Rectal Neuroendocrine Tumor

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Introduction

Neuroendocrine tumors (NETs), also termed carcinoids, are composed of morphologically and biologically heterogeneous tumors that possess malignant potential. Gastrointestinal NETs have been classified by their embryological site of origin (i.e. foregut, midgut, or hindgut).

The rectum is the common site for gastrointestinal NETs and the diagnosis are increasing. Most of the rectal NETs are diagnosed incidentally during routine colonoscopies. Rectal carcinoids are epithelial tumors that develop in the deep portion of glands. They typically invade through the muscularis mucosa into the submucosa and resemble submucosal tumors.

In this review the epidemiology, recent changes in the classification, diagnosis, treatment and prognosis will be discussed.

Epidemiology

The age-adjusted annual incidence of rectal NETs has increased from 0.2 per 100,000 in 1973 to 0.86 per 100,000 in the 2003. Rectal NETs comprise 27% of all gastrointestinal NETs and 16% of all NETs. The racial distribution of rectal NETs in the United States differs significantly with higher rates observed in blacks and Asians compared with whites. There is a very slight male preponderance, with a male-to-female ratio of 1.1. The mean age of diagnosis for rectal NETs is 56 years.

In Korea, rectum is the most common primary site and comprises 55.8% of all gastrointestinal and hepatopancreaticobiliary NETs.

Clinical Presentation

Rectal NETs generally indolent in clinical course, and approximately 50% of patients with rectal carcinoids are asymptomatic. Presenting symptoms can include change in bowel habit, blood per rectum, anorectal symptoms (e.g. tenesmus, discomfort or pain) and weight loss. Rectal tumors present with the features of the carcinoid syndrome are very rare.

Pathologic Classification

Recently WHO introduced new classification for gastroenteropancreatic (GEP) NETs. This classification stratifies the pure GEP NETs into three groups): neuroendocrine tumors (NETs, equivalent to carcinoids) that are well differentiated and graded according to their proliferative activity into G1 or G2, and neuroendocrine carcinomas (NECs) that are poorly differentiated and graded as G3. The poorly differentiated NECs are divided into small cell and large cell neoplasms (Tables 1, 2).

Diagnostic Procedures

Rectal NETs often incidentally diagnosed on endoscopic evaluation for colorectal cancer screening or other unrelated indications. Rectal NETs appear as smooth, round, mobile, submucosal nodules, or focal areas of mucosal or submucosal thickening, and may have normal-appearing or yellow-discolored mucosa. The size of rectal NETs varies from diminutive to several centimeters in diameter. Rectal NETs appear most frequently in the mid-rectum, between 5 and 10 cm proximal to the anal verge. Biopsy of these lesions may reveal neuroendocrine features, which usually prompt the pathologist to order special immunohistochemical stains.
Endoscopic ultrasound (EUS) is a highly sensitive diagnostic tool for NETs in the rectum, which are usually well-demarcated isoechoic or hypoechoic masses. EUS should be the next diagnostic test of choice, after routine endoscopic evaluation with biopsy for a suspected rectal NETs. The main intent of performing EUS is to evaluate tumor size and to determine if the tumor is confined to the mucosa or submucosa, or if it has invaded into the muscularis propria or beyond. The sensitivity and specificity of EUS for assessing depth-of-wall penetration in early rectal tumors has been reported to be 87% and 93%, respectively. EUS is an accurate method to assess for perirectal lymphadenopathy. Thus, EUS can determine the appropriateness of endoscopic removal versus transanal excision or radical surgery.

Contrasted computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis are reasonable adjunctive tests to evaluate for liver metastasis and distant lymphadenopathy, which are not detectable by rectal EUS. However, staging cross-sectional radiographic studies are not routinely recommended in rectal NETs that are smaller than 2 cm and confined to the mucosa or submucosa.

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.

### Prognosis and Staging

Rectal NETs have the highest 5-year survival rate of 88% compared with other GEP-NETs. It is because the vast majority (85-100%) of rectal NETs are detected at an early stage and localized at diagnosis, with a median size of only 0.6 cm. Histologically nodal-negative rectal NETs that are ≤1 cm in size and do not show angioinvasion or infiltration of the muscular layer have an excellent 5-year-survival rate of 98.9-100%.

Tumor size, depth of invasion, and lymph node involvement significantly predict malignant behavior in localized rectal NETs. 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. 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. Lymphovascular invasion and elevated mitotic rate are the risk factors in addition to tumor size and depth of invasion.

