Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumours: Well-Differentiated Colon and Rectum Tumour/Carcinoma

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Introduction

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 carcinoids are rare, totalling 7.84\% of all carcinoid tumours in the Modlin series\textsuperscript{[1]}. Caecal tumours alone made up 3.47\% of the late SEER subset, leaving a small number of true hindgut colonic tumours. Non-appendiceal colonic carcinoids have a predominance for a white ethnic background (black:white ratio 0.62 in the USA). 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\%), possibly because of the later presentation due to the absence of early symptoms. Metastases are frequently found in the liver, lymph nodes, mesentery or peritoneum and patients have a 5-year survival rate of about 50\%.

Rectal Tumours. Carcinoid tumours of the rectum are probably increasing in incidence. In the latest subset (1992–1999) of SEER data, rectal carcinoids comprised 18.54\% of all carcinoid tumours, and 27.44\% of all gastrointestinal carcinoids. In the early SEER data subset (1973–1982)...

\textsuperscript{1} See list at the end of the paper.
rectal carcinoids comprised 9.44% of all carcinoids and 15.33% of all gastrointestinal carcinoids. This apparent increase—from 556 cases out of a total of 5,889 (all carcinoids) to 925 cases out of 4,989—is probably genuine but may, in part, be due to increased awareness and increased reporting of small polypoid carcinoid lesions removed at endoscopy [2]. Rectal carcinoids have a threefold higher incidence in the black population compared to the white population (age and gender adjusted) in the USA [1]. Rectal carcinoids are diagnosed in relatively young patients, with a mean age at diagnosis of 56.2 years [1]. 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. Because rectal carcinoids usually contain glucagon and glicentin instead of serotonin, they rarely cause the carcinoid syndrome [3]. Small rectal carcinoids (those < 2 cm) rarely metastasize and endoscopic or other transanal excision is curative. Larger tumours carry a higher malignant potential with subsequent metastases to bone, lymph nodes and liver [4]. Overall distant metastases from rectal carcinoids occur in only 2.3%.

The incidence of functioning tumours in the colon and rectum is extremely low. Soga [5], in his statistical evaluation of 1,271 rectal carcinoids, showed an infrequent (13%) association, but this was higher than other series. Three patients out of 38 had carcinoid syndrome in the Shebani series [3], Federspiel et al. [6] showed 45% serotonin immunostaining but normal plasma levels and 1 of 36 patients in the Alberta series secreted serotonin [7]. Overall, no particular hormone preponderance has been described.

The incidence of multicentric carcinoids 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 [8].

**Minimal Consensus Statement on Classification and Epidemiology**

The former terminology of midgut and hindgut origin is inappropriate and hence these tumours are classified as colonic or rectal NETs. There has been a genuine increased incidence of rectal carcinoids.

**Clinical Presentation**

**Colon Tumours.** Colonic carcinoids 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 [1]. 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. Only 16% of caecal tumours are localized at diagnosis in the latest SEER subset, although the figures have improved for the other colonic sites. More than 40% of caecal tumours have distant metastatic disease at diagnosis. 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 [9]. 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 neuroendocrine tumours can be found and removed routinely at colonoscopy [10]. Such small polyps (<1.0 cm) which are completely removed at endoscopy do not metastasize [11].

**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 [3]. Very rarely, rectal tumours present with features of the carcinoid syndrome, as EC tumours with serotonin production are rare. If it does occur, the symptoms are similar to carcinoid syndrome of ileal origin. 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 carcinoids are localized at diagnosis (75–85%). Distant metastases at diagnosis are uncommon, with between 1.7 and 8.1% in the review by Modlin et al. [1]. In the latest subset of SEER (1992–1999) only 1.7% of the 925 tumours had distant metastases, 2.2% had regional metastases (lymph nodes), but 14.4% were classified as unstaged. The shift towards unstaged or purely localized tumours may reflect the common use of endoscopic resection for diagnosis and treatment of early disease.
**Prognosis**

Colon carcinoids have the worst overall 5-year prognosis of any gastrointestinal tract carcinoid tumour, between 40 and 70% depending on the specific site [1, 12] (small numbers in individual series and definition of colonic sites make good comparisons difficult). These poor outcomes are best explained by the advanced stage at which the tumours are diagnosed [7]. Survival for sigmoid and other distal colonic tumours is considerably better, and has improved over the last decade, probably due to earlier diagnosis and treatment with easier access to high-quality endoscopy.

