

The NANETS Consensus Guidelines for the Diagnosis and Management of Gastrointestinal Neuroendocrine Tumors (NETs)

Well-Differentiated NETs of the Distal Colon and Rectum

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Abstract: Neuroendocrine tumors (NETs) of the distal colon and rectum are also known as *hindgut carcinoids* based on their common embryologic derivation. Their annual incidence in the United States is rising, primarily as a result of increased incidental detection. Symptoms of rectal NETs include hematochezia, pain, and change in bowel habits. Most rectal NETs are small, submucosal in location, and associated with a very low malignant potential. Tumors larger than 2 cm or those invading the muscularis propria are associated with a significantly higher risk of metastatic spread. Colonic NETs proximal to the rectum are rarer and tend to behave more aggressively. The incidence of rectal NETs in African Americans and Asians is substantially higher than in Caucasians. Colorectal NETs are generally not associated with a hormonal syndrome such as flushing or diarrhea. A multidisciplinary approach is recommended in diagnosing and managing hindgut NETs.

Key Words: hindgut, carcinoid, neuroendocrine tumors, colorectal, guidelines, neuroendocrine carcinoma

(*Pancreas* 2010;39: 767–774)

Neuroendocrine tumors (NETs) of the colon and rectum are increasingly diagnosed in the United States. Current incidence is approximately 1 per 100,000.¹ Many are discovered incidentally during routine surveillance endoscopies. Other symptoms include rectal bleeding, pain, and change in bowel habits.^{2,3} Approximately 50% of patients are asymptomatic.³ The risk of malignant behavior is closely related to tumor size and depth of invasion. Rectal carcinoids that are smaller than 1 cm and confined to the submucosa nearly always behave in a benign fashion, whereas tumors that are larger than 2 cm or which invade the muscularis propria are associated with malignant behavior in a substantial proportion of cases. In contrast to midgut NETs, tumors of the distal colon and rectum are rarely associated with a hormonal syndrome such as flushing or diarrhea, even in the metastatic stage.

A multidisciplinary approach is recommended for optimal hindgut NET management. Because randomized prospective

clinical trials are lacking, management decisions are commonly based on experience and expert recommendations. The North American Neuroendocrine Tumor Society (NANETS) convened a panel of leading multispecialty physicians and investigators from the United States, Canada, and Europe to recommend NET management options. The current manuscript describes consensus recommendations for hindgut NETs.

EPIDEMIOLOGY

The age-adjusted annual incidence of rectal carcinoid tumors has increased from approximately 0.2 per 100,000 in 1973 to 0.86 per 100,000 in the 2004 Surveillance, Epidemiology, and End Results (SEER) database.¹ Rectal carcinoid tumors now comprise 27% of all gastrointestinal NETs and 16% of all NETs. Colon carcinoid tumors are diagnosed less frequently, with an annual incidence of approximately 0.2 per 100,000. The true incidence of colorectal NETs may be higher given that tumors that are considered to be benign are often not registered in the SEER database.

The racial distribution of rectal NETs in the United States differs significantly from NETs of other primary sites, with higher rates observed in blacks and Asians compared with whites. According to the SEER database, the population-corrected black versus white and Asian versus non-Asian ratios for rectal NETs are 2.30 and 4.99, respectively.⁴ There is a very slight male preponderance, with a male-to-female ratio⁴ of approximately 1.1. The mean age of diagnosis for colonic and rectal NETs is 65 and 56 years, respectively.

PATHOLOGIC CLASSIFICATION

Neuroendocrine tumors of the distal colon and rectum are divided into well-differentiated and poorly differentiated categories. Elements of the minimum pathologic dataset are shown in Table 1. Systems of nomenclature reflect differentiation and grading features of NETs (Table 2). In essentially all systems, a sharp division is made between well-differentiated and poorly differentiated tumors, with the latter group being clearly designated as high-grade neuroendocrine carcinomas (neuroendocrine carcinoma, grade 3), including small-cell carcinoma and large-cell neuroendocrine carcinoma variants. Combined (mixed) forms with elements of nonneuroendocrine carcinoma (usually adenocarcinoma or squamous cell carcinoma) are also well recognized. The distinction of well-differentiated from poorly differentiated NETs is probably one of the most important pathologic assessments related to these neoplasms because the biologic behavior of the well-differentiated group is often rather indolent, whereas poorly differentiated neuroendocrine carcinomas are very highly aggressive; therapy also differs significantly between these 2 categories of tumors. The term *carcinoma* also has been applied

