

Thursday, November 2, 2006

TOPIC: WELL-DIFFERENTIATED MIDGUT AND HINDGUT ENDOCRINE TUMORS

9:00 – 9:15 a.m. **General presentation of the work format and aims**
W. de Herder, Rotterdam, The Netherlands

9:15 a.m. - 12:30 p.m. Small intestine (jejunum-ileum)
Chair: B. Eriksson, Uppsala, Sweden

9:15 - 9:35 a.m. **Case presentation: small intestine**
B. Eriksson, Uppsala, Sweden

9:40 - 10:40 a.m. **Working Group Sessions**
Pathology and Genetics
Group leader: G. Klöppel, Kiel, Germany
Medicine and Clinical Pathology
Group leader: B. Wiedenmann, Berlin, Germany
Surgery
Group leader: H. Ahlman, Gothenburg, Sweden
Imaging
Group leader: E. Krenning, Rotterdam, The Netherlands

10:40 - 11:10 a.m. **COFFEE BREAK**

11:10 a.m. - 12:30 p.m. **General assembly**
Presentation of statements by the session chairs & general discussion
B. Eriksson, Uppsala, Sweden

Color Codes

 Pathology and Genetics  Medicine and Clinical Pathology  Surgery  Imaging

ENETS Guidelines *Neuroendocrinology 2004;80:394–424*

Endocrine tumors of lower jejunum and ileum

Epidemiology

The incidence of endocrine midgut tumours is much higher than those arising in the oesophagus, stomach and duodenum (foregut) and those arising in the hindgut (left-sided colon, rectum) [3–7]. Incidence rates of 0.28–0.8 per 100,000 population per year have been reported. Tumours of the lower jejunum and ileum account for 23–28% of all gastrointestinal endocrine tumours and are more frequent than those of the appendix [3, 6]. Midgut endocrine tumours occur in equal proportion in males and females with an age peak in the 6th and 7th decade [3]. Endocrine midgut tumours (carcinoids) are often multicentric and in 15% are associated with metachronous

malignancies as gastrointestinal adenocarcinoma, breast cancer and others [3]. The majority of tumours are located in the terminal ileum close to the ileocaecal valve.

Clinicopathological Staging [15]

Endocrine midgut tumours are EC (enterochromaffin) cell tumours containing serotonin. A minority of tumours consist of cells containing enteroglucagon, and/or pancreatic polypeptide, tachykinin or peptide YY [15].

1. Well-differentiated endocrine tumour (carcinoid): benign behaviour: confined to the mucosa-submucosa, non-angioinvasive, ≤ 1 cm in size

1.1. Serotonin-producing tumour

1.2. Enteroglucagon-producing tumour **X**

2. Uncertain behaviour: non-functioning, confined to mucosa-submucosa, >1 cm in size, or angioinvasive
 - 2.1. Serotonin-producing tumour
 - 2.2. Enteroglucagon-producing tumour **X**
3. Well-differentiated endocrine carcinoma (malignant carcinoid), low-grade malignant, deeply invasive (muscularis propria or beyond), or with metastases
 - 3.1. Serotonin-producing tumour with or without carcinoid syndrome
 - 3.2. Enteroglucagon-producing carcinoma **X**
4. Poorly differentiated endocrine carcinoma (small-cell carcinoma), high-grade malignant
5. Mixed exocrine-endocrine carcinoma – moderate to high-grade malignant

Addition by pathology group: **X** these tumors are extremely rare.

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

Clinical incidence is considerably lower than autopsy incidence (1/150). Clinical symptomatology and by this incidence is (probably) higher than stated in the literature.

Q2: In your experience and according to the literature, is there a gender, age and race preferential distribution?

There is no gender preference, there is some racial preference (specify).

Q3: In your experience and according to the literature, what is the incidence (to be replaced by rate) of functioning tumors?

Approximately one third of pts present with a specific hormonal hypersecretion syndrome (carcinoid syndrome).

Q4: Is the subtyping of endocrine cell (EC vs L) tumors useful for patient management?

In practical terms it is not important (neither clinically nor from a pathological view)

Q5: In your experience and according to the literature, what is the incidence (to be replaced by percentage) of multicentric tumors?

Moertel figures: 46/183

Q6: When multicentric, are tumors more often associated with hormonal hyperfunction?

