ENETS Consensus Guidelines

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ENETS Consensus Guidelines for the Management of Peritoneal Carcinomatosis from Neuroendocrine Tumors

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Epidemiology and Clinicopathological Features

Peritoneal carcinomatosis (PC) from gastroenteropancreatic (GEP) neuroendocrine tumors (NET) is a rare event and there are insufficient data regarding its exact prevalence and treatment [1]. Therefore, these guidelines regarding diagnosis and treatment of PC from GEP-NET are based on level 2–3 published articles.

PC from GEP tumors seems to have two particularities: (1) it is more frequently associated with large (non-gastrinomas) pancreaticoduodenal GEP tumors or GEP tumors of midgut origin (carcinoids) and (2) PC infrequently is an isolated event [2–4]. Lymph nodes are present in most of the patients at the time of diagnosis and 30–80% of patients present with synchronous PC and liver metastases [2–4]. The two series of patients with PC from GEP tumors were published in 1996 (n = 11) and 2005 (n = 37), reporting a total number of 48 patients [2, 4]. The two series documented an overall PC prevalence of 10 and 33%, respectively. The primary tumor was of midgut origin in 8 of 11 patients (73%) in the series of Vasseur et al. [4] and 20 of 37 patients (54%) in the series of Elias et al. [2]. The US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data in 2003 [5] reported a 13.6% PC prevalence among intestinal origin tumors (carcinoid).

[1] See list at the end of the paper.

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There are no specific symptoms related to PC in GEP tumors and the symptom profile is similar to PC of other tumor types [6–8]. Some patients have symptoms predominately related to the primary tumors. Clinically, almost half of the patients are asymptomatic at the time of diagnosis or present with nonspecific symptoms such as abdominal pain and discomfort. Peritoneal disease is thus discovered fortuitously either at morphological examinations or during surgical exploration [9]. Symptoms likely to indicate the presence of PC are those related to intestinal occlusion such as the Koenig sign (either acute or more frequently subacute in nature), which usually indicates the presence of symptoms related to incomplete small intestine stenosis such as those observed in inflammatory diseases [10, 11]. Abdominal pain may also be associated with weight loss or perhaps weight gain, the latter if secondary to ascites. Patients can also present with carcinoid syndrome in either the presence or the absence of LM [2, 4, 12–14].

Minimal Consensus Statements on Epidemiology and Clinicopathological Features

PC from GEP-NET is a rare event. The majority of cases with PC in this setting has large pancreaticoduodenal or midgut tumor origin (approximately 13% of patients with midgut tumors will have PC at the time of diagnosis). Lymph nodes and liver metastases frequently accompany PC at presentation. Symptoms may be related to the primary tumor and half of the patients with PC will not have specific symptoms related to PC or present with nonspecific abdominal pain and discomfort. Specific symptoms likely to indicate the presence of PC are related to either acute or subacute intestinal occlusion; patients may present with ascites.

Diagnostic Procedures

From a morphological viewpoint, as for liver metastases, large nodules >1 cm are often visualized on CT scan, MRI and/or somatostatin receptor scintigraphy while small nodules are often not seen on standard imaging [15]. The presence of ascites is a suspicious finding but requires cytological examination of the fluid to confirm its malignant nature. Importantly, negative cytology of ascites does not mean absence of PC as demonstrated in the paper by Vasseur et al. [4]. In the report by Elias et al. [2], patients were highly selected as all had proven PC at the time of exploration which was mainly for treatment of the primary and/or liver metastases. Mini-invasive staging laparoscopy can in selected patients who have not undergone major previous abdominal surgery confirm the diagnosis and lead to precise staging by exploring the entire abdominal cavity including the pelvis (especially ovaries), mesenteric vascular axes, greater omentum (infiltration and its type), the visible surface of the liver including the whole left lobe and both subdiaphragmatic spaces [16]. Surgical exploration also affords the possibility of obtaining tissue specimens to confirm a histological diagnosis of PC and additionally allows for intraoperative liver ultrasound; indeed, using this approach more liver nodules have been detected than on preoperative imaging examinations [16–23]. Surgical exploration also helps in detailing the extent of the disease, the involvement of one or multiple compartments such as the liver, peritoneum, distant lymph nodes and the degree and difficulties of an eventual resection. With this in mind, with both pre- and intraoperative explorations, particular attention should be given to the right and left subdiaphragmatic spaces, the small and great omentum (especially in patients who have small intestinal GEP tumors), lateral abdominal spaces close to the colon, mesenteric vessels and pelvis (pouch of Douglas). In patients with small bowel obstruction, which may be secondary to the primary tumor, peritoneal nodules and/or associated mesenteric retraction, entero-CT scan or entero-MRI may be useful in both diagnosis and therapeutic planning [13, 17, 18, 20, 24–27].

