statement on Clinical Presentation and Prognosis

Colonic and rectal NETs are often an incidental finding at endoscopy. Right-sided colonic NETs have the worst prognosis and have often metastasized at presentation. Rectal NETs <2 cm have excellent long-term survival.

Diagnostic Procedures: Imaging (Including Endoscopy) and Laboratory Tests

Imaging

Endoscopy. The majority of lesions in the rectum will be diagnosed endoscopically. Many lesions present as polyps, which are completely removed by snare polypectomy, with the diagnosis being made after histological studies. Full colonoscopic assessment is required to exclude concomitant colonic disease as part of staging, and the possibility of synchronous carcinoma must be excluded. All other polyps should be removed or biopsied and marked for future surgical/endoscopic removal. The endoscopic features of rectal NET tumours are well described [3], and these findings should be detailed and carefully reported. Central mucosal depression or ulceration suggests high metastatic potential.

Computed Tomography (CT)/Magnetic Resonance Imaging (MRI). CT colonography (barium enema has a much lower sensitivity for colorectal neoplasms) may demonstrate a colonic tumour and the eventual multifocality of the lesions. Once the lesion(s) is detected, endoscopy will be required to make the histological diagnosis of NET as there are no specific criteria to differentiate NET from adenocarcinoma on barium enema/CT colonography. Furthermore CT colonography is able to detect infiltration of perirectal fat and the perirectal fascia, as well as peri- and pararectal lymph nodes.

Multi-slice CT with multi-phasic liver scanning is the most useful for staging the thorax, abdomen and pelvis [3, 24, 25], although MRI is superior for determining liver metastases, particularly when diffusion-weighted imaging and hepatospecific contrast medium are being used. An MRI of the pelvis is mandatory prior to surgical

resection of a rectal carcinoid. MRI is the imaging of choice for T2, T3, T4, and nodal-positive tumours [26]. As with adenocarcinoma, any rectal tumour that has not been completely removed at endoscopy requires pelvic scanning (MRI is probably most accurate) to assess local spread with involvement of other pelvic structures and to determine resectability.

Ultrasound of Abdomen. Transabdominal ultrasound has low sensitivity for primary and local disease but is useful for assessing liver metastases and guiding biopsy of suspected liver lesions.

Endoanal/Rectal Ultrasound (EUS) [27]. EUS is very useful in assessing rectal NET tumours preoperatively. EUS can accurately assess tumour size for T1, T2, and T3 tumours, depth of invasion and the presence or absence of pararectal lymph node metastases. In conjunction with other investigative techniques and endoscopy, this provides important information with respect to the choice of therapy.

Indium-111 Octreotide Scanning. As colonic NETs are relatively uncommon, the sensitivity of indium-111 octreotide scanning is difficult to determine. However, it is useful for determining metastatic disease. Detection of the primary tumour in the rectum with background activity can be difficult [28]. Additionally the higher-grade colorectal NET lesions are often negative for indium-111 octreotide uptake, and other modalities have to be relied on to detect extrapelvic disease. Positron emission tomography (PET) may be useful for octreotide negative tumours.

PET Imaging. FDG PET can be helpful in staging high-grade/poorly differentiated colorectal NETs. Gallium-68 DOTA octreotide(ate) PET currently has limited availability but appears to be a more sensitive imaging modality than indium-111 octreotide scintigraphy [29–31].

In summary, the minimum imaging requirements for colonic tumours would be colonoscopy (+ biopsy) and contrast CT chest/abdomen/pelvis. For rectal tumour, endoanal ultrasound and consideration of pelvic MRI would be required. If a small tumour <10 mm were removed endoscopically and with a low Ki67, no further staging would be required. If colonoscopy were incomplete, CT colonography would be required. Follow-up would depend on the likely risk of recurrence and metastases (see above). Small rectal tumours removed at endoscopy with low Ki67 may not need any follow-up.

Laboratory Tests – Biochemical Diagnosis

Serum chromogranin A may be elevated and if so may reflect tumour burden [32–34]. Twenty-four hour urinary 5-HIAA is usually negative. Serum acid phosphatase levels may be raised in prostate-specific acid phosphatase-positive tumours [35, 36] β-HCG levels may also be increased [37]. For assessment of rectal NET, measuring pancreatic polypeptide may be useful.