Unknown (2003 AJSP) 18/68 cases multicentric, 3/18 with functional syndrome, probably related to more advanced disease

ENETS Guidelines Neuroendocrinology 2004;80:394–424

Prognosis/Survival

The prognosis of tumours arising in the distal small intestine is generally unfavourable if compared to that of duodenal, gastric (ECL cell carcinoids) and rectal endocrine tumours, since they frequently lead to metastases of the adjacent lymph nodes and later to the liver and elsewhere [8, 9]. Ten-year survival is approximately 60% in the absence of liver metastases at diagnosis, 15–25% in the presence of liver metastases and, according to a retrospective study, more favourable if the primary tumour is removed. Survival of endocrine midgut tumours correlates closely with the stage of the disease at presentation with a 5-year survival of 65% in patients with localized or regional disease and 36% in those with distant metastases [3, 8–10]. Patients with slow-growing well-differentiated tumours and those with a low Ki-67 live longer than those with more rapidly growing well-differentiated tumours and those with a high Ki-67 [11].

Q7: Is your experience consistent with the above, with particular reference to the “stage” of the disease and proliferative (Ki67) index?

Update of references; consider 5- and 10-year-survival as far as lit. gives information. Survival rates are (probably) better now (regional 5-year: app. 60-70%/ metastatic disease 50-60%, 10-year regional: app. 45% / metastatic disease: app. <40%, expert opinion), reevaluate SERR-numbers; differentiate between distant mets vs. local disease. References with regard to “extensive” metastatic disease unclear

Prognosis of carcinoid heart disease

Comment on better survival rates: more aggressive Tx recently.

Reevaluation in the face of decision on a new TNM-classification necessary.

Room for a M2-stage? Discuss with pathology group. Specify M stage with L (=liver) BM (=bone marrow)-> needs validation

ENETS Guidelines Neuroendocrinology 2004;80:394–424

Clinical presentation

1. Non-Functioning Tumours

Asymptomatic small endocrine tumours of the distal small intestine are discovered while searching for a primary in patients with newly discovered liver metastases originating from an endocrine tumour or incidentally during colonoscopy and intubation of the terminal ileum.

Tumours of >1 cm in diameter are mostly malignant with metastases to regional lymph nodes and later to the liver and elsewhere [15]. Leading symptoms are intermittent abdominal discomfort existing sometimes for years and frequently misinterpreted as a functional disorder. Later, complaints worsen and can lead to intermittent intestinal obstruction due to angulation of the small bowel resulting from a desmoplastic reaction of the mesenterium and not due to the size of the tumour.

2. Functioning Tumours

Leading Symptoms: 4–10% of patients with liver metastases due to an endocrine tumour of the distal small bowel present with carcinoid syndrome [5, 8]. Signs and symptoms of carcinoid syndrome can include one or any of the following: flushing, diarrhoea, carcinoid heart disease, intermittent bronchoconstriction.

Associated Symptoms: Abdominal pain due to desmoplastic reaction of the mesenterium as a consequence of growth factors secreted by the primary and its lymph node metastases. Pellagra-like skin reactions (very rare).

Carcinoid Crisis: A rare but frequently fatal exacerbation of symptoms mostly during anaesthesia or surgery if patients are not under continuous somatostatin treatment. It includes severe and long-lasting flushing, hyper and hypotension, severe bronchospasm and cardiac arrhythmias.

Q8: Is your experience consistent with the above?

Bone pain in pts with bone metastasis

Rate of functionality app. 30%

Ischemia may be another cause of pain and chronic diarrhea. (publication coming soon)

Episodic bronchoconstriction is extremely rare – no part of the initial description.

Q9: What is the most frequent presentation symptom in functioning cases? In non-functioning cases?

Flushing – chronic diarrhea in functioning cases roughly the same.

Abdominal pain in nonfunctioning

Q10: What proportion of patients present the “typical carcinoid syndrome”?

20-30%

no atypical carcinoid syndrome in midgut-NET reported

Q11: In your experience, are functioning tumors metastatic to the liver? If so, in what proportion as compared to those with syndrome in absence of liver metastasis?

App. 95% with liver metastasis, app. 5% without liver metastasis (mostly peritoneal carcinosis)-publications to be added

ENETS Guidelines Neuroendocrinology 2004;80:394–424

Diagnostic procedures

1. Tumor imaging

Abdominal ultrasound, contrast-enhanced CT or MRI of the upper and lower abdomen, octreotide scintigraphy (Octreoscan ®), endoscopy, echocardiography, bone scan or spine MRI

to prove bone metastases if Octreoscan ® is negative.