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TABLE 1. Minimum Pathology Dataset: Information to Be Included in Pathology Reports on NETs of the Hindgut

For Resection of Primary Tumors:
Anatomic site of tumor
Diagnosis (functional status need not be included in the pathology report)
Size (in 3 dimensions)
Presence of unusual histologic features (oncocyctic, clear cell, gland-forming, and other features)
Presence of multicentric disease
[OPTIONAL: immunohistochemical staining for general neuroendocrine markers]
Chromogranin
Synaptophysin
Grade (specify grading system used)
Mitotic rate (number of mitoses per 10 high-power fields or 2 mm ² ; count 50 high-power fields in the most active regions)
[OPTIONAL: Ki67 labeling index (count multiple regions with highest labeling density, report mean percentage; eyeballed estimate is adequate)]
Presence of nonischemic tumor necrosis
Presence of other pathologic components (eg, nonneuroendocrine components)
Extent of invasion
Depth of invasion into/through bowel wall
Involvement of serosal/peritoneal surfaces
Invasion of adjacent organs or structures
Presence of vascular invasion [OPTIONAL: perform immunohistochemical stains for endothelial markers if needed]
Presence of perineural invasion
Lymph node metastases
Number of positive nodes
Total number of nodes examined
TNM staging (specify staging system used)
Resection margins (positive/negative/close) [OPTIONAL measure distance from margin if within 0.5 cm]
For Biopsy of Primary Tumors:
Anatomic site of tumor
Diagnosis (functional status need not be included in the pathology report)
Presence of unusual histologic features (oncocyctic, clear cell, gland forming, and other features)
[OPTIONAL: immunohistochemical staining for general neuroendocrine markers]
Chromogranin
Synaptophysin
Grade (specify grading system used)
Mitotic rate (number of mitoses per 10 high-power fields or 2 mm ² ; count up to 50 high-power fields)
Ki67 labeling index, for biopsies in which a diagnosis of high-grade neuroendocrine carcinoma cannot be excluded (count multiple regions with highest labeling density, report mean percentage; eyeballed estimate is adequate)
Presence of nonischemic tumor necrosis
Presence of other pathologic components (eg, non-neuroendocrine components)

behavior, such as vascular invasion, gross local invasion, or metastases. Others have argued to use the term *carcinoma* for all NETs to specify that all are regarded to be malignant.⁵ However, the use of the same term for all grades of NETs implies a relationship between the well-differentiated and poorly differentiated groups, which does not exist in most instances. It is most important to recognize that the unqualified terms *neuroendocrine carcinoma* or *neuroendocrine tumor*, without reference to grade or differentiation, are inadequate for prognostication or therapy and considered inappropriate in pathology reports.

Well-differentiated (low and intermediate grade) tumors have been variably termed *carcinoid tumor*, *neuroendocrine tumor* (grade 1 and grade 2, respectively), or *neuroendocrine carcinoma* (low grade and intermediate grade, respectively), among other options. Table 2 displays a comparison of the various systems of nomenclature currently in use for NETs of the hindgut. Although the criteria that define each category do not perfectly match between the various systems, there are several common themes. Each system recognizes 3 grades. In each system, the low and intermediate grades are closely related, well differentiated, and distinguished largely by proliferative rate (or necrosis). Finally, each system generally recognizes that individual tumors rarely display hybrid well-differentiated and poorly differentiated features.

