Digestive endocrine tumors

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Introduction

• The term “endocrine tumor” used in the document replaces other terms for these cancers: carcinoid, neuroendocrine, apudoma, etc.
• From a practical point of view, functioning tumors (responsible for symptoms related to peptide or amine production) are distinguished from nonfunctioning tumors (no symptoms related to peptide or amine production), the first requiring specific symptomatic treatment.
• Obtaining pathological proof (with analysis according to the WHO 2000 classification) by biopsy or surgery is a priority goal (Annex 1). In disease management, poorly differentiated tumors are distinguished from all others.
• Certain tumors can be integrated into diseases with genetic predisposition: multiple endocrine neoplasia type 1 (MEN-1), exceptionally von Hippel-Lindau disease, von Recklinghausen neurofibromatosis, and Bourneville tuberous sclerosis.
• Endocrine tumors can be located throughout the digestive tract, from the esophagus to the rectum, with preferential sites being the ileum, the appendix, the rectum, and the duodenopancreatic region.
• The main factors of poor prognosis are low tumor differentiation and tumor stage, in particular liver metastases.
• The rare occurrence of these tumors explains the low number of well-conducted studies published; therefore, unless otherwise indicated, the recommendations suggested are expert opinions.

Pretherapy explorations for digestive endocrine tumors

The following explorations do not apply to benign tumors that were totally resected from the start, notably well-differentiated appendix and rectal endocrine tumors <1 cm.

Initial morphological tests

References

• Abdominopelvic CT
• Somatostatin receptor scintigraphy (OctreoScan®)
• Endoscopic ultrasonography of gastric, duodenal, pancreatic, or rectal tumors, except if it does not change their management (nonresectable liver metastases, invasive tumor)

COMPLEMENTARY MORPHOLOGICAL TESTS

References

• Complementary imaging on positive sites using OctreoScan®
• If Zollinger-Ellison syndrome (ZES) is suspected: gastroscopy with attention paid to the duodenum (search for gastrinoma) and careful examination of the fundus with biopsies (ECL cell hyperplasia and ECLomas)
• In cases of hepatic metastases: standard bone scintigraphy looking for bone metastases in the absence of positive sites on OctreoScan®
• When there are nonresectable hepatic metastases: biopsy of a metastasis before antitumor treatment
• In cases of hepatic metastases that seem resectable: liver MRI and thoracic CT
• In cases of endocrine hepatic metastases with unknown primary tumor, immunohistochemical analysis can contribute information on the location of the primary tumor. If the patient has already had an appendectomy, check that there is no endocrine appendix tumor; if not, endoscopic ultrasonography of the duodenopancreatic region, gastroscopy with careful examination of the duodenum and the papilla, colonoscopy, but the therapeutic impact is debatable; suggest nondigestive tract primary tumor (thoracic CT).

Alternatives

• In cases of hepatic metastases: systematic thoracic CT.
• In cases of resectable hepatic metastases: CATP, MRI of the spinal cord.
• In case a small intestine endocrine tumor is suspected: abdominal CT with enteroclysis.
• In cases of endocrine hepatic metastases with unknown primary tumor: bronchial fibroscopy.
• The PET scan has not been correctly evaluated.

PATHOLOGICAL ANALYSIS

• According to the WHO 2000 classification [1], with
evaluation of the differentiation, the number of mitoses, and the proliferation rate (Ki67 or MIB1) (Annex I).

**BIOCHEMICAL TESTS**

**References**

- Calcemia, phosphoremia, glycemia. If hypercalcemia, dose PTH and if PTH is low, dose PTHrP
- Serum chromogranin A
- If there is duodenopancreatic endocrine functioning tumor: peptide dosage depends on functioning symptoms + adapted dynamic tests (secretin test if ZES suspected – caution with risk of ZES decompensation during cessation of antisecretory drugs, fasting test if insulinoma suspected)
- If there is tumor of small intestine or right colon (mid-gut): 24-h urine 5HIAA x 2–3 days
- Cardiac ultrasound looking for carcinoid cardiopathy in case of carcinoid syndrome or high serotonin or 5HIAA levels.
- Multiple fundus endocrine tumors: gastrinemia, look for atrophic gastritis of the fundus and pernicious anemia; if absent, look for ZES and MEN-1

**Alternatives**

- Duodenopancreatic tumor: systematic dosages of gastrin, insulin, C peptide, glucagon, VIP, somatostatin, 5HIAA, thyrocalcitonin, alpha subunit of glycoprotein hormones, pancreatic polypeptide, ACTH are recommended by some, but their utility for disease management has not been demonstrated.

