

Thursday, November 2, 2006

**TOPIC: WELL-DIFFERENTIATED MIDGUT AND HINDGUT ENDOCRINE TUMORS**

**2:30 - 5:20 p.m. Well-differentiated tumors of the colon and rectum**  
*Chair: M. Caplin, London, United Kingdom*

2:30 - 2:50 p.m. **Case presentation: colonic and rectal tumor**  
*M. Caplin, London, United Kingdom*

2:55 - 3:55 p.m. **Working Group Sessions**  
**Pathology and Genetics**  
*Group leader: P. Komminoth, Baden, Switzerland*  
**Medicine and Clinical Pathology**  
*Group leader: J. Ramage, Hampshire, United Kingdom*  
**Surgery**  
*Group leader: P. Goretzki, Neuss, Germany*  
**Imaging**  
*Group leader: R. Manfredi, Verona, Italy*

3:55 - 4:20 p.m. **COFFEE BREAK**

4:20 - 5:20 p.m. **General assembly**  
**Presentation of statements by the session chairs & general discussion**  
*M. Caplin, London, United Kingdom*

 **Pathology and Genetics** **Medicine and Clinical Pathology** **Surgery** **Imaging**

ENETS Guidelines Neuroendocrinology 2004;80:394–424

## Endocrine Tumors of the Colon and Rectum

### *Epidemiology*

**Rectal Tumours.** The incidence of carcinoid tumours of the rectum is on the increase in clinical practice. 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 (1973–1991) rectal carcinoids comprised 9.44% of all carcinoids and 15.33% of all gastrointestinal carcinoids [1]. This apparent increase is probably genuine but may, in part, be due to increased awareness and increased reporting of small polypoid carcinoid lesions removed at endoscopy. Other authors have also reported a higher incidence, which may reflect more aggressive endoscopic surveillance over many years of practice [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, on average 56.2 years of age at diagnosis as reported in the SEER data set [1].

**Colon Tumours.** Colonic carcinoids are particularly rare, totaling 7.84% of all carcinoid tumours in the review by Modlin et al. [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).

*Clinico-Pathological Staging and Classification* [4, 5].

Well-Differentiated Endocrine Tumour – Carcinoid.

Benign non-functioning tumour of small size (<2 cm), within the mucosa or submucosa, without angio-invasion:

– Trabecular enteroglucagon-producing tumours.

– Serotonin-producing tumours usually in the caecum or rarely the colon.  
 Uncertain behaviour: non-functioning tumour within the mucosa or submucosa, >2 cm or with angio-invasion.

– Trabecular enteroglucagon-producing tumours.

– Serotonin-producing tumours usually in the caecum or colon.

Well-Differentiated Endocrine Carcinoma – Malignant Carcinoid. Low-grade malignant – deeply invasive or with metastasis.

– Enteroglucagon-producing carcinoma.

– Serotonin-producing carcinoma with or without syndrome.

Poorly Differentiated Endocrine Carcinoma – Small Cell Carcinoma. High-grade malignant.

**Q1:** Do you agree with the above statements concerning the epidemiology and clinical settings?

Yes ; reverse colonic first, then rectal

About half of colonic NE tumors are localized in the coecum and are often poorly differentiated [Modlin et al. Gastroenterology, 2005, 128, 6, 1717-51]. Anatomical tumor distinction strongly recommended [see above].

**Q2:** Is there an increase of colo-rectal endocrine tumors in your current practice?

Increase

**Q3:** In your experience and according to the literature, is there a gender, age and race preferential distribution?

Colonic more prevalent in white-caucasian, rectal more prevalent in African-American (SEER)

Japanese with a higher incidence of rectal NET

**Q4:** In your experience and according to the literature, what is the incidence of functioning tumors?

Very rare < 1%

**Q5:** Which type of hyperfunctional syndrome has been described? Which is the most frequent?

N.A.

**Q6:** Is the subtyping of endocrine cell (EC vs L) tumors useful for patient management?

No

**Q7:** In your experience and according to the literature, can multicentric tumors be seen in the hindgut?

No (in terms of NET)

Comment on increased meta- /synchronous NPL incidence

**Q8:** When multicentric, are they associated with hormonal hyperfunction?

N.A.