Minimal Consensus Statement on Diagnostic Procedures

Imaging

Colonoscopy is the gold standard for detecting and characterizing colorectal polyps. CT/MRI are required for staging if residual or metastatic disease is suspected. Indium-111 octreotide scanning or gallium-68 octreotide PET is also required for staging of suspected residual or metastatic disease. EUS is important for assessing rectal NETs.

Laboratory Tests – Biochemical Markers

The minimum biochemical marker is serum CgA.

Surgical Therapy: Indications and Type of Surgery

Surgery for Local Disease

Colonic Tumours. NETs of the colon present and are treated in a similar way to adenocarcinoma of the colon. Lesions <2 cm may be excised endoscopically by polypectomy or endoscopic mucosal resection. In the case of incomplete resection or G3, an oncological resection should follow. Since the majority of tumours are in fact invasive through the muscularis propria and >2 cm, a localized colectomy with oncological resection of the lymph drainage is appropriate. These lesions may well be obstructive, and treatment is advised in most cases even if only palliative in nature. Advanced disease may, however, be considered different to adenocarcinomas, although the evidence is limited. Often patients will require surgical resection of the primary tumour because of the obstructive features, and the metastatic disease is treated as per protocol (see below). It is likely that more tumours may be diagnosed at an earlier stage by endoscopy. No evidence base is currently available, but it is advised that any invasive disease be resected surgically as is practiced with adenocarcinoma [38].

Rectal NET. The only guaranteed curative option is complete resection of a localised lesion. The benefit of radical surgery for more advanced disease is not clear. The size of the tumour provides the simplest way of predicting behaviour, although other features and patient factors should also be taken into consideration. Muscularis propria invasion on histology is an indicator of ag-

gressive behaviour and, combined with size, provides the best prediction of behaviour. Other features of the tumour such as atypia and a high mitotic index are important. Imaging may suggest locally or systemically advanced disease prior to resection. Lesions <1 cm have a low risk of metastatic disease and should be completely resected endoscopically or by another local transanal technique [39, 40]. Endoscopic ultrasound and MRI are indicated for determining tumour invasion. The risk of metastases has been estimated at less than 3% for rectal NETs <1 cm in diameter. Standard polypectomy is commonly performed, but in certain situations considered inadequate, especially if there is evidence of local invasion [41]. Band-snare resection [42], aspiration lumpectomy [41, 43] or strip biopsy [44, 45] may be performed endoscopically where appropriate. Transanal resection using a variety of techniques and equipment offers the ability to resect higher lesions and a full-thickness mucosal-muscular resection. Aggressive surgery, such as anterior resection, carries a higher risk to benefit ratio for small lesions (<1 cm), hence adequate local resection is appropriate. The outcome of a lesion between 1 and 2 cm is unclear. The metastatic risk is considered to be between 10 and 15% [46]. Some studies demonstrate no benefit with aggressive management [47]. It may be possible to recognise tumours with particular atypia and high mitotic index before embarking on radical surgery. Assessment of tumours endoscopically and by endoanal ultrasound should also guide treatment in this group of patients. In general, tumours up to 2 cm with a low mitotic rate and no invasion of muscularis propria can mostly be removed by local resection. Patients will have to be informed of the lack of strong evidence for many of these decisions.

Lesions >2 cm have a significantly higher metastatic risk [3, 46, 47], considered to be between 60 and 80%. Invasion of the muscularis propria is common in this group, and indicates a high metastatic potential. In practice most of these patients will have major surgery using 'total mesorectal excision' in the hope of cure but without guaranteed survival benefit. Local resection is unlikely to benefit patient survival with metastatic disease, but will provide local symptomatic relief [48]. Locoregional resection may be argued to control local symptoms and pelvic disease without improving survival. Studies are limited and the numbers are invariably small. Occasionally small lesions may present with perirectal lymph nodes on radiology, suggesting a very aggressive metastatic tumour. Multidisciplinary treatment options should be offered in conjunction with a specialist team.

Factors Favouring Metastatic Behaviour. Size >2 cm, G3/high-grade, poorly differentiated histology, muscularis propria invasion lymphatic and vascular invasion, angiogenesis, neural invasion, increased tumour proliferative index – mitotic index, Ki67, endoscopic features, endoanal ultrasound features [3, 39–46].

Effect of Surgery on Outcome. Any metastatic disease at diagnosis will indicate a worse prognosis. Survival is probably not altered by offering aggressive therapy to the primary lesion in these cases, but quality of life issues may dictate individual decisions. Surgery may improve symptom control of local complications associated with an advanced rectal tumour mass. In patients with factors favouring metastatic disease, but no evidence of metastatic disease at diagnosis, the survival advantage of surgery is unknown. However, individual cases with high metastatic risk, but where subsequently metastatic disease was not evident, have been cured by aggressive surgery [39]. This is a difficult judgement which calls for further studies on predictors of metastatic risk.