**Clinical trial**

- Assess the advantage of chromogranin A dosage in following up subjects with endocrine tumor.

**SEARCH FOR GENETIC PREDISPOSITION**

**References**

- When there is duodenopancreatic or gastric tumor, search for MEN-1
  - Question patient and collect family antecedents
  - Basal ionized calcemia values and basal PTH
- In high-risk situations of MEN-1: ZES, multiple duodenopancreatic tumors, suggestive family history, hyperparathyroidism, etc.
  - In addition, in consultation with an endocrinologist, search for hyperparathyroidism, pituitary adenoma, adrenal tumor, and bronchial or thymic endocrine tumor
  - Search for constitutional mutations of the menin gene after informed consent from the patient (Annex III)

**Alternatives**

- In cases of apparently sporadic endocrine tumor of the duodenopancreatic area: systematic search for constitutional mutations of the menin gene after informed consent from the patient and systematic exhaustive workup for MEN-1 (see high-risk MEN-1 situations)

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**Operability criteria for digestive endocrine tumors**

- Search for co-morbidities
- Optimal control of hormonal hypersecretion and their biological consequences (tumor and associated secretions: e.g., hypercalcemia of hyperparathyroidism) should be obtained before surgery. The anesthesiologist should be made aware of possible necessary treatments during intra- and postoperative periods (proton-pump inhibitor in ZES, somatostatin analogs in carcinoid syndrome, glucose level control in insulinoma, etc.)
- If there are well-differentiated liver metastases, always plan for their resection if subtotal resection of the primary and secondary mass is possible (cytoreduction surgery), using other tumor destruction techniques (radiofrequency, etc.) if necessary [2, 3]

**Treatment of digestive endocrine tumors**

**Treatment of symptoms**

Treatment of symptoms is the priority; it should be begun during the exploration phase.

**References**

- ZES: proton-pump inhibitor at doses adapted to the clinical, endoscopic, and secretory response
- Insulinoma: diazoxide
- Carcinoid syndrome, diarrhea from VIPoma, symptomatic glucagonoma: somatostatin analog (octreotide or lanreotide) at doses adapted to symptoms.

**Alternatives**

- Insulinoma: if hypoglycemia persists or if there is intolerance to diazoxide: somatostatin analog with monitoring (risk of hypoglycemia), continuous glucose perfusion
- Carcinoid syndrome: interferon alfa
- Antitumor treatment in case symptomatic treatment fails, notably surgery or chemoembolization

**Antitumor treatment in absence of liver metastases**

**DUODENOPANCREATIC TUMORS**

**References**

- In absence of MEN-1: surgery indicated, even if regional extension, except if operative risk is too high.
- If there is MEN-1: indications for surgery limited to particular situations: tumors >2 cm or those increasing in size, insulinoma, glucagonoma, VIPoma or other symptomatic functioning tumor despite symptomatic treatment.
- Systematic intraoperative explorations: exploration of the entire abdominal cavity (ectopic tumors), liver and pancreas sonography, endoscopic duodenal transillumination if ZES.
Alternatives
- In cases of MEN-1, surgery can remove tumors of any size.
- ZES: systematic duodenotomy (diagnosis and resection of duodenal gastrinomas).