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*Prognosis/Survival*

**Rectum.** The majority of rectal carcinoids are localised at diagnosis (75–85%). Distant metastases at diagnosis are uncommon, between 1.7 and 8.1% in 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 localised tumours may reflect the common use of endoscopic resection for diagnosis and treatment of early disease. Rectal carcinoids in the series by Modlin et al. [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%.

**Colon.** The clinical picture at presentation and prognosis of colonic carcinoids contrasts greatly with rectal carcinoids. Colon carcinoids have the worst overall 5-year prognosis of any

gastrointestinal tract carcinoid tumour, between 33 and 60% depending on specific site. (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. Only 16% of caecal tumours are localised 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. 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.

**Q9:** As for both rectal and colonic tumors, is your experience consistent with the above?

Insert more references

**Q10:** As for both rectal and colonic tumors, based on your experience how much do the “stage” of the disease and proliferative (Ki67) index affect survival?

Nothing published for Ki67 Refrence from 2005 on rectal NET?), based on experience it does

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#### *Clinical presentation*

**Rectal Tumours.** They may present with blood per rectum, incidental findings on sigmoidoscopy or colonoscopy (asymptomatic), change in bowel habit, anorectal symptoms, i.e. tenesmus, discomfort or pain, non-specific complaints for example related to anaemia [8]. Very rarely do rectal tumours present with features of the carcinoid syndrome, as EC tumours with serotonin production are rare. In that unusual scenario the symptoms are similar to carcinoid syndrome of ileal origin. Malignant metastatic disease may present with generalized symptoms of carcinomatosis, i.e. right upper quadrant abdominal pain, lethargy, wasting, anorexia and hepatomegaly. Bowel obstruction from rectal tumours is rare, but may occur with recto-sigmoid or sigmoid lesions, or advanced intra-abdominal disease.

**Colon Tumours.** Colonic carcinoids usually present late, being large tumours often with extensive metastatic disease when diagnosis is made. Patients therefore may present with nonspecific complaints of malaise, lethargy, vague abdominal pains. More specific complaints may include altered bowel habit, right upper quadrant pain or weight loss. Clinically, anaemia may be the first presenting feature. Hepatomegaly or a palpable abdominal mass may be present. Bowel obstruction is a possible presentation as an emergency. Usually the presumptive diagnosis of colonic adenocarcinoma is made until histology distinguishes the neuroendocrine nature. A tissue diagnosis is often made on colonoscopic biopsy.

**Q11:** Is your experience consistent with the above?

Right sided pain, frequently asymptomatic

**Q12:** What are the most frequent reasons for incidental finding?

Screening endoscopy, Ultrasound (liver mets)

**Q13:** What is the most frequent presentation symptom in non-functioning cases? In functioning cases?

Bleeding / n.a.

**Q14:** What proportion of patients present the “typical carcinoid syndrome”?

<1%

**Q15:** In your experience, what proportion of cases present with liver metastases?

Colonic: 30% (SEER, distant)

Rectal: 2,3% (SEER, distant)

Split up into size of primary (see surgical chapter), also consider TNM

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#### *Diagnostic procedures and 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 can 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 [14], and these findings should be detailed and carefully reported. Central mucosal depression or ulceration suggests high metastatic potential [2] .

Barium Enema. Barium enema may demonstrate colonic tumours where endoscopy is not first performed.

Endoanal/Rectal Ultrasound (EUS) [14–18]. EUS is very useful in assessing rectal carcinoid tumours pre-operatively. EUS can accurately assess tumour size, 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 choice of therapy.

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 lesions.

Computed Tomography (CT)/Magnetic Resonance Imaging (MRI). These are much more sensitive imaging modalities. Spiral CT is probably the most useful for staging the thorax, abdomen and pelvis, although MRI is probably superior for determining liver metastases [19]. Any lesions with evidence of malignant potential or extension require a pelvic CT/MRI to assess local advancement and involvement of other pelvic structures and respectability.

111-Indium Octreotide Scanning. As hindgut carcinoids are relatively uncommon, the sensitivity of 111-indium octreotide scanning is difficult to determine. However, it is useful for determining metastatic disease. Although detection of the primary tumour especially in the rectum with background activity can be difficult [20]. Additionally the high-grade hindgut lesions are often negative for 111-indium octreotide uptake, and other modalities have to be relied on to detect extra-pelvic disease.