The American Joint Cancer Commission (AJCC) published a TNM classification system for colorectal NETs in 2010 (Table 3).

### Treatment

#### Localized tumor

Most rectal NETs are small, localized, and submucosal in location. Treatment is determined by the size of the primary tumor. For rectal NETs that are small (<1-2 cm) and confined to the mucosa or submucosa can be managed with endoscopic resection.

Endoscopic polypectomy can be used for rectal NETs. However, conventional polypectomy reported a positive resection margin in 17% of polypectomy cases. Using a 2-channel colonoscopy, polypectomy can be performed by pulling the tumor into a snare using forceps. Various techniques to treat localized rectal NETs have been introduced. Band-snare resection has also been used, and involves lifting a submucosal lesion with saline or a saline-epinephrine mixture, which is then followed by suction cap-
assisted band ligation of the desired tissue. Finally, standard snare resection is performed on the tissue that has been pinched-off by the band. Endoscopic mucosal resection (EMR) using both suction cap-assisted aspiration lumpectomy and saline-assisted snare techniques were included in the study and the authors reported a complete resection rate of 89% and adverse events were limited to immediate or delayed post-EMR bleeding. Recently, there has been increasing interest in endoscopic submucosal dissection (ESD) and reported that compared with EMR, ESD resulted in a higher histologically complete resection rate, had a similar complication rate, and took slightly longer to perform. Given the advantages of complete resection, these findings indicate that ESD may be considered for treatment of rectal NETs.

Tumors 1-2 cm in diameter can be treated either by local excision or radical resection, and the decision should be based on actual size of the tumor, extent of invasion. Transanal excision is commonly performed for wide-based or intermediate-sized (1-2 cm) distal rectal tumors confined to the submucosa. Patients with small tumors invading the muscularis propria in whom lymph node metastases are excluded by EUS may also consider transanal excision.

Transanal endoscopic microsurgery (TEM) is a minimally invasive procedure that offers high visualization, exposure, and access to tumors in the proximal rectum and enables full-thickness excisions under high magnification. There are no controlled prospective studies available that have compared the endoscopic to the surgical approach for these 1-2 cm sized rectal NETs. TEM may be preferred to surgery in patients with high surgical risk.

Lesions more than 2 cm have a significantly higher metastatic risk. Invasion of the muscularis propria is common in this group, and indicates a high metastatic potential. These lesions should be managed similarly to rectal adenocarcinoma, with standard rectal resection techniques including low anterior resection or abdominoperineal resection depending on the distance from the anal verge.

Regional or distant disease
Rectal NETs invaded muscularis propria, or show evidence of metastatic spread, cannot be treated or cured by local excision. In most nonlocalized rectal NETs, surgery is indicated for curative and palliative intent. Conventional treatment options include

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<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>I</td>
<td>T1</td>
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<td>M0</td>
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<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
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### Table 3. Staging of NETs of the Colon and Rectum (AJCC)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Tumor (T)</th>
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<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
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<tr>
<td>T1</td>
<td>Tumor invades lamina propria or submucosa and size 2 cm</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor size &lt; 1 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor size 1-2 cm in greatest dimension</td>
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<tr>
<td>T2</td>
<td>Tumor invades muscularis propria or size &gt; 2 cm with invasion of lamina propria or submucosa</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through muscularis propria into subserosa or into nonperitonealized pericolic or peri rectal tissue</td>
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<tr>
<td>T4</td>
<td>Tumor invades peritoneum or other organs</td>
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Regional Lymph Node (N)
- Nx: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastases
- N1: Regional lymph node metastases

Distant Metastases (M)
- M0: No Distant Metastases
- M1: Distant Metastases
somatostatin analogs, IFN-α, hepatic arterial embolization, cytotoxic chemotherapy, and surgical cytoreduction. Investigational therapies include radiolabeled somatostatin analogs, angiogenesis inhibitors, and mTOR inhibitors. Chemotherapeutic agents (e.g. streptozocin, 5-FU, doxorubicin, cyclophosphamide, etoposide, etc.) have been disappointing and reveal poor response rates.

**Posttreatment Surveillance**

Current guidelines published by NANETS do not recommend follow-up of patients with well-differentiated rectal NETs of 1-2 cm in size that have been completely resected and that had not invaded the muscular layer. Posttreatment 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.

**REFERENCES**