Most systems of grading rely extensively on the proliferative rate to separate low-, intermediate-, and high-grade NETs. Some systems (such as the WHO classification for lung and thymus) include the presence of necrosis as a feature to distinguish intermediate grade from low grade within the well-differentiated group. The proliferative rate can be assessed as the number of mitoses per unit area of tumor (usually expressed as mitoses per 10 high-power microscopic fields, or per 2 mm²), or as the percentage of neoplastic cells immunolabeling for the proliferation marker Ki67. The WHO classification of lung and thymus tumors relies only on the mitotic rate, whereas the system recently proposed for gastroenteropancreatic NETs, including those of the hindgut, by the European Neuroendocrine Tumor Society (ENETS) and also now recommended by the WHO (shown in Table 3) uses either mitotic rate or Ki67 labeling index.⁶ It is recommended to specify the actual proliferative rate in the pathology report in addition to designating a grade based on a system that is specifically referenced.

The use of mitotic counts versus Ki67 index is controversial. In Europe, where the ENETS system is already in widespread use, Ki67 labeling indices are commonly reported for all NETs. When the amount of tumor tissue is limited (eg, in a biopsy from a primary tumor or a metastatic focus), it may not be possible to perform an accurate mitotic count because it is recommended to count 40 to 50 high-power fields—more than most biopsy samples include. In these cases, Ki67 staining provides a more accurate assessment of proliferative rate, and it is particularly helpful to separate well-differentiated (low or intermediate grade) tumors from poorly differentiated (high-grade) neuroendocrine carcinomas, which usually have dramatically different Ki67 labeling rates.^{6,7} However, when adequate tissue is present to perform an accurate mitotic count, there are no data to demonstrate that the Ki67 labeling index adds important additional information, and in some cases, the 2 measures of proliferative rate may provide conflicting information about grading.

DIAGNOSIS AND ENDOSCOPIC EVALUATION

Rectal NET is diagnosed incidentally on endoscopic evaluation for colorectal cancer or other unrelated indications in approximately one half of the patients with the disease. Other

to well-differentiated tumors, however. In some systems (particularly the 2001 and 2004 versions of the WHO classifications of digestive and pancreatic NETs), *carcinoma* was used in the place of *tumor* when the neoplasm had obvious evidence of malignant

TABLE 2. Nomenclature for NETs of the Hindgut

Grade	Traditional	ENETS, WHO	Moran et al ⁵
Low grade	Carcinoid tumor	Neuroendocrine tumor, grade 1 (G1)	Neuroendocrine carcinoma, grade 1
Intermediate grade	Carcinoid tumor*	Neuroendocrine tumor, grade 2 (G2)	Neuroendocrine carcinoma, grade 2
High grade	Small-cell carcinoma	Neuroendocrine carcinoma, grade 3 (G3), small-cell carcinoma	Neuroendocrine carcinoma, grade 3, small-cell carcinoma
	Large-cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3 (G3), large-cell Neuroendocrine	Neuroendocrine carcinoma, grade 3, large-cell neuroendocrine carcinoma

*Criteria to define a category of “atypical carcinoid tumor” have never been developed for the colon and rectum.

symptoms include hematochezia, rectal pain, or changes in bowel habits.^{2,8} Most rectal NETs arise in the mid-rectum, 5 to 10 cm from the anal verge⁹ and are submucosal in location.³ Endoscopic ultrasonography (EUS) is often useful in the evaluation of rectal NETs to assess tumor size, depth of invasion, and lymph node involvement.^{8,10} Thus, EUS can determine the appropriateness of endoscopic removal versus transanal excision or radical surgery.

STAGING AND PROGNOSIS

Compared with other primary NET sites, rectal NETs are associated with the highest 5-year survival rate of 88%.⁴ This finding reflects that most of rectal carcinoid tumors (82%)⁴ are localized at diagnosis, with a median size of only 0.6 cm.¹¹ Colon NETs proximal to the rectum are more aggressive on average, with a 5-year survival of only 62% across all stages.⁴

Tumor size, depth of invasion, and lymph node involvement significantly predict malignant behavior in localized rectal NETs. According to one analysis of the literature, metastases were observed in 2% of patients with rectal NETs measuring less than 1.0 cm, 10% to 15% of tumors measuring 1.0 to 2.0 cm, and 60% to 80% in patients with tumors measuring greater than 2.0 cm.¹² Another study reported that metastases occurred in only 2% of tumors smaller than 2 cm, which had not invaded the muscularis propria, compared to 48% in tumors invading the muscularis layer.¹³ A multivariate analysis by Fahy et al¹⁴ validated a stratification system that included lymphovascular invasion and elevated mitotic rate ($\leq 2/50$ high-power fields) as risk factors in addition to tumor size and depth of invasion.