Positron Emission Tomography (PET) Imaging. PET is currently considered experimental but may be of use with labels based on dopa for well-differentiated tumours and FDG for poorly differentiated tumours [21].

Bone Scintigraphy. Bone scintigraphy is important in assessing bone metastases [22] .

**Q16:** Which procedure(s) is/are required for a **minimal** diagnostic approach?

Endoscopy & biopsy, depending on size also: rectal ultrasound in rectal, pelvic MRI and/or CT, SRS (optional)

**Q17:** Which procedure should be done first?

Endoscopy & biopsy for Dx, CT for staging

**Q18:** Is EUS required? When is it recommended? CT/MRI? Octreotide scintigraphy?

Diagnosis: Colonoscopy plus biopsy. No other examinations.

(In case of complete removal of a small (<10mm) tumor with low (<10%) KI67: no staging)

In case of incomplete colonoscopy: contrast enhanced Colon CT with neutral enema in order to rule out multicentricity.

Staging:

EUS

multiphasic contrast enhanced CT Abdomen, chest and pelvis. Octreoscan for high KI67 or higher than stage T1 tumors. In case of negative octreoscan: FDG scan.

No role for routine bone scintigraphy.

Planning rectal surgery: rectal MRI, (EUS complementary?).

Follow up: dependant on initial findings and investigations, as well as treatment outcome.

**Q19:** Please suggest your imaging/procedure flow-chart for colonic and rectal tumors.

See Q18.

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*Biochemical diagnosis*

Serum chromogranin A is likely to be elevated and levels often reflect tumour burden [4, 5, 13]. For assessment of rectal carcinoid, analysis of pancreatic polypeptide and enteroglucagon may be useful. 24-Hour urinary 5-HIAA is often negative. Serum acid phosphatase levels may be raised in prostate-specific acid phosphatase-positive tumours [8, 13]. Beta-HCG levels may be increased [8, 9] .

**Q20:** What are the **minimal** required biochemical diagnosis in patients with colonic-rectal tumors?

CgA (often negative), optional: acid phosphatase

**Q21:** What is the minimal biochemical work-up for functioning tumors?

N.A.

**Q22:** When should biochemical tests be performed?

At diagnosis and follow-up

**Q23:** Is germline DNA testing recommended?

No.

If so, which genes?

No.

Which method?

No.

**Q24:** Is somatic (tumor) DNA testing recommended?

No.

If so, which genes?

No.

Which method?

No.

**Q25:** When is genetic counseling recommended?

No.

**Q26:** Would you recommend collecting a consensus statement for genetic testing?

N.A.

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3. Histopathology

*General Overview*

The histological classification of ‘carcinoid’ tumours is initially according to 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 Ki67 index, deep wall invasion often with evident invasion of blood vessels, lymphatics and perineum [3] . Mucin production may also be observed. Endocrine tumours of the rectum and distal colon are mainly asymptomatic and thus considered non-functional. However, many produce enteroglucagon or pancreatic polypeptide-related hormones whereas serotonin production is observed infrequently

[4, 5].

*General Neuroendocrine Phenotyping.* The cells may stain positively for neuron-specific enolase and PGP9.5, but the specificity of these markers is not absolute. The staining is diffusely cytosolic and nuclear, and may co-localise. Synaptophysin is associated with the small vesicles, and a sensitive marker for neuroendocrine tumours. Chromogranin A is localised to the secretory granules and is regarded as a powerful universal marker for neuroendocrine tumours [4, 5].

*Specific Neuroendocrine Differentiation.* As for any other sites of the gastrointestinal tract, endocrine tumours are categorised into well-differentiated and poorly differentiated. Two types of well-differentiated endocrine tumours have been identified in the hindgut, 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 extremely rare in the rectum [4, 5]. Specific markers that should be performed when investigating rectal neuroendocrine tumours are those that identify the L cells. Markers such as glucagon-29, glucagon-37, glicentin, PYY and PP and their precursors are useful. Argentaffin staining and serotonin positivity is rare, but should be excluded [4–6]. Proximal colonic tumours (midgut) on the other hand are usually EC-cell tumours, and may produce serotonin. Metastatic disease may 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 [7, 8]. Alfa-HCG may be expressed, and may relate to the malignant potential of the lesions [9]. Attempts to identify lesions of high malignant potential should include mitotic indexing and Ki-67 staining to determine the tumour proliferative index [10–12].