Comments

No accepted TNM classification of endocrine midgut tumours exists. Once an endocrine midgut tumour is assumed by suspicious symptoms and/or the presence of liver metastases, the tumour load should be assessed before specific therapeutic measures are discussed. Abdominal ultrasound is in most patients the initial imaging procedure showing either liver metastases or lesions previously misinterpreted as haemangiomas or focal nodular hyperplasia with a specificity and sensitivity of 95%. If lesions are growing, correct diagnosis will be made by additional contrast enhanced CT or MRI followed by fine-needle biopsy. CT and MRI are complementary procedures with a similar sensitivity in detecting endocrine tumour lesions in the abdomen and their metastases [16–18]. Whereas liver metastases are easily detectable by ultrasound, CT and/or MRI, localisation of the primary within the distal small bowel and the presence of enlarged mesenteric lymph nodes with and without a desmoplastic reaction can be more difficult and requires experience. After confirming the histological diagnosis by fine-needle biopsy, the next diagnostic procedure is 111 In-pentetreotide (Octreoscan ®) which is positive in 80–90% of the patients with midgut endocrine tumours [19]. It eventually unmask the primary and its regional lymph node metastases and additional tumour manifestations within lung, skin, breast, brain and other locations. Limitation of the technique is related to the size of the lesion (> 0.5 cm) and the receptor density. In 10–15%, midgut endocrine tumours do not express somatostatin receptors. Additional CT scans or MRI of the positive areas should follow to estimate the size of the lesions. CT or MRI of the lower abdomen can visualize mesenteric lymph node metastases and desmoplastic reaction of the mesentery in the neighbourhood of the primary. Staging is important to

judge the respectability of the primary. In case of an unknown primary suspected to be present in the midgut, colonoscopy can identify a primary in the distal ileum, at the ileocaecal valve or in the right-sided colon. Small bowel enteroclysis is an established technique for the detection of midgut endocrine tumours [20]. CT and MRI enteroclysis [21, 22], capsule endoscopy or double balloon enteroscopy are promising new methods for identifying a primary in the distal small intestine, but their significance, specificity and sensitivity have not been evaluated so far. More importantly, it is unsettled whether or not localization of a non-symptomatic primary at these locations has therapeutic consequences if

distant metastases are present. Surgeons argue that early removal of a primary (or of multiple small endocrine tumours) can prevent later occurring obstruction through slowly growing primaries or later occurring desmoplastic reactions. 18 F-dopa whole-body PET is a promising imaging procedure but can presently not be recommended as a routine diagnostic procedure since its sensitivity and specificity have not been investigated [23]. If spine and/or bone metastases are indicated by Octreoscan ®, MRI is recommended to estimate the true tumour mass within the respective skeleton and to prove or disprove the risk of fracture. If Octreoscan ® is negative, bone scan can be performed to exclude bone metastases but it is less sensitive than MRI. Echocardiography is mandatory in patients with carcinoid syndrome to confirm or to exclude coexisting carcinoid heart disease and to judge the severity

of the manifestation. Concerning the time interval of restaging investigations in patients with metastatic endocrine midgut tumours, accepted recommendations do not exist. Time intervals depend mainly on the growth characteristics of the tumour and should be longer (every half year) in slowly growing tumours. For economic reasons and outside prospective trials, ultrasound is frequently the method of choice to judge tumour load and to follow tumour growth.

Q12: Is conventional endoscopy recommended?

Expert opinion: colonoscopy: yes (lack of valid publications), also in the context of increased risk of synchronous neoplastic disease.

Double-balloon-enteroscopy will have a role in the future, but it will have to be evaluated.

Q13: Is capsule videoendoscopy recommended or required for a minimal approach?

It can be useful after enteroclysm in the context of other methods. (Taal et al Gastrointest Endoscopy 2006), commentary

Q14: Should capsule videoendoscopy be initially performed?

Can be used

Q15: Is EUS required? When is it recommended? Are CT/MRI and SRS required? If so, under what circumstances?

EUS not recommended.

CT or MRI yes, choice dependent on local situation. SRS yes.

Q16: Please suggest your imaging/procedure flow-chart necessary in the diagnosis.

In case of incidental finding of liver and or lymphnode mets CT abdomen plus chest, alternatively MRI based on local situation. SRI for staging.

In case of incidental finding after colonoscopy incl distal ileum including histology :
staging

In case of local abdominal symptoms not due to acute obstruction CT abdomen plus pelvis.

In case of negative CT and positive 5HIAA enteroCT with neutral oral contrast (water or PEG) in case of planned surgery for local disease .

In all cases for staging CT abdomen plus chest, alternatively MRI based on local situation. SRI always for staging.

Preferably SPECT/CT (OctreoScan plus diagnostic enhanced CT) in same session.

Alternatively preferably PET/CT (SRI plus diagnostic CT).

In somatostatin receptor negative disease F DOPA PET or FDG may be considered.

Flow-chart needs to be commented on for simplicity.

All investigations according to guidelines or procedures.

ENETS Guidelines Neuroendocrinology 2004;80:394–424

2. Specific Biochemical Diagnosis

Chromogranin A, 5-HIAA in 24-hour urine.