Examination of the SEER database confirms the findings of the aforementioned institutional studies. One survival analysis of nearly 5000 cases in the SEER database demonstrated that both tumor size and invasiveness predicted for 5-year survival in rectal NETs.¹¹ The survival rate was 100% among patients whose tumors were 2 cm or less and did not invade the muscularis propria, a category that included most of the cases. Five-year survival rates were considerably lower among patients whose tumors invaded beyond the muscularis propria or had metastasized to locoregional lymph nodes.

There are less data on the biologic behavior of colon NETs. Unlike rectal NETs, which are typically small and localized at diagnosis, colon NETs are distributed in roughly equal numbers between local, regional, and metastatic stage.⁴ According to an analysis of the SEER database, 5-year survival rates were 76% in patients with localized tumors and 72% in patients with regional lymph node involvement.

Once they have metastasized, NETs originating in both the colon and the rectum tend to behave in a relatively aggressive fashion compared with NETs of the midgut. Five-year survival rates of 32% and 30% are observed with metastatic tumors of the rectum and the colon, respectively (compared to 50% among metastatic NETs of the small intestine).⁴

New staging classifications for NETs of the colon and the rectum reflect the findings of the aforementioned prognostic studies. In 2010, the American Joint Cancer Commission for the first time published a TNM classification system for colorectal NETs,¹⁵ which incorporates both tumor size and depth of invasion into the T-stage classification (Table 4). This staging system is identical to one proposed by the ENETS in 2007.¹⁶ It is expected that widespread international adoption of these staging systems will lead to improved analysis of outcomes and development of more detailed stage-specific treatment recommendations.

IMAGING AND STAGING STUDIES

Rectal NETs that are smaller than 2 cm and confined to the mucosa or submucosa are associated with an exceptionally small risk of metastatic spread. Staging cross-sectional radiographic studies are therefore not routinely recommended. Patients with larger or more invasive tumors should undergo computed tomography or magnetic resonance imaging of the abdomen and pelvis to rule out distant metastases. The role of somatostatin-receptor scintigraphy (octreoscan) for staging localized tumors is controversial because there is little evidence that octreoscans significantly improve the sensitivity of standard cross-sectional imaging techniques. In patients with known metastases, octreoscans can help establish whether metastatic tumors express somatostatin receptors, specifically receptor subtype 2 (*sst*₂; Fig. 1). This information may have therapeutic implications (see the “Treatment of Metastatic Disease” section).

Endoscopic ultrasonography is ideally suited for evaluation of localized rectal NETs, which are usually well-demarcated isoechoic or hypoechoic masses.⁸ By focusing on the submucosa, which is the hyperechoic third layer of the rectum, tumors as small as 2 mm in diameter can be detected. In one study of 52 rectal carcinoid patients, EUS achieved an accuracy of 100% in gauging the depth of invasion.⁸

BLOOD BIOMARKERS

Only a small fraction of hindgut NETs (<1%) produce and secrete serotonin or other bioactive hormones.¹² Therefore, routine analysis of serum serotonin or urine 5-hydroxyindoleacetic

TABLE 3. Grading Systems for Neuroendocrine Tumors of the Hindgut

Grade	Criteria
Low grade (G1)	<2 mitoses/10 hpf AND <3% Ki67 index
Intermediate	2–20 mitoses/10 hpf OR 3%–20% Ki67 index grade (G2)
High grade (G3)	>20 mitoses / 10 hpf OR >20% Ki67 index