Q27: Is histology required?

Yes.

Q28: Is cytology recommended and in which clinical situations?

No.

Q29: What are the minimal ancillary tests to be done to support the histological diagnosis?

CgA, Synaptophysin.

Q30: Is the mitotic index necessary?

Yes.

If so, which method?

See VA06 TNM paper.

Q31: Is the Ki67 index necessary?

Yes.

If so, which method?

See VA06 TNM paper. The percent assessment of each tumor [if multiple] and its reporting is recommended.

Q32: Is IHC required for tumor cell subtyping and, if so, when?

No.

Q33: Would you recommend IHC staining for p53 and prostate markers (rectal only)?

P53 maybe helpful for the diagnosis of poorly differentiated. Prostate markers not necessary.

Q34: Would you recommend IHC for SSR2A receptor?

On demand.

Q35-Q35-Q35-Q35: Do we need a tumor grading system?

All groups: Yes

Q36-Q36-Q36-Q36: Do we need a TNM classification? Please see the proposal for tumors of the colon and rectum and make your comments.

All groups: Yes (see table at the end of chapter)

*Surgical therapy*

**Local disease**

Rectal Carcinoid. 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 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 investigations may suggest locally or systemic advanced disease even 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 [3, 23]. The risk of metastases has been estimated at less than 3% [24] 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. [15] especially if there is evidence of local invasion. Band-snare resection [25], aspiration lumpectomy [26] or strip biopsy [16] 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 [27]. Aggressive surgery, such as anterior resections, carries a higher risk for the small lesions <1 cm than the metastatic potential of the lesion, whereas adequate local resection carries a comparatively low risk.

The outcome of a lesion between 1 and 2 cm is unclear. The metastatic risk is considered to be between 10 and 15% [24]. Some studies demonstrate no benefit with aggressive management [3]. Other authors have reported successful treatment with local or radical surgery, with disease-free survival in several cases [2, 28]. 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 endo-anal ultrasound should also guide treatment [14] in this group of patients.

Lesions of >2 cm have a significantly higher metastatic risk [1, 3, 29], considered to be between 60 and 80% [24]. Invasion of the muscularis propria is common in this group, and indicates a high metastatic potential. Local resection is unlikely to benefit patient survival with metastatic disease, but will provide local symptomatic relief [30]. Loco-regional resection may be argued to control local symptoms and pelvic disease without improving survival [25, 31]. Aggressive surgery has not been shown to improve the survival outcome in this group of patients. Studies are limited and the numbers are invariably small. Occasionally small lesions may present with peri-rectal lymph nodes on radiology, suggesting a very aggressive metastatic tumour. In young patients aggressive surgery may be a reasonable option, although cure cannot be guaranteed.

Multidisciplinary treatment options should be offered in conjunction with a specialist team.

Factors Favouring Metastatic Behaviour. Size >2 cm [19], high grade, poorly differentiated histology [3, 30], muscularis propria invasion [24], lymphatic and vascular invasion [31], angiogenesis [32], neural invasion, increased tumour proliferative index – mitotic index [12], Ki-67 [10], endoscopic features [2, 15], endo-anal ultrasound features [14].

Effect of Surgery on Outcome. Any metastatic disease at diagnosis dictates prognosis. Survival is not altered by offering aggressive therapy to the primary lesion in these cases [3, 29, 30]. Surgery may improve symptom control of local complications associated with an advanced rectal tumour mass [30]. 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 [30]. This is a difficult judgement which calls for further studies on predictors of metastatic risk. In patients with rectal carcinoids with low metastatic potential, aggressive surgical intervention carries significant risk, both in morbidity and mortality, and local resection alone is advocated.

**Colonic Tumours.** Carcinoid tumours of the colon present and are treated in a fashion similar to adenocarcinoma of the colon. Since the vast 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 particular evidence is available, but it should be advised that any invasive disease be resected surgically as is practiced with adenocarcinoma.