Minimal Consensus Statements on Diagnostic Procedures

Large PC nodules, >1 cm, are often visualized on CT scan, MRI and/or somatostatin receptor scintigraphy. Laparoscopy can in selected patients provide biopsies after precise staging. Entero-CT scan or entero-MRI may be useful in patients with small bowel obstruction (due to primary tumor, peritoneal nodules and/or associated mesenteric retraction) for both diagnosis and therapeutic planning.

Classification and Pathology

Histopathology

It is important to obtain histopathological confirmation of PC. Biopsy-proven PC can be obtained at standard surgery (either electively for primary tumor or in patients undergoing emergency surgery for intestinal occlusion) or as part of a staging laparoscopy or laparotomy procedure. Standard immunohistochemistry should be applied using at least chromogranin A, synaptophysin and the Ki-67 proliferation index. WHO tumor staging and

Table 1. Gilly classification is based on nodule size and simplified extent of intraperitoneal involvement (localized or diffuse)

Stage 0	No macroscopic disease
Stage 1	Malignant granulations less than 5 mm in diameter localized in one part of the abdomen
Stage 2	Malignant granulations less than 5 mm in diameter diffuse to the whole abdomen
Stage 3	Localized or diffuse malignant granulations 5–20 mm in diameter
Stage 4	Localized or diffuse large malignant masses (more than 2 cm in diameter)

Scores vary from 0 to 4. Patients with Gilly stage 3 or 4 have macroscopic advanced disease which is often associated with a worse prognosis.

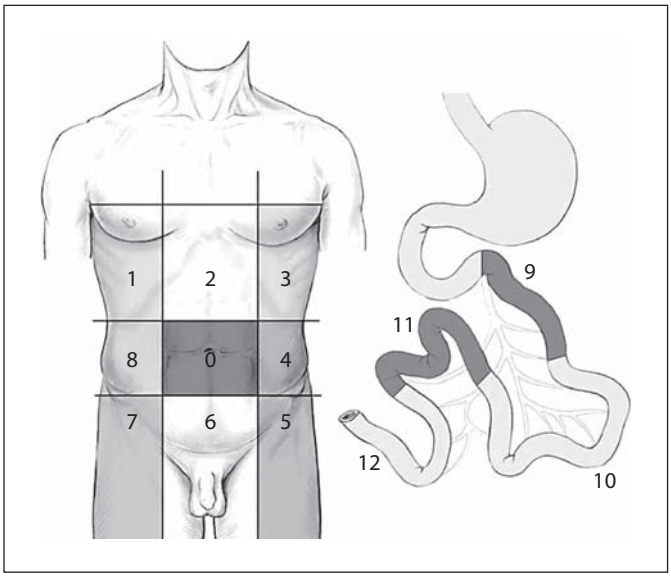

Fig. 1. PCI classification. The abdomen and the pelvic regions are divided by lines into nine regions (0–8). The small bowel is then divided into four regions. Regions 9 and 10 define the upper and lower portions of the jejunum; regions 11 and 12 define the upper and lower portions of the ileum. The LS (i.e., the largest implant size) is scored in each abdominal region. Implants are scored as LS-0 to LS-3. LS-0 means no implants are seen throughout the region; this measurement is made after complete adhesiolysis and complete inspection of all parietal and visceral peritoneal surfaces. LS-1 refers to implants that are visible up to 0.5 cm in greatest diameter. LS-2 identifies nodules greater than 0.5 cm and up to 5 cm. LS-3 refers to implants 5 cm or greater in diameter.

TNM staging/grading should be performed. Special stains are usually not needed. Cytology from patients with ascites may give a clue to a neuroendocrine origin but obtaining a tissue sample is usually better. However, in a patient with a biopsy-proven primary NET, suspicious cytology may be sufficient.

Classification Systems

Much of the work in relation to classification systems has been drawn from PC of other primary tumor origins, especially those of colorectal and appendiceal cancers [10, 28, 29]. To clarify both the extent and severity of PC, pre- and intraoperative classifications are used. Two classifications are often used by surgeons intraoperatively. It is important to note that both classifications evaluate the extent of the peritoneal disease and not the degree of surgical difficulties and/or resectability.