TABLE 4. Staging of NETs of the Colon and Rectum

Stage	AJCC				ENETS			
	Primary Tumor (T)				T-Primary Tumor			
Tx	Primary tumor cannot be assessed				Primary tumor cannot be assessed			
T0	No evidence of primary tumor				No evidence of primary tumor			
T1	Tumor invades lamina propria or submucosa and size ≤2 cm				Tumor invades mucosa or submucosa			
T1a	Tumor size <1 cm in greatest dimension				Size <1 cm			
T1b	Tumor size 1–2 cm in greatest dimension				Size 1–2 cm			
T2	Tumor invades muscularis propria or size >2 cm with invasion of lamina propria or submucosa				Tumor invades muscularis propria or size >2 cm			
T3	Tumor invades through muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissue				Tumor invades subserosa/pericolic/perirectal fat			
T4	Tumor invades peritoneum or other organs				Tumor directly invades other organs/structures and/or perforates visceral peritoneum			
	Regional Lymph Nodes (N)				N-Regional Lymph Nodes			
NX	Regional lymph nodes cannot be assessed				Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastases				No regional lymph node metastases			
N1	Regional lymph node metastases				Regional lymph node metastases			
	Distant Metastases (M)				M-Distant Metastases (Subspecifications as in Small Bowel)			
M0	No Distant Metastases				No Distant Metastases			
M1	Distant Metastases				Distant Metastases			
	Stage	T	N	M	Stage	T	N	M
	I	T1	N0	M0	IA	T1a	N0	M0
					IB	T1b	N0	M0
	IIA	T2	N0	M0	IIA	T2	N0	M0
	IIB	T3	N0	M0	IIB	T3	N0	M0
	IIIA	T4	N0	M0	IIIA	T4	N0	M0
	IIIB	AnyT	N1	M0	IIIB	AnyT	N1	M0
	IV	AnyT	AnyN	M1	IV	AnyT	AnyN	M1

acid (5-HIAA) is not recommended. The serum chromogranin A (CgA) can be a useful tumor marker for monitoring patients with metastatic disease^{17,18} or for surveillance in patients with resected stage II or III tumors. It is important to note that false-positive elevations in the serum CgA are frequently associated with the use of proton-pump inhibitors. Spurious elevated levels of CgA can also occur in patients with chronic gastritis, renal insufficiency, and other inflammatory diseases.

ENDOSCOPIC AND SURGICAL TREATMENT OF LOCALIZED TUMORS

Most rectal carcinoids are small, localized, and submucosal in location. Treatment is determined by the size of the primary (Fig. 2). Because of their low risk of metastatic spread, tumors that are small (<1–2 cm) and confined to the mucosa or submucosa (T1) can be managed with endoscopic resection. Endoscopic polypectomy is commonly performed for small superficial or polypoid tumors.⁸ Using a 2-channel colonoscopy, polypectomy can be performed by pulling the tumor into a snare using forceps. In one study, no recurrences were observed after conventional endoscopic resection in patients whose tumors were smaller than 1 cm and which did not infiltrate beyond the submucosa.¹⁹ Another study, however, reported a positive resection margin in 7 (17%) of 41 endoscopic polypectomies.⁸ Only one patient with a positive margin had a local recurrence

16 years after the initial polypectomy. Because of the small risk of positive margins after conventional polypectomies, other endoscopic resection techniques have been described including band snares,²⁰ endoscopic submucosal dissection,^{21,22} band ligation,²³ and aspiration lumpectomy.²⁴ There are currently insufficient comparative data to recommend a specific endoscopic resection technique. Endoscopists should consider tattooing the area of polypectomy to help facilitate the lesion site location in case positive margins are identified and further resection is indicated.

Transanal excision is commonly performed for wide-based or intermediate-sized (1–2 cm) distal rectal tumors confined to the submucosa (T1). Patients with small tumors invading the muscularis propria (T2) in whom lymph node metastases are excluded by EUS may also consider transanal excision.²⁵ Transanal endoscopic microsurgery (TEM) is a minimally invasive procedure²⁶ that offers high visualization, exposure, and access to tumors in the proximal rectum and enables full-thickness excisions under high magnification. In rectal carcinoid tumors, it can be used to resect tumors that seem difficult to excise using conventional polypectomy techniques or as a salvage option in patients with residual positive margins after polypectomy.^{27,28} The routine use of TEM is limited by its high expense and complexity.