**Advanced Metastatic Disease** (*Amended from Midgut Experience*)

*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 hindgut carcinoid as compared with midgut carcinoid.

**Q37:** When is curative surgery NOT recommended?

Surgery is generally recommended, general contraindications to surgery must be considered

**Q38:** When is local tumor ablation (e.g., endoscopic) or minimal alternative surgery recommended?

Tumours < 1 cm, no metastases known.

Endosonography should always be performed prior to surgery in rectal NEC.  
Cytology is preferable to biopsy of NEC tumours.

In rectal NECs full-thickness resection can be performed in tumours up to 2 cms.

**Q39:** When is curative surgery recommended?

If curative surgery can be achieved, it should always be performed.

**Q40:** Which type of surgical resection would you recommend?

Colonic tumours: Proceed as for colonic adenocarcinoma.

Rectal tumours: Local resection may be considered if  
 Under 1 cm  
 no infiltration beyond the muscularis propria  
 endosonography neg. for lymph nodes (well differentiated)  
 "Incidentaloma"

"Grey zone"  
 Radical resection including TME (Total mesorectal excision)  
 In all other cases  
 step up surgery  
 tumours 1 .. 2 cms,  
 infiltration of the muscularis propria without lymph node involvement.  
 high surgical risk, loss of continuity  
 procedure must be discussed with patient, individual decision

**Q41:** Is surgery for liver metastases recommended along with elective surgery?

Generally not, liver surgery should be performed as the second procedure.

**Q42:** Which type of palliative surgery is recommended?

Indication for symptoms as pain, obstruction, bleeding etc.

The type of operation should be decided individually.

**Q43:** Does tumor multiplicity affect therapeutic management?

Tumour multiplicity is rare, consider coincidence of NEC and adenocarcinoma.

**Q44:** Do you agree with the suggested surgical approach in the case of invasive/advanced disease?

This heterogenous group of patients need an individual decision.

The major aspect for the decision is quality of life.

This has to be discussed thoroughly with the patients.

**Q45-Q45:** Do you agree with the statement that survival is not altered by aggressive surgical therapy?

Medical group: Possibly true for PDEC, depends on size of tumor and grade; WDEC should undergo aggressive local surgery

Surgery group: There are no conclusive data. But consider quality of life of the patients.

**Q46-Q46:** In a **curative surgical setting** (specify), is medical therapy required? If so, which type, modality and timing should be adopted?

Medical group: No evidence for (neo-) adjuvant Tx in WDEC

Surgery group: Related to risk and patient profile.

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*Surgery of Liver Metastases*

Hindgut tumours rarely have functional symptoms hence resection for a hormonal syndrome is unlikely. There is no evidence for debulking resection for hindgut tumours; however, for bi-lobar liver metastases a twostage liver resection strategy is an option. As for midgut carcinoid, most tumours recur after palliative surgery; however, there may be a delay of progressive tumour disease. Surgery should only be undertaken if at least 90% of the tumour mass can be removed successfully. A prerequisite to hepatic surgery is sufficient hepatic reserve after resection. If criteria for extensive hepatic surgery are fulfilled, mortality of palliative hepatic surgery should not be higher than 3–5% and morbidity about 30%. Metastatic disease should be confined to the liver. It is unclear whether hepatic surgery should be performed only after prior surgery of the primary, synchronous with surgery of the primary or even in the case of a non-resectable primary. Cholecystectomy should be undertaken synchronously with hepatic surgery to prevent the formation of gallstones in patients requiring somatostatin analogue therapy and ischaemic complications of the gallbladder subsequent to chemo-embolisation.

**Q47:** What is the best treatment option for liver metastases from hindgut tumors?

The treatment should follow the guidelines for liver metastases of colorectal adenocarcinomas.

**Q48:** When is surgical treatment for liver metastases recommended?

The indication for treatment should follow the guidelines for liver metastases of colorectal adenocarcinomas.

**Q49:** Which type of loco-regional ablative therapy is recommended?

The treatment should follow the guidelines for liver metastases of colorectal adenocarcinomas.