Peritoneal Carcinomatosis Index

The peritoneal carcinomatosis index (PCI) quantifies intraoperatively the extent of disease within each region of the abdomen and pelvis, and can be summarized as a numerical score varying from 1 to 39 for the whole abdominal cavity. It is based on the site and size of tumor nodules or 'granulations' (fig. 1) [30]. The PCI classification is complete but difficult to apply in nonspecialized centers. The abdomen and the pelvic regions are divided by lines into nine regions (0–8). The small bowel is then divided into four regions. Regions 9 and 10 define the upper and lower portions of the jejunum; regions 11 and 12 define the upper and lower portions of the ileum. The lesion size (LS; i.e., the largest implant size) is scored in each abdominal region. Implants are scored as LS 0 through 3 (LS-0 to LS-3). LS-0 means no implants are seen throughout the region; this measurement is made after complete adhesiolysis and complete inspection of all parietal and visceral peritoneal surfaces. LS-1 refers to implants that are visible up to 0.5 cm in greatest diameter. LS-2 identifies nodules greater than 0.5 cm and up to 5 cm. LS-3 refers to implants 5 cm or greater in diameter. When the PCI score is more than 20, the disease is usually at an advanced stage and is considered unresectable [31]. Some specialized centers propose performing PCI before and after cytoreductive surgery.

Gilly's Classification

Here, the stages range from 0 to 4 [29]. This intraoperative classification is easy and realistic for clinicians and can be easily applied to retrospective and prospective studies upon surgical reports (table 1). Patients with Gil-

Table 2. ENETS proposal of GPS grading system based on the association of PC with lymph node and liver metastases

	0 point	1 point	2 points	3 points
Lymph node metastases	local[1]	regional[2]	distant abdominal (retroperitoneal, hepatic pedicle)	extra-abdominal
Liver metastases	no macroscopic nodule	one lobe less than 5 nodules	both lobes 5–10 nodules	both lobes more than 10 nodules
PC	no macroscopic nodule	Gilly I–II resectable	Gilly III–IV resectable	Gilly I–II–III–IV unresectable

GPS grade A: 0–3 points, GPS grade B: 4–6 points, GPS grade C: 7–9 points. To avoid including patients with nonmalignant ascites, patients with positive malignant cells obtained by peritoneal biopsies and/or positive cytology of the peritoneal fluid are considered as having proven PC.
[1] Local: first (adjacent) to the primary tumor territory relay. [2] Regional: secondary tumor drainage territory relay.

ly stage 3 or 4 have macroscopic advanced disease and are often associated with a worse prognosis. However, the Gilly classification is not precise concerning respectability of the peritoneal nodules.

Other than staging scores, it is important to specify the presence of lymph nodes, liver metastases (one lobe or bilateral disease), the presence or absence of mesenteric retraction, Douglas bend involvement, and the type of PC: (a) nodular, (b) infiltrative or (c) both. It is also important to document the type of peritoneal infiltration with respect to the primary tumor location, as it could be involved either by (a) continuity-contiguity, (b) distant metastases or (c) both types.

PC in GEP tumors usually accompanies both lymph node and other metastatic sites (notably liver); therefore, from a practical point of view, it appears that all of the reported classifications take into account exclusively the extent of PC. The ENETS expert group therefore set out to propose a scoring system to include the importance of the global intra-abdominal metastatic disease. As for colorectal cancers, the peritoneum was considered as a compartment as well as lymphatic nodes and the liver [8, 13, 28, 31, 32]. With this in mind, we propose an abdominal gravity PC score (GPS) (table 2) specific to PC from GEP tumors having one or multiple metastatic sites including lymph nodes and liver. The overall score will vary from 0 to 9. Patients with <3 points are scored as GPS grade A and are considered as having a 'low risk' of abdominal spread; those with 4–6 points are scored as grade B and as having an 'intermediate risk', and those with 7–9 points are scored as grade C and as having a 'high risk'. Such a scoring system will have to be evaluated prospectively prior to validation.

Minimal Consensus Statements of Histopathology and Staging

Biopsy-proven PC is required with standard immunohistochemistry with chromogranin A, synaptophysin and the Ki-67. WHO and TNM staging/grading should be applied. Cytology from patients with ascites may be helpful but negative cytology does not exclude PC.