Tumors larger than 2 cm, tumors invading the muscularis propria, or tumors with locoregional lymph node involvement should generally be managed similarly to rectal adenocarcinoma,

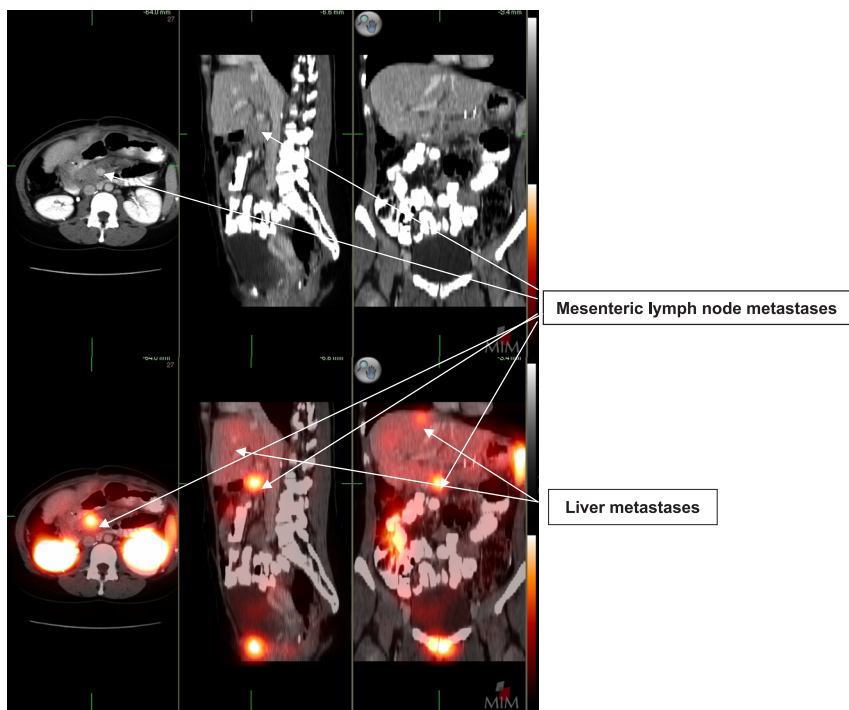


FIGURE 1. Transaxial, sagittal, and coronal cross-sectional computed tomographic (CT) and nuclear images in hindgut NETs. Top panel, Multi-phasic thin-section CT images with oral contrast demonstrating metastatic nodal disease in the left panel (transaxial), middle (sagittal), and right (coronal) panels. Lower panel, ^{111}In -diethylene triamine pentaacetic acid octreotide scintigraphy with CT fusion demonstrating somatostatin receptor 2 and/or 5 bearing tumor (liver and lymph nodes) in the same patient.

with standard rectal resection techniques including low anterior resection (LAR) or abdominoperineal resection (APR) depending on the distance from the anal verge.²⁵

POSTTREATMENT SURVEILLANCE

Neuroendocrine tumors can recur many years after resection. The value of long-term surveillance is unknown. For stage I tumors (submucosal, ≤ 2 cm), the exceptionally low risk of recurrence after tumor resection does not justify long-term endoscopic or radiographic surveillance. For patients with stage II or III tumors (invading into or beyond the muscularis propria or involving locoregional lymph nodes), radiographic surveillance may be warranted. Routine surveillance visits and scans (computed tomography or magnetic resonance imaging) may be performed on an annual basis. Because metastatic spread may occur many years after the initial diagnosis, long-term surveillance beyond 5 years should be considered in many cases.

TREATMENT OF METASTATIC DISEASE

There are currently no published data on treatment outcomes for patients with metastatic colorectal NETs. Consequently, recommendations must be extrapolated from trials of other gastrointestinal NETs. Conventional treatment options include somatostatin analogs, interferon alpha (IFN- α), hepatic arterial embolization, cytotoxic chemotherapy, and surgical cytoreduction. Investigational therapies include radiolabeled somatostatin analogs, angiogenesis inhibitors, and mTOR inhibitors.