Rectal carcinoids in the SEER database [1] have an overall 5-year survival rate of 75.2–88.3%. If localized at diagnosis, the 5-year survival rate is 84–90.8%. The 5-year survival decreases to 36.3–48.9% with regional disease and 20.6–32.3% with distant disease. The vast majority therefore have a survival expectancy in excess of 80% at 5 years, comparing favourably with the overall survival for all gastrointestinal carcinoids of 67%. Factors influencing survival are tumour size and histology.

**Minimal Consensus Statement on Clinical Presentation and Prognosis**

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

**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 carcinoid tumours are described [13], with a standardized incidence ratio for offspring of 4.65.

**Minimal Consensus Statement on the Manifestation of Colorectal NET in Hereditary Tumour Syndrome**

Hereditary tumour syndromes are very rare in colorectal NETs.

**Diagnostic Procedures**

**Imaging (Including Endoscopy)**

**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 carcinoid tumours are well described [2], and these findings should be detailed and carefully reported. Central mucosal depression or ulceration suggests high metastatic potential.

**Barium Enema or CT Colonography.** Barium enema or CT colonography 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, since there are no specific criteria to differentiate NET from adenocarcinoma on barium enema/CT colonography. Furthermore, CT colonography is able to detect infiltration of periurethral fat and the perirectal fascia, as well as peri- and pararectal lymph nodes.

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

**Computed Tomography (CT)/Magnetic Resonance Imaging (MRI).** These are more sensitive imaging modalities than ultrasound. Multi-slice triple phase CT is the most useful for staging the thorax, abdomen and pelvis [2, 15], although MRI is probably superior for determining liver metastases. 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.

**111In-Octreotide Scanning.** As colonic carcinoids are relatively uncommon, the sensitivity of 111In-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 [16]. Additionally, the higher-grade colorectal NET lesions are often negative for 111In-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.
**Positron Emission Tomography Imaging** [17]. PET is currently considered experimental but may be of use with labels based on DOPA or gallium-68 DOTA octreotate for well-differentiated tumours and FDG for poorly-differentiated tumours [18, 19].

In summary, the minimum imaging requirements for colonic tumours would be colonoscopy (+ biopsy) and contrast CT chest/abdomen/pelvis. For rectal tumours, endoanal ultrasound and consideration of pelvic MRI would be required. If a small tumour <10 mm were removed endoscopically and with a low Ki-67, 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 Ki-67 may not need any follow-up.

**Minimal Consensus Statement on Imaging**

Colonoscopy is the gold standard for detecting and characterizing colorectal polyps. CT colonography/MR imaging and $^{111}$In-octreotide scanning is required for staging if residual or metastatic disease is suspected. EUS is important for assessing rectal carcinoids.

**Laboratory Tests**

**Biochemistry**

Serum chromogranin A may be elevated and, if so, may reflect tumour burden [20–22]. 24-hour urinary 5-HIAA is usually negative. Serum acid phosphatase levels may be raised in prostate-specific acid phosphatase-positive tumours [23, 24]. For assessment of rectal carcinoid, measuring pancreatic polypeptide and enteroglucagon may be useful. β-HCG levels may be increased [25].

**Minimal Consensus Statement on Laboratory Tests for Diagnosis and Follow-Up**

The minimum biochemical markers are serum CgA and acid phosphatase.

**Pathology and Genetics**

The histological classification of ‘carcinoid’ tumours is initially by differentiation and site. Well-differentiated carcinoid tumours (WHO group 1) are recognized by uniform cells, rare mitotic cells and no mucin production, arranged as submucosal nests and strands with less likely invasion of lymphatics, blood vessels perineum or muscularis propria. A similar histology is observed for well-differentiated endocrine carcinomas or malignant carcinoids (WHO group 2) though with a higher mitotic index, deep wall invasion, lymphoid and angioinvasion. Poorly-differentiated small cell endocrine carcinomas (WHO group 3) display a solid structure with abundant central necrosis, severe atypia with high mitotic counts and Ki-67 index, deep wall invasion often with evident invasion of blood vessels, lymphatics and perineum [26]. Mucin production may also be observed. Many produce enteroglucagon or pancreatic polypeptide-related hormones whereas serotonin production is observed infrequently (see clinical presentation above).