Two intraoperative classifications are used to determine the extent and severity of PC. The PCI is a complex but detailed system. The score depends on the site and size of tumor nodules. High PCI scores, >20, indicate an advanced disease stage and are usually unresectable. Gilly's classification based on nodule size and the simplified extent of intraperitoneal involvement (localized or diffuse) scores from 0 to 4 and is easier to use. Patients with Gilly stage 3 or 4 have macroscopic advanced disease and are often associated with a worse prognosis.

As PC rarely occurs isolated, the ENETS expert group proposed the GPS which incorporates the Gilly classification with the extent of lymph node and liver metastases. Scores range from 0 to 9 (<3 points: GPS grade A deemed 'low risk' of abdominal spread; 4–6 points: grade B considered as having an 'intermediate risk,' and >7: grade C considered as having a 'high risk' and usually unresectable). This is, however, a proposition and will require prospective examination for validation.

Surgical Therapy, Cytoreduction and Other Innovative Approaches

Like in other metastatic diseases, in GEP tumors, surgery may be divided into curative and palliative strategies. There are no prospective data regarding the usefulness of resection or other aggressive treatments of PC in GEP tumors, as is the case for the treatment of liver metastases [32]. However, surgical resection may be discussed and indicated for the following reasons: (1) to

avoid intraluminal obstruction or invagination, (2) to avoid consequences related to fibrosis due to mesenteric retraction or vascular involvement, (3) to avoid external bowel compression in patients with pouch of Douglas macronodules, (4) digestive hemorrhage and (5) for segmental portal hypertension (left pancreas). Even in some patients with unresectable liver disease, the resection of the primary together with macroscopic nodules makes it possible to focus further therapies exclusively on the liver disease [13, 24].

As for the treatment of liver metastases, surgery for PC should take into account the potential benefit/risk ratio on a case-by-case basis [31, 33]. For Vasseur et al. [4], the presence of PC was not statistically associated with a significant decrease in life expectancy in a small series of patients compared to the presence of liver metastases which was associated with a poor outcome. These authors recommended a cautious surgical approach before treating PC from GEP tumors, reserving surgery for highly selected patients. Elias et al. [2] compared 20 patients with unresected PC to 17 with resected PC, all with synchronous liver metastases. PC was reported to be the direct cause of death in 40% of patients when not specifically treated. Despite a high morbidity rate (47%), mainly due to one-step surgery of both liver and peritoneal metastases, the authors suggested treating both liver and peritoneal metastases when technically feasible. The same group subsequently reported that the presence of resectable PC with concomitant resection of liver metastases is not significantly different in terms of overall and disease-free survivals [34].

The consensus expert view without adequate referential data tends to propose resection of both PC and liver metastases in specialized centers using selective conditions and when the surgical risk is acceptable. Low morbid operations should be considered in patients with good performance status, with GPS grades A or B (i.e., if minor liver and peritoneal cytoreductive surgery is required). In patients requiring major liver resection, such as for bilobar liver metastases, a multistep strategy may be discussed following multidisciplinary discussions [13, 24].

When surgical exploration is indicated and validated by the expert anesthetists, it is commonly made through a large median incision. In patients with carcinoid syndrome the heart should be explored to eliminate carcinoid heart disease [35, 36]. Pre- and intraoperative preparations by somatostatin analogue therapy are usually indicated in patients with carcinoid tumors to avoid hemodynamic disorders due to tumor manipulation during the operation [35, 36]. The first step is to perform a detailed staging through a large midline incision (fig. 1). Then, reevaluation of the possibility of macroscopic R0/R1 cure should be undertaken. If an R0/R1 resection is not possible, palliative procedures such as internal bypass or resection of major nodules may be considered mainly to avoid postoperative complications. In a curative-intent setting, all of the upper and lower mesocolonic regions should be explored. A long and cautious dissection of abdominal quadrants (right and left diaphragmatic peritoneum, small and great omentum, posterior face of stomach, mesenteric axes, and the pelvis) is often necessary. Some organs such as the appendix and the great omentum, including its subsplenic portion en bloc with the great curve vessels, are easily removed. In females >55 years, it is usually recommended to remove both ovaries (after preoperative discussion and consent); in younger patients the ovaries are removed only if involved by metastases. All macroscopic nodules are removed or physically destroyed (some surgeons use argon laser) [29]. Multiple intestinal resections might be necessary; however, the risk/benefit ratio regarding the possibility of short bowel syndrome should be discussed with the patients. Peritonectomy is performed when required because of the extent of the disease [37, 38]. The pelvic peritoneum is removed if nodules are present in the Douglas bend (pouch).