Initial clinical trials of the somatostatin analogs octreotide and lanreotide investigated their ability to ameliorate the carcinoid syndrome by inhibiting secretion of serotonin and other

vasoactive substances.^{29–31} These studies did not include hindgut NETs, which are generally unassociated with a hormonal syndrome. Subsequent experience suggested that somatostatin analogs may also exert an inhibitory effect on NET growth.^{32,33} Preclinical evidence supporting this concept included an analysis of a human rectal NET cell line demonstrating inhibition of angiogenesis in xenografted mice treated with octreotide.³⁴ Recently, a randomized placebo-controlled clinical trial confirmed the antiproliferative effect of depot-octreotide LAR in metastatic midgut NETs by demonstrating a significant prolongation in time to tumor progression.³⁵ It is unknown whether this tumor-stabilizing effect is equally robust in nonmidgut NETs. Octreotide LAR can be considered as a treatment option for patients with metastatic colorectal NETs, particularly in cases where radiotracer uptake on octreoscan indicates somatostatin receptor expression. Further randomized clinical trials are needed to confirm whether this strategy improves survival outcomes for patients with nonmidgut NETs.

The biologic agent IFN- α also seems to exert an antisecretory and antiproliferative effect on metastatic neuroendocrine carcinomas.^{36–38} Adverse effects are dose related and include fevers, chills, myalgias, and myelosuppression. There are no specific data on IFN- α in hindgut NETs. The use of IFN- α may be considered in cases where radiographic progression is documented on octreotide LAR; however, the toxicities associated with interferon may be prohibitive in many cases.

Hepatic arterial embolization or chemoembolization is often performed in patients with diffuse, symptomatic, and unresectable liver metastases. To limit morbidity, individual hepatic arterial branches are embolized selectively in 2 to 3 stages. Various embolic materials have been tested with or without the addition of antineoplastic agents. Radiographic response rates of