TUMORS OF THE SMALL INTESTINE

Reference
- Surgery even if retractile mesenteritis and peritoneal carcinomatosis (unless there is risk of a short small intestine or alteration in the patient’s general condition), with exploration of the entire abdominal cavity and small intestine (several tumors in the small intestine, 20%; associated exocrine tumors, colon)

TUMORS OF THE RECTUM

Reference
- ≤2 cm, well differentiated, limited to the mucosa/submucosa, with no perirectal lymph nodes (endoscopic ultrasonography), and fewer than two mitoses for every 10 high power fields: endoscopic resection (mucosectomy with clips or tattoo to locate scar later if necessary) or surgical excision by transanal approach
- if not: oncological surgery of the adenocarcinoma type

TUMORS OF THE APPENDIX

References
- ≤1 cm: no complementary treatment after appendectomy
- >2 cm: right colectomy after tests searching for metastases
- Between 1 and 2 cm: discussion on complementary surgery (right colectomy) if base invaded, lymph node metastases, extension into mesoappendix, venous or lymphatic emboli, or if adenocarcinoid tumor.

TUMORS OF THE STOMACH

References
- In the context of atrophic gastritis of the fundus or ZES/MEN-1
  - ≤1 cm: destruction or endoscopic resection (mucosectomy if necessary)
  - >1 cm or extension beyond muscularis (endoscopic ultrasonography): discussion of surgical or endoscopic resection or antrectomy (only if atrophic gastritis of the fundus) depending on patient condition, tumor extension, and number of tumors. Very exceptionally, total gastrectomy.
- Outside of the context of atrophic gastritis of the fundus or ZES/MEN-1: oncological surgery of the adenocarcinoma type

Alternatives
- Multiple fundus tumors with atrophic gastritis of the fundus or ZES/MEN-1: somatostatin analog (not validated)

TUMORS OF THE COLON

Reference
- Oncological surgery of the adenocarcinoma type

TUMORS THAT ARE POORLY DIFFERENTIATED NO MATTER WHERE THEY ARE SEATED

No consensus between experts:
- Surgery if it is expected to be curative
- Or chemotherapy (CDDP-etoposide) +/- radiotherapy (cf. infra).

ANTITUMOR TREATMENT IN PRESENCE OF LIVER METASTASES

- Metastasis resection

Synchronous or metachronous liver metastases should be resected if the primary tumor and the metastases are resectable, and when there are no nonresectable extrhepatic metastases (level D).
- When the tumor is well differentiated, nonsurgical treatment of nonresectable liver metastases is generally indicated if they are evolutive according to the WHO or RECIST criteria (imaging at 3 months, then every 6 months with CT or MRI) or if they remain symptomatic despite symptomatic treatment. Immediate antitumor treatment must be discussed in cases of extrhepatic metastases (particularly of the bone) or greater than 50% liver invasion.
- If tumors are poorly differentiated, chemotherapy is the immediate indication.
- Evaluating the antitumor effect

Monitoring the medical antitumor treatments is clinical, biological, and morphological. It can be done every 3-4 cycles for well-differentiated tumors and every 2 cycles for poorly differentiated tumors. Treatment is stopped if there is progression or toxicity; cessation should be discussed in case of prolonged stability.

RESECTABLE LIVER METASTASES

Reference
- Surgical resection of metastases, eventually completed by other tumor destruction techniques, and resection of the primary tumor
- No complementary antitumor treatment

Alternatives
- Well-differentiated duodenopancreatic tumors: CT (adriamycin-streptozotocin) if surgical contraindication
- Percutaneous destruction of liver metastases (radiofrequency)

NONRESECTABLE LIVER METASTASES

Metastatic well-differentiated duodenopancreatic tumors:
- Treatment of primary cancer: highly selected indications for surgery depending on potential complications and later transplantation possibilities
- Treatment of hepatic metastases:

References
- Nonsymptomatic, nonprogressive metastases, liver invasion <50%: monitoring progression.
• Progressive and/or symptomatic metastases despite symptomatic treatment and/or invasion of liver >50%:
  — no extrahepatic metastases (bone, etc.):
  — CT (Adriamycin-streptozotocin or 5FU-streptozotocin if contraindication to Adriamycin) [4] (level B)
  — Or chemoembolization in specialized center [5,6] (level C)
  — with extrahepatic metastases: CT (Adriamycin-streptozotocin or 5FU-streptozotocine if contraindication to Adriamycin) [4]