Comments

Chromogranin A, a regulator of secretory granule biogenesis, serves as a sensitive but non-specific tumour marker in non-functioning and in functioning endocrine midgut tumours. Excessively elevated levels (> 1,000 pg/ml) indicate an unfavourable prognosis [24] . 5-HIAA is an excretory product of serotonin. It serves as a sensitive tumour marker for diagnosis and follow-up in patients with carcinoid syndrome and should be estimated in two 24-hour urine collections. In patients with carcinoid syndrome treated with long-acting somatostatin analogues, a decrease in chromogranin A and urinary 5-HIAA mirror relief of symptoms as flushing and diarrhoea. Available assays for the estimation of chromogranin A may differ due to different antibody specificities [25] . This should be kept in mind if levels originating from different laboratories are compared. There is a slight increase in circulating chromogranin A in patients taking proton pump inhibitors and a marked increase in patients with type-A gastritis [26]. Falsely elevated 5-HIAA urine levels can be caused by foods such as avocado, pineapple, banana, kiwi, melon, plum, walnuts and by drugs such as acetaminophenol, coumarin, reserpine, nicotine, caffeine, melphalan, paracetamol, phenacetin, phenobarbital. Falsely low levels can be caused by ethanol, aspirin, MAO inhibitors, ranitidine and others. Serotonin should not be used as a marker for endocrine tumours due to difficulties in reliable measurement [24].

Q17: What are the minimal required biochemical tests?

CgA, 5-HIAA

Q18: Is chromogranin A measurement recommended?

Yes

Q19: When should biochemical tests be performed?

Prior to treatment, for follow-up

Q20: Is germline DNA testing recommended? Which genes? Which method?

NO for all.

Q21: Is somatic (tumor) DNA testing recommended? Which genes? Which method?

No for all.

Q22: When is genetic counseling recommended?

No.

Q23: Would you recommend collecting a consensus statement for genetic testing?

N.A.

ENETS Guidelines Neuroendocrinology 2004;80:394–424

Histopathology [27]

EC cell tumours are characteristically formed by rounded nests of closely packed tumour cells, often with peripheral palisading (type A). Tumour nests may reveal rosette type and/or glandular-like structures [called such because of a mixed insular plus glandular structure (type A plus C) and have a more favourable prognosis. Abundant desmoplastic reaction is frequently observed. Mesenteric arteries and veins located near the tumour may be thickened and their lumen narrowed or occluded by elastic sclerosis leading to ischaemic lesions in the intestine. Most tumour cells are argyrophilic and react with chromogranin A antibodies. 30% of tumour cells are reactive for prostatic acid phosphatase. Identification as EC cell tumours is ascertained by staining for serotonin. In addition, some tumours contain PP/PYY-reactive cells and can be positive for glucagon/enteroglucagon. [---] High Ki-67 and mitotic counts serve as a parameter for poor prognosis. In the absence of defined limits, Ki-67 1 10% and mitotic counts 6 10/HPF may be used as indicative of aggressive endocrine carcinoma.

Q24: Is histology required?

Yes.

Q25: What are the minimal ancillary tests to be done to support the histological diagnosis?

Chromogranin A, synaptophysin (consensus) and serotonin (consensus by pathologists, helpful confirming midgut origin, no consensus in the group).

Q26: Should the mitotic index be calculated?

Yes.

If so, by which method?

See VA06 paper on foregut TNM

Q27: Is the Ki-67 index necessary?

YES, preferred.

If so, which method?

See VA06 paper on foregut TNM. The percent assessment of each individual tumor and its reporting is recommended.

Q28: Is IHC required for tumor cell subtyping and, if so, when?

Serotonin IHC is required in all cases.

Q29: Would you recommend IHC staining for p53?

No.

Q30: Would you recommend IHC for SSR2A receptor at histology?

On demand.

Q31-Q31-Q31-Q31: Do we need a tumor grading system?

All groups: Yes

Q32-Q32-Q32-Q32: Do we need a TNM classification? Please see the proposal for ileal tumors and make your comments.

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

ENETS Guidelines Neuroendocrinology 2004;80:394–424

Curative Surgical Therapy

1. Localized Disease.

Curative surgery should be intended for patients with midgut tumours and localised disease. The size of the primary does not correspond to the metastatic propensity. As microscopic tumour spread to lymph nodes and metastatic liver disease are seen even in patients with small (≤ 1 cm) primary lesions at diagnosis, surgery of the primary should adhere to oncological principles. The surgical treatment of primary neuroendocrine carcinoids and loco-regional disease is not controversial [1–6].

2. Disease Metastatic to the Liver.

Surgery is the only therapy with curative potential. Curative tumour resection, i.e., removal of the primary, regional lymph nodes, and resectable liver metastases, is possible in up to 20% of the patients [3, 9, 10]. Peri-operative mortality is $<3\%$ in most reports and post-operative 5-year survival rate is 61% and even higher in some centres (table 1) [9–16]. Surgical results depend on the experience of the centre [13].