Adjuvant Therapy

There is no evidence for adjuvant medical therapy after surgery in any of these tumours, although an argument could be made for using chemotherapy in G3/poorly differentiated tumours with incomplete resection.

Palliative Surgery: Advanced Metastatic Disease

Surgical. Intra-Abdominal Debulking, Excluding Liver Metastases

Removal of a non-functioning or functioning primary according to oncological criteria may be indicated to prevent intestinal obstruction or ischaemic complications due to tumour mass. Desmoplastic reaction is not as evident in distal colorectal NET when compared with small intestinal and proximal colonic NET.

For surgery of liver metastases, this is usually performed as a separate procedure to the bowel operation unless small and limited resections (wedge resections) are performed.

Minimal Consensus Statement on Surgery for Local Disease and Palliative Surgery

Rectal tumours >2 cm, T3 or T4 stage, with G3 grading, or rectal tumours with locoregional lymph node involvement should be treated similarly to adenocarcinoma. For rectal NETs >2 cm, anterior resection with total mesorectal excision or abdominoperineal exstirpation according to the distance to the

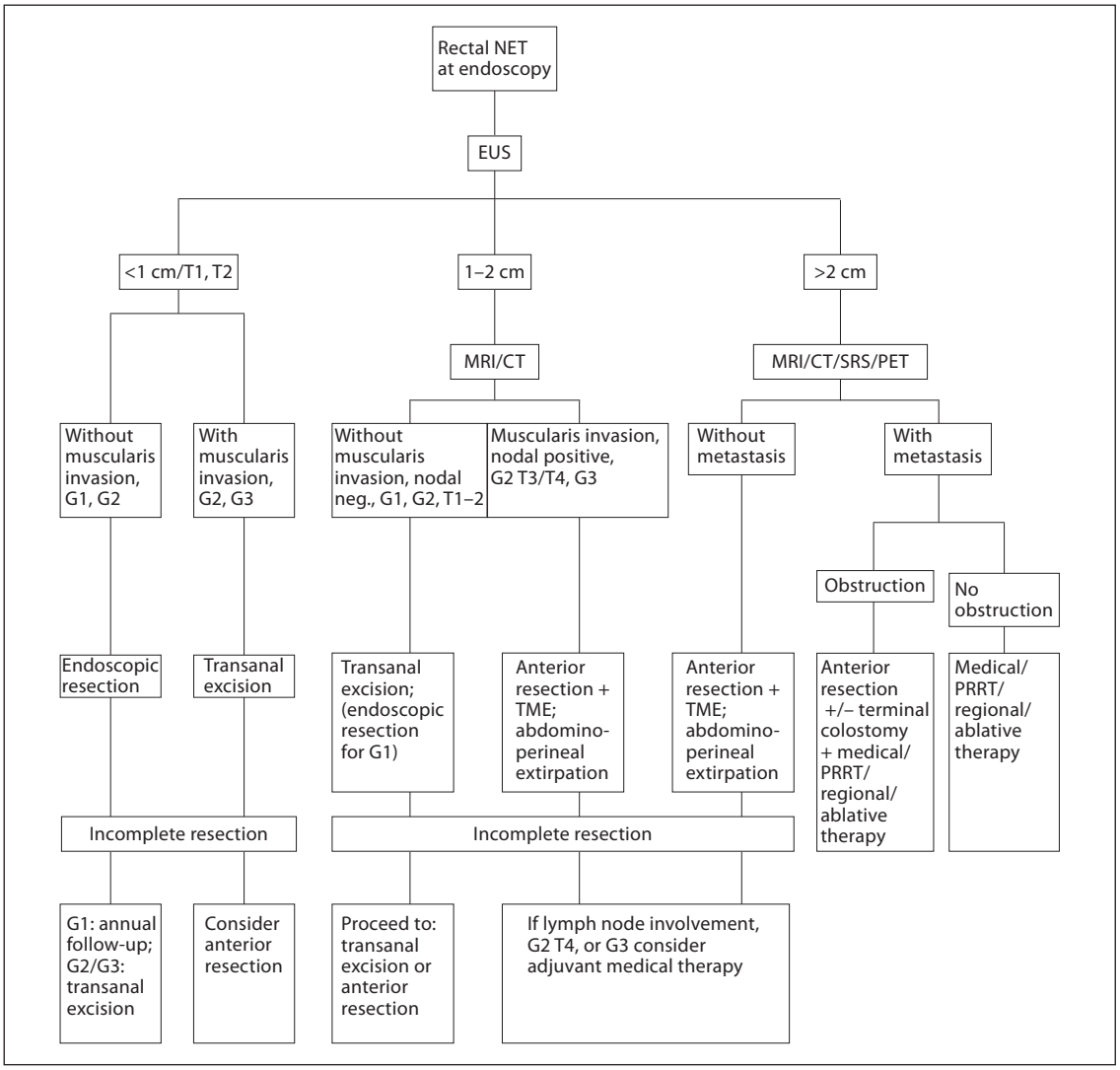

Fig. 1. Treatment algorithm rectal NENs.

anal verge is appropriate. Local resection using standard oncological criteria is appropriate for small tumours. For patients with metastatic NETs, resection of the primary tumour is appropriate for patients with impending obstruction but there is no clear survival benefit. There is no evidence base for adjuvant therapy.

Colonic tumours >2 cm, tumours with muscularis invasion, and G3 tumours are treated according to the surgical guidelines for adenocarcinoma.

For surgery and other therapies for liver metastases, there are not enough data relating specifically to colorectal NET, hence the guidelines for small intestinal NET where there is more evidence base are followed (fig. 1).

Medical Therapy of Advanced Disease

Treatment of advanced disease is updated in a separate and comprehensive chapter (see list at the end of the article) [48]. Here is a brief summary.

Biotherapy

Somatostatin Analogues. Carcinoid syndrome is very uncommon in patients with colorectal NETs. As per metastatic small bowel NETs, somatostatin analogues improve symptoms effectively in patients with the carcinoid syndrome. There is currently only limited evidence to suggest the use of somatostatin analogues as anti-tumour agents for non-functioning colorectal NETs [49].