Alternatives

• Somatostatin analogs for their antitumor properties (stabilization obtained in 30%–50% of cases of evolutive metastases) [7-10] (level C)
• Interferon [11,12] (level C)
• No indication for combining somatostatin analog and interferon [13] (level C)
• Dacarbazine (particularly if there is glucagonoma) [14] associated or not with other drugs (5FU, epirubicin) [15] (level D)
• Continuous 5FU
• Hepatic artery embolization (or repeated with occluder) associated or not with peripheral chemotherapy (Adriamycin-dacarbazine and 5 FU-STZ alternated) [16, 17] (level D)
• Liver transplantation if there are no extrahepatic metastases, if the subject is young [18, 19] (level D)
• Metabolic radiotherapy with radioactive somatostatin analogs (not available in France)

OTHER METASTATIC DIFFERENTIATED DIGESTIVE ENDOCRINE TUMORS

• Treatment of primary tumor: resection of primary intestinal tumor and lymph node extension to avoid later complications, unless contraindication related to patient’s overall condition
• Treatment of liver metastases:

References

• Nonprogressive and nonsymptomatic metastases, liver invasion <50%: monitoring progression.
• Progressive and/or symptomatic metastases despite their symptomatic treatment and/or liver invasion >50%:
  — if no extrahepatic metastases:
    — if no contraindication for chemoembolization: chemoembolization in specialized center (5, 6) (level B)
    — if contraindication for chemoembolization: CT (5 FU-streptozotocin) [20] or interferon [11, 12] (level C)
  — if there are extrahepatic metastases: CT (5 FU-streptozotocin) [20] or interferon [11, 12] (level C)

Alternatives

• Somatostatin analogs for their antitumor properties (stabilization) [7-10] (level C)
• Continuous 5FU
• Dacarbazine [21] associated or not with other drugs [15] (see tumors of duodenopancreatic tumors) (level D)
• Hepatic artery embolization (or repeated ischemia with occluder) associated or not with peripheral chemotherapy (Adriamycin-dacarbazine and 5FU-STZ alternated) [16, 17] (level D)
• Chemoembolization even if there are extrahepatic metastases

• Metabolic radiotherapy (MIBG) [22] (level D) or with radioactive somatostatin analogs (not available in France)
• Liver transplantation if there are no extrahepatic metastases, if the subject is young [18, 19] (level D)

POORLY DIFFERENTIATED ENDOCRINE TUMORS

Reference

• CT (CDDP-etoposide) immediately [23, 24]

Alternative

• Irinotecan–CDDP [25] (level D)

TREATMENT OF BONE METASTASES

• Radiotherapy and surgery should be discussed
• Symptomatic treatment

Post-therapy monitoring

Liver metastases

• After resection, CT or MRI at 3 months and OctreoScan® (if test was initially contributive) at 3–6 months
• Imaging (the choice between CT and MRI depends on their ability to visualize metastases in the particular patient) [26] and initially abnormal biological markers every 3 months for 6 months, then every 6 months
• Diagnosis of bone metastases if there are clinical warning signs with bone scintigraphy or OctreoScan® + complementary imaging depending on location
• Cardiac ultrasound searching for carcinoid cardiopathy every 6 months if carcinoid syndrome or increase in 5HIAA

If no liver metastases

• Since distant metastases can occur very late, the patient should be informed of the need for long-term monitoring depending on prognostic and follow-up factors, useless in situations with no risk of metastases or local recurrence.
• After curative surgery, in 3–6 months redo OctreoScan® if initially contributive.
• Liver ultrasound is the basic screening test for liver metastases (availability, cost). Its performance is nevertheless less good than the performance of other imaging techniques (CT, MRI, OctreoScan®).
• Poorly differentiated tumors (all locations): close clinical monitoring (1–3 months) and, at least every 3 months, liver ultrasound + other tests depending on location and treatment
• Well-differentiated rectal tumors <2 cm not reaching the muscularis and totally resected with no lymphatic metastases and with less than 2 mitoses for every 10 high power fields: no follow-up
• Appendix tumors ≤1 cm or 1–2 cm, base not invaded, no lymphatic metastases in mesoappendix, no venous or lymphatic emboli, not adenocarcinoid in nature: no follow-up
• Other situations: minimal annual follow-up including questioning, clinical examination, eventual check of symptomatic treatment efficacy + dosage of initially abnormal
markers and chromogranin A (and 5HIAA x 3 days if tumor of the small intestine or right colon) + liver ultrasound + local follow-up depending on organ. If hereditary syndrome, specific adapted monitoring.