Comments

Historical data indicate a survival rate of 8 years after the onset of symptoms [17–19]. In contrast, in patients with midgut carcinoids and liver metastases without surgical therapy, recent publications give a 5-year survival rate of 30% (range 13–54%), with a median survival of 3–4 years [9, 10, 14, 17, 18, 20, 21]. In interpreting the data, it has to be kept in mind that most published studies were retrospective analyses of pooled data from neuroendocrine tumours of foregut and midgut origin. In the reports cited, hindgut or appendiceal tumours are a negligible minority. In addition, published data are based mostly on single-institution experience, compared to historical controls [13]. No prospective randomized studies comparing medical therapy with surgery alone are available [9]. Curative intent in these studies was defined as the possibility of complete tumour resection (R0 or R1). As randomized prospective studies are not feasible in these rare tumours, selection bias may well improve the reported outcome [3]. Preoperative imaging may underestimate the number of hepatic lesions and, due to intra-operative findings, the initial curative intent results are changed to palliative surgery. As a prerequisite for these extended procedures, mortality should be $<5\%$ and morbidity $<30\%$. In metastasized non-functional midgut tumours, distant metastases other than liver metastases should preclude liver surgery [9, 10, 16–27].

Addition by surgery group: Operative procedures should always be performed under protection with somatostatin analogues.

Q33: How does tumor multiplicity affect therapeutic management?

Tumor multicentricity equals multiple primaries. This may appear in up to 20% of all cases. The best procedures to locate these prior to surgery are Octreotide scintigraphy and CT, intraoperatively palpation and/or endoscopy. Multicentricity does not change the indication for surgery.

Q34: Which type of surgical resection would you recommend?

Segmental resection with wide lymphnode adenectomy. Cholecystectomy is always recommended. In case of lymph node involvement around the S.M.A. high lymph node dissection is recommended.

In some cases with fibrotic reaction around the S.M.A. and tumor radical resection may be a problem that can not be solved.

Q35: Do you agree with the suggested non-surgical approach in the case of distant metastases?

To prevent acute obstruction we recommend resection of the primary plus lymph node dissection also in case of distant metastases.

Q36: Which distant metastases are more frequently seen as responsible for a poor outcome?

The distant metastases, not liver, are associated with poor prognosis including the so called frozen mesenteric root and peritoneal carcinomatosis

Q37-Q37: In a curative surgical setting, is the medical therapy required? If so, which type, modality and timing should be adopted?

Medical group: No, unless functional syndrome requires pre- and perioperative Tx - cave: carcinoid crisis!

Surgery group: At the present no data exist for indication of medical therapy after radical surgery with curative intent

ENETS Guidelines Neuroendocrinology 2004;80:394–424

Palliative Surgery

1. Primary Tumours and Liver Metastases.

Cyto-reductive surgery can be considered in all patients in whom 90% of the tumour can be safely removed [12, 14, 16, 28]. Surgical intervention can be divided into resection of the primary with loco-regional metastases or intra-abdominal debulking, resection of liver metastases alone or synchronous resection of primary and liver metastases. Compared to non-functional midgut tumours, survival is reduced in patients with functional midgut tumours, i.e. the carcinoid syndrome. However, such a difference is no longer evident after palliative surgery [13].

2. Primary Tumours excluding Liver Metastases.

Removal of the primary according to oncological criteria is indicated to prevent intestinal obstruction or ischaemic complications due to a fibrotic reaction of the mesentery or compression of the mesenteric vein due to the tumour mass. As symptoms correlate with tumour mass, a reduction of tumour mass provides symptomatic relief in 70–100% of the patients. Intra-abdominal tumour resection (liver excluded) increased survival significantly from 69 (no treatment) to 139 months [16, 28].

Comments

Before transferring these surgical study data into practical recommendations it is worthwhile to consider some inherent problems of these investigations. In most studies reporting on palliative surgery in neuroendocrine tumours, surgery is only one part of a multimodal approach and may be combined or followed by other means of cytoreductive therapy, biotherapy or systemic/regional chemotherapy. Thus, the effect of surgery alone is difficult to estimate. Furthermore, most reports give univariate survival analyses, which may be potentially misleading. Surgery is mostly done in patients with less extensive disease and thus prolonged survival of patients undergoing debulking procedures may be an aspect due to the stage of the tumour [10].

Q38: How does tumor multiple localizations (primary + metastases) affect therapeutic management?

We try to make liver metastases the only persisting problem.

Q39: When is intra-abdominal debulking recommended? Please elaborate on the recommended profile of a “good candidate” for tumor debulking.