Interferon. Anecdotal evidence only suggests there may be benefit of interferon in patients with tumours of low proliferative index.

Minimal Consensus Statement on Biotherapy

It is unusual for colorectal NETs to be associated with carcinoid syndrome. There is only very limited evidence for the use of somatostatin analogue and interferon as anti-tumour agents.

Systemic Chemotherapy

Systemic chemotherapy is rarely indicated for G1 or G2 NETs [50]. When used for progressive disease, streptozotocin in combination with 5-fluorouracil ± doxorubicin is most often used, but the response rate is <25%. Newer anti-angiogenesis or mTOR inhibitors may be considered within clinical trials. There may be a role for consideration of temozolomide regimens. The efficacy of systemic chemotherapy is best in G3 NECs. Platinum regimens have proven to be effective in these neoplasms.

Minimal Consensus Statement on Chemotherapy

Chemotherapy is appropriate for G3 NECs but has little role in G1 and G2 colorectal NETs.

Peptide-Receptor Radiotargeted Radiotherapy

Peptide-receptor radiotargeted radiotherapy (PRRT) can be considered in patients with inoperable metastatic disease and a positive indium-111 octreotide scan. Therapy using yttrium-90 or lutetium-177 labelled to octreotide or octreotate [50, 51] may be considered. Results specifically in colorectal NET are few, but results in NETs of other sites of origin with similar histology are encouraging.

Minimal Consensus Statements on PRRT

PRRT may be considered in patients with metastatic disease and positive nuclear medicine imaging.

Follow-Up

Follow-Up Strategies after Surgery or Endoscopic Removal

(G1, G2) <1 cm: no LN involvement/no invasion of muscularis: no data to recommend regular follow-up.

<1 cm G3 and G1–3 NET 1–2 cm: annual follow-up then as per adenomatous polyp follow-up protocols.

2 cm: always follow up. For G1–2 patients (see above): one endoscopy/scan/serum marker within the first year; for G3 patients: every 4–6 months in the first year, and thereafter at least annually.

Methods of Follow-Up

Rectal: EUS, colonoscopy, MRI.

Colon: CT, colonoscopy.

Liver: MRI with hepatospecific contrast medium or multi-slice CT with multi-phasic liver scanning.

Serum Chromogranin A

Follow-up is normally up to 10 years, although occasionally metastatic disease can occur after this.

Minimal Consensus Statements on Follow-Up

All lesions >2 cm will require follow-up even after 'curative' resection. Smaller tumours require follow-up in the presence of negative prognostic features.

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