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*Medical therapy*

*1. Biotherapy*

1.1 Somatostatin Analogues.

Carcinoid syndrome is uncommon in patients with hindgut carcinoid tumours. As per midgut tumours, somatostatin analogues improve symptoms effectively in patients with the carcinoid syndrome. There is currently no evidence to suggest use of a somatostatin analogue as an anti-tumour agent for non-functioning hindgut tumours.

1.2 Interferon.

Interferon may be tried within a prospective trial protocol for anti-tumour effect in patients with metastatic hindgut carcinoid, but there is no evidence base for current recommendation. Anecdotal evidence suggests there may be benefit of interferon in patients with tumours of low proliferative index.

**Q50:** Is somatostatin analog therapy recommended? If so, when and how?

No published evidence Controversial: Not in general, but in Octreoscan-positive, non-resectable disease SOM-analogues can be considered.

**Q51:** Is interferon therapy recommended? If so, when and how?

No published evidence, can be considered in progressive disease.

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##### *Medical therapy*

##### *2. Systemic Chemotherapy*

Systemic chemotherapy is rarely indicated in slowgrowing carcinoids. When used for progressive disease streptozotocin in combination with 5-fluorouracil or 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 plus etoposide have proven to be effective [23].

**Q52:** When is chemotherapy recommended?

No evidence published, can be considered for progressive disease, agents to be determined

**Q53:** Which cytotoxic agents and protocols are recommended?

Unknown, clinical trials should be encouraged

**Q54:** Can chemotherapy be proposed in an adjuvant setting?

No data

**Q55:** Can PRRT be recommended? If so, when and which type?

Somatostatin receptor positive tumors, inoperable or metastatic.

For highly proliferative tumors (KI 67>15%?) chemotherapy as first option.

Lu or Y coupled analogues.

Comment from medical group: In Octreoscan-positive pts. it can be considered.

**Q56-Q56:** What is the scheduled follow-up for patients after curative surgical treatment?

Medical group:

Depends on size and stage of disease.

<1cm and no LN-involvement: no follow-up

1-2 cm: f/u if adverse features (angioinvasion, invasion into muscularis, atypical histology)

>2cm: always f/u

Surgery group:

For low risk patients (see above): only one control within the first year.

In all other cases: In the first year every 3 to 6 months, and thereafter at least annually.

**Q57-Q57:** What are the minimal examinations required and for how long?

Medical group:

Rectal: EUS, endoscopy, MRI

Colon: CT, endoscopy

6 months interval

CgA if positive pre-OP

Change to annual intervals after 5 years, up to 10 years

Surgery group:

Colonoscopy, endosonography in rectal tumours.

US / CT for liver metastases.

MRI (PET, no evidence in NET, depending on local expertise) is preferred to CT for detection of local recurrences in the pelvis.

## Proposal for a TNM classification and disease staging for NET of the colon and rectum

### TNM

#### **T-primary tumor**

TX	tumor not assessed
T0	no evidence of primary tumor
T1	tumor invades mucosa or submucosa and size $\leq 2$ cm
T2	tumor invades muscularis propria or size $> 2$ cm
T3	tumor invades subserosa/pericolic/perirectal fat
T4	tumor directly invades other organs/structures and/or perforates visceral peritoneum
	For any T add (m) for multiple tumors

#### **N-regional lymph nodes**

NX	regional lymph node status cannot be assessed
N0	no regional lymph node metastasis
N1	regional lymph node metastasis

#### **M-distant metastases (sub-specification as in small bowel)**

MX	distant metastasis cannot be assessed
M0	no distant metastases
M1	distant metastasis

\*M1 specific sites defined according to Sobin LH, Wittekind C (ed) (2002) TNM Classification of malignant tumours. Wiley-Liss, New York-Toronto.

### STAGE

#### Disease Stages

Stage IA	T1a	N0	M0
Stage IB	T1b	N0/1*	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	any T	N1	M0
Stage IV	any T	any N	M1

Mod from: Sobin LH and Witteking Ch. TNM Classification of Malignant Tumours, UICC, 6th Ed 2002, Wiley, NY.

#### **\*Discussion by medical group**

Addition from pathology group: Maximum tumor dimension should be reported [the largest if multiple].

Additions from surgery group: Differentiation necessary between well and poorly differentiated tumours.

Proposal from surgery group:

T1a	<1 cm
T1b	1 - 2 cm (see above)

Reevaluation of the stages.