In all patients presumed to benefit from tumor reduction, in accordance with given guidelines.

Q40: When is palliative surgery recommended?

For symptomatic reasons and for improving other therapeutic modalities i.e. medical and radionuclide.

Q41: Which type of surgical resections is recommended?

The approach must be individualized and no general approach can be given

Q42: When should surgery be scheduled as referred to the treatment of concurrent liver metastases?

If a surgical procedure is feasible the primary lesion should be removed first, see Q43 If liver metastases require a minor resection it can be done at the same operation. Otherwise it can be planned to be performed in a second approach.

Q43-Q44: In a palliative surgical setting, is the medical therapy required? Which type, modality and timing should be adopted?

Medical group: If functional syndrome requires pre- and perioperative Tx - cave: carcinoid crisis

Surgery group: Yes

ENETS Guidelines Neuroendocrinology 2004;80:394-424

Medical therapy

1. Biotherapy

1.1 Somatostatin Analogues

Somatostatin analogues effectively improve symptoms in patients with the carcinoid syndrome. This antisecretory effect results in a reduction of biochemical markers in up to 40% [59–65] and in symptomatic improvement in 40–80% [66–72] of the patients. The duration of remission can be limited due to desensitisation or tachyphylaxis. The anti-proliferative effect of somatostatin analogues is unknown, and partial and complete response can be observed in fewer than 10% of the patients. Overall 30 patients with partial tumour regression have been reported so far. Stabilization of tumour growth occurs in 24–57% of patients with documented tumour progress before somatostatin analogue therapy [62, 63, 70, 73, 74]. Indication: Somatostatin analogues are clearly indicated for symptomatic therapy in functioning midgut carcinoids. Whether somatostatin analogues inhibit tumour growth or induce tumour reduction has still to be demonstrated.

Comments

Generalised conclusions should be interpreted with caution as most studies report on a mixed tumour cohort. Demonstration of progressive disease before initializing somatostatin analogue therapy has been a prerequisite in only a small number of studies. No placebo group was included in any of the studies. Most trials were performed in patients pre-treated with other therapeutic modalities. The duration of therapy was rather short in most trials. Standardized schemes for evaluating therapeutic efficacy have not been universally employed and sufficient information on spontaneous tumour growth is lacking. Despite these shortfalls a consistent pattern of the efficacy of somatostatin analogues on symptom control can be demonstrated. Tolerance to somatostatin analogues (nausea, newly developed diarrhoea, abdominal pain) and efficacy in an individual patient should be tested, by initiating therapy with short-acting analogues (e.g. octreotide). Thereafter, depot formulations, usually lanreotide-SR i.m. (every 2 weeks), lanreotide autogel s.c. or octreotide-LAR i.m. (every 4 weeks), are effective in suppressing symptoms. The dose for symptomatic treatment should be individually titrated. The efficacy of lanreotide and octreotide is comparable [65, 66, 70]. Minor, initial side effects, usually subsiding within a few weeks, are abdominal discomfort, bloating and sometimes steatorrhoea [61, 66, 67, 75]. In patients with steatorrhoea, pancreatic enzyme supplementation may be of help. Major side effects are the development of gallstones (about 50%, rarely symptomatic), and in a few cases persistent steatorrhoea resulting in malabsorption [75, 76]. To prevent carcinoid crisis, somatostatin analogues should be given during an interventional procedure in patients with carcinoid syndrome. Serotonin antagonists and morphine analogues can influence diarrhoea due to the hypersecretion syndrome. As diarrhoea may be due to several different mechanisms (bile acid loss, bacterial overgrowth after abdominal surgery), additional treatment options, such as cholestyramine and antibiotics, should be kept in mind.

Q44: Is SOM analog therapy recommended in patients with **functioning** midgut tumors? Which regimen?

Yes

Cholecystectomy is recommended (in combination with other intraabdominal surgical procedures), however, complications have been observed (almost) exclusively with short acting SOM-analogues not so with long-acting formulas (due to extensive inhibition of gall bladder motility)

Surveillance parameters in pts. On SOM-analogue Tx: Vit-B12-levels (oral supplementation)

Q43: Is SOM analog therapy recommended in patients with **non-functioning** midgut tumors? Which regimen?

Controversial: regimen depends on study results of ongoing studies. Is SOM-analogues in progressive tumors. Octreoscan-positivity required.

Q40: Does SOM analog therapy affect patient QOL? If so, is there any relationship to dosage?

Yes

Relationship to dosage: no

Q47: Which other medication should be scheduled routinely on top of SOM analog therapy and why?

Loperamide in cases of diarrhea.