- The advantage of OctreoScan®, systematically for monitoring of patients operated on with curative intent, has not been validated.

### Treatment of digestive endocrine tumor recurrence

#### References

- Symptomatic treatment: priority
- Same antitumor treatments as indicated above for evolutio-ve metastases, after verification that there are no contraindications (accumulated cardiac toxicity of adriamycin, very frequent renal toxicity induced by streptozotocin, etc.)
- In cases of hepatic metastasis recurrence, re-evaluate the possibilities of surgical resection
- Radiotherapy: bone, decompression, etc.

#### Summary of therapeutic protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5 FU-streptozotocin</strong></td>
<td>400 mg/m²/day in 2-h perfusion, 250 ml of 5% isotonic glucose solution + streptozotocin 500 mg/m²/day in 2-h perfusion in 250 ml of 5% isotonic glucose solution (in Y 5FU IV) from D1 to D5 every 42 days</td>
</tr>
<tr>
<td><strong>Adriamycin-streptozotocin</strong></td>
<td>50 mg/m²/day, slow strict IV on D1 and D22 + streptozotocin 500 mg/m²/day in 1-h perfusion in 250 ml of 5% isotonic glucose solution every 42 days from D1 to D5</td>
</tr>
<tr>
<td><strong>Dacarbazine</strong></td>
<td>250 mg/m²/day in 30-min perfusion in 100 ml of 5% isotonic glucose solution from D1 to D5 every 28 days</td>
</tr>
</tbody>
</table>

#### CDDP-etoposide

- Etoposide 100 mg/m²/day in 2-h perfusion in 250 ml of 5% isotonic glucose solution from D1 to D3 + CDDP 100 mg/m² in 2-h perfusion in 250 ml of isotonic solution on D1 every 21 days
- or
- Etoposide 120 mg/m²/day in 1-h perfusion in 250 ml of 5% isotonic glucose solution from D1 to D3 + CDDP 100 mg/m² in 1-h perfusion in 250 ml of isotonic solution on D2 every 28 days [24] (highly hematotoxic)

#### Irinotecan-CDDP

- Irinotecan 60 mg/m²/day in 90-min perfusion in 250 ml of 5% isotonic glucose solution on D1, D8 and D15 + CDDP 60 mg/m² in 1-h perfusion in 250 ml of isotonic solution on D1 every 28 days

#### Chemoembolization

- Absolute contraindications: portal vein thrombosis, severe hepatic cirrhosis, jaundice; relative contraindications: biliary and digestive anastomosis or biliary stent
- Every 8–12 weeks until stabilization (minimum 2 courses)
- Choice of chemotherapy product:
  - Adriamycin (50 mg/m²)
  - Streptozotocin (1500 mg/m²)
  - Adriamycin (50 mg) + cisplatin (150 mg)
  - 5FU (350 mg) + STZ (1000–2000 mg)
- Requires general anesthetic when STZ used (intense pain)
- Risk of liver failure: only embolize one lobe at a time (if liver invasion >60%)
- Sufficient hydration
- In cases of carcinoid syndrome, prevent carcinoid attack with octreotide before act and up to 48 h

#### ACKNOWLEDGMENTS TO READERS

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Annex. I

WHO endocrine tumor classification


The Table below is taken from the following reference: Rawage JK et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut 2005;54(suppl IV):iv1-iv16.