**General Neuroendocrine Phenotyping.** The cells may stain positively for neuron-specific enolase and PGP9.5, but the specificity of these markers is not 100%. The staining is diffusely cytosolic and nuclear, and may co-localize. Synaptophysin is seen in the small vesicles, and a sensitive marker for neuroendocrine tumours. Chromogranin is localized to the secretory granules and is positive in the majority of colorectal carcinoids, with chromogranin B also found in some tumours [6, 27]. The minimum requirements for staining these tumours are therefore chromogranin and synaptophysin.

**Specific Neuroendocrine Differentiation.** As for any other sites of the gastrointestinal tract, endocrine tumours are categorized into well- and poorly-differentiated. Two types of well-differentiated endocrine tumours have been identified in the colon and rectum, L-cell tumours and EC-cell tumours. Rectal tumours are usually L-cell tumours, producing glicentin-related products and PP-PYY peptides. The tumours may contain subsets of other neuroendocrine cells among the L cells. Argentaffin EC tumours with typical serotonin production are rare in the rectum [6, 27]. Specific markers that may be performed when investigating rectal neuroendocrine tumours are those that identify the L cells, such as glucagon-29, glucagon-37, glicentin, PYY and PP and their precursors. These would generally only be performed for research and in specialized centres. Argentaffin staining and serotonin positivity are unusual, but should be excluded. Proximal colonic tumours are usually EC-cell tumours. Metastatic disease may rarely be associated with the carcinoid syndrome in EC-cell tumours. Poorly-differentiated small cell carcinomas usually display extensive expression of synaptophysin and cytosol markers of neuroendocrine differentiation like PGP9.5 and neuron-specific enolase.

**Other Markers.** Prostate-specific acid phosphatase is expressed in 80–100% of rectal carcinoids [6], and this may be useful clinically. P53 may be useful as a marker of poorly-differentiated tumours. Immunohistochemistry
for somatostatin receptor-2A (SSR2A) may be performed in specialized laboratories. β-HCG may be expressed, and may relate to the malignant potential of the lesions [28]. Attempts to identify lesions of high malignant potential should include mitotic indexing and percentage of Ki-67 staining to determine the tumour proliferative index [29, 30].

A clinicopathological classification is suggested below. The tumours can be split into EC- and L-cell pathologically but this has no obvious clinical correlation.

Clinico-Pathological Staging and Classification [31]. (1) Well-differentiated endocrine tumour – carcinoid: (a) Benign non-functioning tumour of small size (<2 cm), within the mucosa or submucosa, without angioinvasion. (b) Uncertain behaviour: non-functioning tumour within the mucosa or submucosa, >2 cm or with angioinvasion. (2) Well-differentiated endocrine carcinoma – malignant carcinoid: Low-grade malignant – deeply invasive or with metastasis. (3) Poorly-differentiated endocrine carcinoma – small cell carcinoma: High-grade malignant.

A proposal for a TNM-classification for tumours of colon and rectum has been recently published [Rindi et al., in press, 2007].

Minimal Consensus Statement on Histopathology and Genetics

Histological classification is according to WHO criteria. The minimum immunocytochemistry includes chromogranin, synaptophysin and Ki-67. In absence of known genetic background there is no indication to perform genetic counselling, germline or somatic DNA testing.

Surgical Therapy

Indications and Type of Surgery

Local Disease

Colonic Tumours. Carcinoid tumours of the colon present and are treated in a similar way to adenocarcinoma of the colon. 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.