Colestyramin after ileocecal/ileal resection

Pancreatic enzyme substitution

ENETS Guidelines Neuroendocrinology 2004;80:394–424

Medical therapy

1.2 Interferon

Interferon is given for the same indications as somatostatin analogues, with the exception of carcinoid crisis. Control of symptoms, though with a delayed response, is comparable to somatostatin analogues. Thirteen trials (1986–2003) report data on 302 patients, 92% with midgut tumours. Ninety-five (287/302) percent of the patients were evaluable for tumour response to interferon therapy (table 2) [76–87]. A biochemical and symptomatic response could be noted in up to 50% of patients, whereas partial remission of tumour volume could only be demonstrated in about 10% of the patients. Time to progression from start of therapy was a median of 12 months, while median survival ranged from 44 to 80 months in the 5 studies where these parameters were indicated. Due to a larger range of side effects, interferon is generally used as a second-line therapy for symptomatic control. Comments As with somatostatin therapy, generalized conclusions should be interpreted with caution as most studies report on a mixed tumour cohort. The demonstration of progressive disease before initializing somatostatin analogue therapy has been a prerequisite in only a small number of studies and sufficient information on spontaneous tumour growth is lacking. Furthermore, no placebo group was included in any of the studies. Most trials were performed in patients pre-treated with other therapeutic modalities. The duration of therapy was rather short in most trials, and standardized schemes for evaluating therapeutic efficacy have not been used throughout. There are no studies using a randomised, prospective, multi-centre approach including only tumours with demonstrated progress. Most trials used secondary endpoints such as tumour shrinkage or a decrease in tumour markers for the evaluation of drug efficacy. Endpoint analysis, i.e., time to progression or overall survival, was reported in only 5/14 trials. Despite these shortfalls a consistent pattern of the efficacy of interferon on symptom control can be demonstrated. Pegylated interferon, i.e. a long-acting formulation of interferon, is available but still not registered. Comparative studies with subcutaneous interferon are required. Minor side effects are a flu-like syndrome, easily relieved by paracetamol, anorexia with weight loss and fatigue. Major side effects are hepatotoxicity, autoimmune reactions, depression and mental disturbances. Severe bone marrow depression is rare. Whether the combination of somatostatin analogues and interferon- does increase therapeutic efficacy is still a matter of discussion [70, 89–91].

Q48: Is interferon therapy recommended in patients with functioning midgut tumors? Which regimen?

Yes, second-line in addition to SOM-analogues. s.c. 3-4 x/week, individually titrated

Q49: Is interferon therapy recommended in patients with non-functioning midgut tumors? Which regimen?

Controversial, can be recommended (commentary to be agreed upon, balance statements for SOM-analogues and IFN)

Q50: Which other medication should be scheduled routinely on top of interferon therapy and why?

Loperamide in cases of diarrhea.

Colestyramin after ileocecal/ileal resection

Pancreatic enzyme substitution

Apply at night for better tolerability of side-effects

Q51: Is the combination of interferon and SOM analog therapy recommended and, if so, when?

For antiproliferative purpose: controversial, efficacy not (yet) proven

For symptom control indicated (see Q48)

ENETS Guidelines Neuroendocrinology 2004;80:394–424

2. Systemic Chemotherapy

Results with systemic chemotherapy have been poor in patients with metastatic midgut carcinoids with response rates below 10% [92–96]. Therefore it is generally not indicated in patients with well-differentiated metastatic endocrine midgut tumours. Single-agent therapy with either adriamycin or 5-fluorouracil (5-FU) gave response rates of 120% [95], while dacarbazine was even less effective [97]. Furthermore, in these early studies, reports of tumour therapy referred to less strict criteria than are used today and thus probably overestimated therapeutic efficacy. Results of polychemotherapy (5-FU, dacarbazine and epirubicin) have been reported by Bajetta et al. [98] with 50% partial remission, 25% stabilization and 3% progressive disease in 12 patients with midgut tumours. In contrast, Ollivier et al. [99] achieved a poor response rate (1 of 9 carcinoid patients) with the combination of 5-FU, dacarbazine and leucovorin. The efficacy of systemic chemotherapy is best in fast-growing or poorly differentiated tumours. In fast-growing tumours cisplatin plus etoposide have proven to be effective [100–102]. The number of treated patients with midgut tumours is low and the overall 2-year survival in this aggressive subgroup of neuroendocrine tumours is still below 20%. High-dose paclitaxel recently has been used in patients with advanced neuroendocrine tumours with significant toxicity and lack of anti-tumour activity [103].

Q52: When is chemotherapy recommended? Specify the active and appropriate regimens.