<table>
<thead>
<tr>
<th>Site</th>
<th>Well differentiated endocrine tumour (benign behaviour)</th>
<th>Well differentiated endocrine tumour (uncertain behaviour)</th>
<th>Well differentiated endocrine carcinoma (low grade malignant)</th>
<th>Poorly differentiated endocrine carcinoma (high grade malignant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Confined to pancreas</td>
<td>Confined to pancreas</td>
<td>Well to moderately differentiated</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>≤ 2 cm</td>
<td>≥ 2% Ki-67 positive cells or vascular invasion</td>
<td>- Gross local invasion and/or metastases</td>
<td>- Necrosis common</td>
</tr>
<tr>
<td></td>
<td>≤ 2 mitoses per 10 HPF</td>
<td></td>
<td>- Mitotic rate often higher</td>
<td>&gt; 10 mitoses per 10 HPF</td>
</tr>
<tr>
<td></td>
<td>No vascular invasion</td>
<td></td>
<td>- Ki-67 index &gt; 5%</td>
<td>&gt; 15% Ki-67 positive cells</td>
</tr>
<tr>
<td>Stomach</td>
<td>Confined to mucosa-submucosa, ≤ 1 cm</td>
<td>Confined to mucosa-submucosa, &gt; 1 cm or vascular invasion</td>
<td>- Well to moderately differentiated</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Duodenum, upper jejunum</td>
<td>Confined to mucosa-submucosa, ≤ 1 cm</td>
<td>Confined to mucosa-submucosa, &gt; 1 cm or vascular invasion</td>
<td>- Well to moderately differentiated</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>No vascular invasion</td>
<td></td>
<td>- Invasion to muscularis propria or beyond or metastases</td>
<td></td>
</tr>
<tr>
<td>Appendix</td>
<td>Non-functioning</td>
<td>Enteroglucagon-producing</td>
<td>- Well to moderately differentiated</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Confined to appendiceal wall</td>
<td>Confined to subserosa</td>
<td>- Invasion to mesoappendix or beyond or metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤ 2 cm</td>
<td>&gt; 2 cm or vascular invasion</td>
<td></td>
<td></td>
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</tbody>
</table>

HPF: high power field

Annex. II

Advantage of serum dosage of chromogranin A in the follow-up of patients with gastroenteropancreatic tumors.

The follow-up of patients with gastroenteropancreatic endocrine tumors is currently based on a succession of complex, costly, and time-consuming morphological and scintigraphic tests.

Recent demonstration of a generalist biological marker of endocrine tumors that demonstrates the secretory activity of such tumors – chromogranin A – means that this marker may be interesting in the follow-up of these patients.

The objective of this study is to evaluate the diagnostic advantages of the chromogranin A dosage in predicting tumor progression in patients presenting a gastroenteropancreatic endocrine tumor.

Patients and methods: between 150 and 250 patients with well-differentiated GEP endocrine tumors will be included in this study. The biological dosage of chromogranin A will be centralized and performed using the IRMA technique (Ki Cis Bio: normal <100 ng/ml). For each subject, a dosage will be determined at the beginning of the study and at 6 months. Standardized morphological and scintigraphic tests will be done at 0 and 6 months and will serve as the study’s standard.

Patients will be classified as morphologically progressive or not morphologically progressive according to the RECIST criteria. For chromogranin A progression, patients will be classified as progressive or nonprogressive depending on a relative variation threshold that will be determined once the ROC curves have been established.

This French prospective multicenter study will be conducted on a group of endocrine tumors with eight French centers participating.

At the end of this study, if the hypothesis is validated, patient follow-up could be considerably simplified and will be based on simple biological dosages of chromogranin A.

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Annex. III

The search for menin gene anomalies is available from the secretariat of the Groupe des Tumeurs Endocrines (GTE): Prof. Alain Calender; Unité de Génétique et Cancer, hôpital Edouard Herriot, Pavillon E, 69437 Lyon cedex 03; telephone: 33 4 72 11 73 80; fax: 33 4 72 11 73 81; alain.calender@chu-lyon.fr or on the site: http://rockefeller.univ-lyon1.fr/GENEM/new/index.html

REFERENCES