Rectal Carcinoid. The only guaranteed curative option is complete resection of a localized 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 aggressive 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 of <1 cm have a low risk of metastatic disease and should be completely resected endoscopically or by another local trans-anal technique [32]. Endoscopic ultrasound is important in determining tumour invasion. The risk of metastases has been estimated at less than 3% for rectal carcinoids of <1 cm in diameter. Standard polypectomy is commonly performed, but in certain situations considered inadequate as argued by Matsushita et al. [33], especially if there is evidence of local invasion. Band-snare resection [34], aspiration lumpectomy [34, 35] or strip biopsy [34, 36] may be performed endoscopically where appropriate. Trans-anal resection using a variety of techniques and equipment offers the ability to resect higher lesions and a full thickness mucosal-muscular resection [37]. 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% [32]. Some studies demonstrate no benefit with aggressive management [26]. Other authors have reported successful treatment with local or radical surgery [2]. It may be possible to recognize 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 [38]. In general, tumours up to 2 cm with low mitotic rate and no invasion of lamina 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 of >2 cm have a significantly higher metastatic risk [2, 26, 39], 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 [2, 40]. Locoregional resection may be argued to control local symptoms and pelvic disease without improving survival [41]. 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 [41], high-grade, poorly-differentiated histology [42], muscularis propria invasion [32], lymphatic and vascular invasion [41, 43], angiogenesis [43], neural invasion, increased tumour proliferative index – mitotic index, Ki-67 [44], endoscopic features [33], endoanal ultrasound features [14].

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 the primary lesion in these cases, but quality-of-life issues probably not altered by offering aggressive therapy to the primary tumour. Multidisciplinary treatment options should be offered in conjunction with a specialist team.

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 poorly-differentiated tumours with incomplete resection.

Palliative Surgery: Advanced Metastatic Disease

Surgical: Intra-Abdominal Debulking, Excluding Liver Metastases. Removal of 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.

Minimal Consensus Statement on Curative and Palliative Surgery

Local resection using standard oncological criteria is appropriate for small tumours. For rectal NETs >2 cm, anterior resection is appropriate. Staging for rectal NETs should include EUS. 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.

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.

Medical Therapy

Biotherapy

Somatostatin Analogue. Carcinoid syndrome is 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 no evidence to suggest the use of somatostatin analogue anti-tumour agents for non-functioning colorectal NETs unless in the context of a clinical trial.

Interferon. Interferon may be tried within a prospective trial protocol for anti-tumour effect in patients with metastatic colorectal carcinoid, but there is no evidence base for use without a trial. Anecdotal evidence 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. Use of somatostatin analogue and interferon as anti-tumour agents should be in the context of a clinical trial.

Systemic Chemotherapy

Systemic chemotherapy is rarely indicated in slow-growing carcinoids [45]. When used for progressive disease, streptozotocin in combination with 5-fluorouracil +/- doxorubicin is most often used, but the response rate is <25%. The efficacy of systemic chemotherapy is best in fast-growing or poorly-differentiated tumours. In these tumours, cisplatin + etoposide have proven to be effective. Newer anti-angiogenesis or mTOR inhibitors may be considered within clinical trials.
Minimal Consensus Statement on Chemotherapy

Chemotherapy is appropriate for poorly-differentiated or high-grade NETs but has little role in moderately- or well-differentiated colorectal NETs.

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) can be considered in patients with inoperable metastatic disease and a positive $^{111}$In-octreotide scan. Therapy using $^{90}$Y [46] or $^{177}$Lu-labeled to octreotide or octreotate [47] may be considered. Results specifically in colorectal NET are few, but results in NETs of other sites of origin with similar histology are encouraging. $^{131}$I-meta-iodobenzyl guanidine (MIBG) targeted radiotherapy has been used extensively in metastatic NET if the diagnostic $^{123}$I-MIBG scan is positive [48].

Minimal Consensus Statement 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: <1 cm and no LN involvement: no follow-up; 1–2 cm: follow-up if adverse features (angioinvasion, invasion into muscularis, atypical histology); >2 cm: always follow-up: for low-risk patients (see above): one scan/serum marker within the first year. In all other cases: every 4–6 months in the first year, and thereafter at least annually.

Methods of Follow-Up. Rectal: EUS, colonoscopy, MRI. Colon: CT, colonoscopy. CgA or acid phosphatase if positive pre-surgery. Follow-up is normally up to 10 years, although occasionally metastatic disease can occur after this.

Minimal Consensus Statement on Follow-up

All lesions >2 cm will require follow-up even after ‘curative’ resection.
References