Never

ENETS Guidelines Neuroendocrinology 2004;80:394–424

3. Somatostatin Receptor Radionuclide Therapy

Most endocrine midgut tumours express somatostatin receptors, especially its subtype 2 (sst2), on their cell membrane [104, 105]. Targeting these receptors with radio-labelled somatostatin analogues may be used not only for imaging but also for radiotherapy [106–110]. Since 1992, different analogues have been investigated for somatostatin receptor radionuclide therapy (SRRT) [111–119]. For metastatic disease with clear-cut tumour expression of sst2 proven by octreotide scintigraphy, two still unapproved analogues for SRRT show very promising results: [90Y-DOTA-Tyr3]octreotide [120–131] and [177Lu-DOTA-Tyr3]octreotate [132–135]. Treatment with these analogues in the context of phase-1 and -2 trials results in improvement in quality of life which is partly due to anti-secretory effects (many patients were refractory to therapy with non-radioactive somatostatin analogues). Partial and minor responses and stabilisation in patients with progressive disease at the start of SRRT occur in 12–34, 12–14, and 28–56%, respectively.

SRRT yielded a median time to progression and median overall survival of 30 and 15.9 months, respectively, for [90Y-DOXA-Tyr3]octreotide treatment, and 13.0 months for a median time to progression and overall survival for [177Lu-DOXA-Tyr3]octreotate. However, the results for the latter are for much shorter follow-up periods. Thus, SRRT is indicated in metastatic endocrine midgut tumours with a positive octreoscan.

Comments

These radiopharmaceuticals are still under investigation and only available in a few centres. Treatment has to be in collaboration with nuclear medicine units since radiation protection and dosimetry are necessary. Side effects are minimal as long as limits for radiation doses to the kidneys and bone marrow are applied; the use of kidney protection by co-infusion of amino acids (lysine and arginine) allows the administration of higher therapeutic doses (within the same kidney limits), resulting in much higher tumour radiation doses [129, 130]. It is likely that combination therapy with the radionuclides 90Y and 177Lu will lead to better SRRT results for metastasised disease as has been shown in animal trials [134]. This is based on the complementary physical characteristics of these radionuclides resulting in a more effective treatment in case of small- and large-sized tumours combined.

Q53: May peptide receptor radionuclide therapy (PRRT) be recommended and in what circumstances?

Yes. Somatostatin receptor positive inoperable disease. Symptomatology patients refractory to medical treatment.

Q54: What type of PRRT should be employed?

Y or Lu coupled somatostatin analogues.

Q55-Q55: What is the scheduled follow-up for patients after surgery with curative intent (surgical treatment)?

Medical group: Every 6 months (except for G3-Tms)

Surgery group: In case of curative surgery the recurrence rate in between 5 years is about 40%. So clinical, biochemical and imaging assessment should be performed at least yearly (6-12 months). A shorter interval can be applied according to clinical needs or aggressiveness of the tumor.

Q56-Q56: What are the minimal examinations required and for how long?

Medical group: 3-phasic CT

(ultrasound can be considered in experienced centers with limited reproducibility), 5-HIAA, CgA

Surgery group: Control should be lifelong

Comment: Somatostatinreceptorscintigraphy may be useful in different centers.

Carcinoid Heart Disease

Screening for carcinoid heart disease should be performed on a regular basis [135–140]. If it develops, heart failure rather than metastatic disease may limit life expectancy [141, 142]. Medical therapy for heart failure should be introduced when necessary and cardiac surgery with valve replacement should be considered for patients with good performance status or before surgery for hepatic metastases [142, 143].

Q57: Which type of screening is recommended for carcinoid heart disease? When and which timing is recommended?

Transthoracic echocardiography, annually; possibly in the future BNP-measurement.

Consider the patients (cardiovascular) performance status.

Q58: May the medical therapy for heart failure affect the anti-tumor biotherapy? Are there recommended drug associations?

May be some affections, but only limited experience

Q59: Do you agree with the above statement on the timing of cardiac surgery?

In cooperation with experienced cardiologists.

**Proposal for a
TNM classification and disease staging for
NET of the lower jejunum and ileum**

TNM

T-primary tumor

- TX primary tumor cannot be assessed
 T0 no evidence of primary tumor
 T1 tumor invades mucosa or submucosa and size ≤ 1 cm

 T2 tumor invades muscularis propria or size > 1 cm
 T3 tumor invades subserosa
 T4 tumor invades peritoneum/other organs
 For any T add (m) for multiple tumors

N-regional lymph nodes

- NX regional lymph nodes cannot be assessed
 N0 no regional lymph node metastasis
 N1 regional lymph node metastasis

M-distant metastasis

- 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 I	T1	N0	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, Wittekind C (ed) (2002) TNM Classification of malignant tumours. Wiley-Liss, New York-Toronto.

Remark by surgery group: Please insert TxNxM1 tumors exist as well as T3N0M0, clinically. From surgical point of view we recommend to define the minimal amount of lymph nodes that have to be extracted, to call it T0 disease.