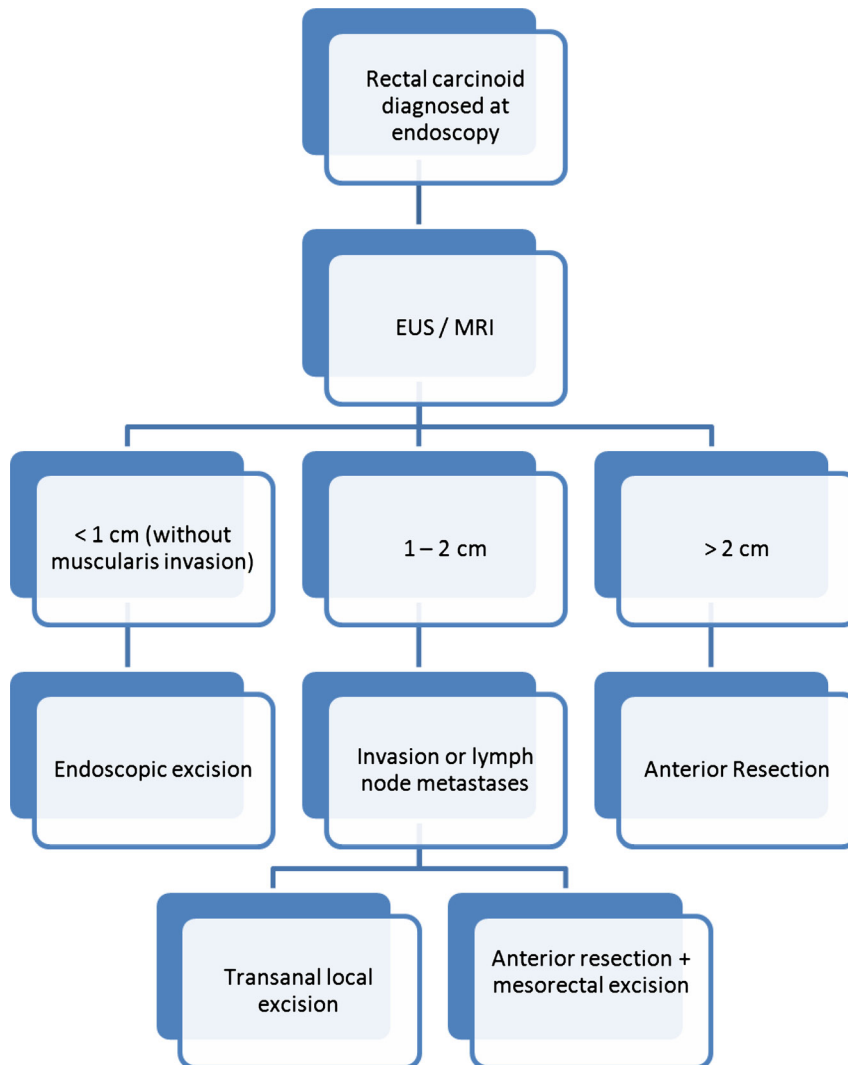


FIGURE 2. Treatment algorithm for rectal NETs.

approximately 50% have been documented in patients with metastatic gastrointestinal and pancreatic NETs.³⁹⁻⁴¹ There are no published data specifying outcomes of patients with colorectal NETs. Hepatic arterial embolization or chemoembolization should be considered in patients with symptomatic or progressive liver metastases, particularly when the bulk of metastatic disease is confined to the liver.

Surgical cytoreduction is often performed in patients with limited metastases, particularly in the liver. Various ablation techniques have also been described including cryoablation and radiofrequency ablation (RFA). Nonrandomized retrospective reports indicate favorable survival outcomes in patients undergoing surgery with curative or near-curative intent.⁴²⁻⁴⁶ There are no specific data on outcomes of patients with colorectal NETs. As in other types of NETs, cytoreductive surgery should be considered if greater than 90% of metastatic tumor burden can be safely resected or ablated.

Trials of cytotoxic chemotherapy have demonstrated variable response rates in patients with metastatic NETs. There are insufficient published data to assess the outcomes of patients with hindgut NETs. Agents used in well-differentiated NETs

include streptozocin, 5-fluorouracil, doxorubicin, capecitabine, and temozolomide. Because of significant toxicities associated with these agents and paucity of outcome data, cytotoxic chemotherapy should be considered only in patients with advanced, clinically aggressive tumors who lack other treatment options.

In recent years, peptide receptor radiotherapy using the radiolabeled somatostatin analogs [⁹⁰Y-DOTA⁰Tyr³]-octreotide and [¹⁷⁷Lu-DOTA⁰Tyr³]-octreotate has emerged as a promising treatment strategy. Radiographic response rates of 30% have been reported in patients with metastatic gastrointestinal NETs expressing somatostatin receptors.⁴⁷⁻⁴⁹ One recent retrospective study evaluated 15 patients with metastatic colorectal NETs and described minor or partial responses (MR/PR) in 27% of cases.⁵⁰ Based on this evidence, the use of radiolabeled somatostatin analogs should be considered for patients with octreoscan-avid, progressive metastatic tumors. Currently, the aforementioned peptide receptor radiotherapy treatments are available only in certain centers in Europe.

Given the lack of high-level evidence supporting any type of treatment for metastatic colorectal NETs, the NANET panel recommends that clinical trials be considered for all lines of

therapy. Promising investigational agents include angiogenesis inhibitors (bevacizumab and sunitinib) and mTOR inhibitors (everolimus and temsirolimus).

CONCLUSIONS AND FUTURE LOOKING STATEMENTS

Hindgut NETs vary in their presenting symptoms depending on stage and primary site. It is not uncommon for these tumors to be asymptomatic and diagnosed on routine endoscopic procedures at an early stage. Local-regional NETs should be resected whenever possible. With the exception of small well-differentiated NET of the rectum, hindgut NETs have substantial risk of relapse after resection and need to be followed for at least 7 years.

Metastatic hindgut NETs are incurable, with survival statistics closer to colorectal adenocarcinoma rather than midgut NET primaries. Optimal management requires a multidisciplinary approach. For those few hindgut patients with functional tumors, somatostatin analogs are effective in the management of carcinoid syndrome and may delay disease progression. Liver-directed therapy and surgical debulking can improve the quality of life for some patients. Systemic therapies are limited, as cancer chemotherapeutic and biotherapeutic agents have limited efficacy and significant toxicity in hindgut NETs. Identifying molecular targets specific for hindgut NETs is necessary to develop new agents and improve outcomes.

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