After surgery, rather than using R0/R1 or R2 resection, it is more appropriate to use the completeness of cytoreduction (CCR) reflecting the quality of resection and the status of the residual PC. The CCR status is reported as follows: CCR-0 = no macroscopic nodule is visible at the end of cytoreduction; CCR-1 = residual microscopic nodules <2.5 mm; CCR-2 = residual nodules between 2.5 mm and 2.5 cm; CCR-3 = residual macronodules >2.5 cm [28]. It is worth noting that for PC from other origins (colorectal cancer, pseudomyxoma peritonei, ovarian cancer), the main prognostic factor of the overall survival following cytoreductive surgery is the CCR status at the end of the procedure and this is independent of the initial extent of the PC before surgery [8, 9, 28, 29]. In all reported studies (including one randomized trial [39]), when patients were CCR-0 or CCR-1 after cytoreductive surgery, a significantly better survival was observed as compared to when they were CCR-2 [9, 28, 29, 40].

Local Intraperitoneal Chemotherapy and Hyperthermic Intraperitoneal Chemotherapy

In analogy to the treatment of PC, and of nonendocrine primaries, some specialized centers with a low level of scientific strength suggest using perioperative intraper-

itoneal chemotherapy to treat residual disease and/or to halt progression of microscopic disease [2]. The rationale of postoperative local chemotherapy and/or intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is based on experimental studies showing the synergistic effect of surgery, heat and intraperitoneal chemotherapy [9, 29]. Cytoreductive surgery even when macroscopically complete treats only the visible disease; therefore, locoregional therapies such as HIPEC can target the residual microscopic disease right after surgery. Also, cytotoxics employed include mitomycin C (which acts on all four cell cycles), platinum derivates, doxorubicin and 5-FU. These are usually efficient in vitro for most solid tumors [9, 29]. Small tumor volumes (millimeters) come into direct contact with high doses of local chemotherapy for 30–90 min. The procedure is proven to be effective when performed immediately before formation of fibrin glue in the abdomen, decreasing its local action with a low systemic effect [9]. Interestingly, hyperthermia from 39 to 43°C significantly enhances the local penetration of cytotoxic drugs into tumor cells, synergizing the antitumor action of intraperitoneal chemotherapy even for cell lines which were resistant to those drugs in vitro at 37°C [9, 29].

Thus, cytoreductive surgery followed by intraperitoneal chemotherapy (or concomitantly with HIPEC) opens innovative fields of application for the treatment of PC. Several retrospective series and 4 randomized trials (1 for colorectal PC, 4 for ovarian PC) reported the results of this procedure [6, 9, 40]. The mortality rate varies from 0 to 10% and the morbidity rate from 10 to 60%. Therefore, the combination of such an aggressive procedure is restricted to patients with good performance status (those with normal renal function and adequate nutrition, excluding patients with a BMI <18 or other contraindications for major abdominal surgery) after multidisciplinary discussions. This strategy should also be avoided in patients with 'end-stage' disease when palliative HIPEC is proven to be ineffective and risky with the exception of highly selected cases [27]. Indeed, we believe that the presence of extensive disease and a GPS score grade C are definite contraindications to HIPEC. In patients with GPS grade A and some selected patients with GPS grade B, this procedure may be applied to treat both PC and LM, such as in the series reported by Elias et al. [2]. In some patients with synchronous diffuse liver and peritoneal metastases, the resection of both the primary tumor and gross macroscopic peritoneal nodules (with or without HIPEC) may allow future therapy to be directly focused on the liver metastases; this may help increase long-term survival and have a significant impact on quality of life [33]. To help decision-making as regards this strategy, preoperative staging laparoscopy would appear interesting [16, 23].

Minimal Consensus Statements on Surgery, Cytoreduction and Intraperitoneal Chemotherapy

Surgery may involve curative or palliative strategies. It may be necessary to avoid mechanical complications such as bowel obstruction. An R0/R1 resection should be discussed as regards risk/benefit ratios. High morbidity can be associated with extensive cytoreductive surgery for PC but this may impact positively on long-term survival (low scientific level). The CCR status is more appropriate than the estimation of R0/R1 resection.

Perioperative intraperitoneal chemotherapy or HIPEC is an experimental option that may increase survival (low scientific level). The combination of surgery and HIPEC has been examined in PC from colorectal cancer, pseudomyxoma and ovarian cancer; however, no data are available for PC of GEP-NET origin.

Medical Treatments

To date, most systemic therapies including streptozotocin-based chemotherapy are inefficient for patients with metastatic midgut (carcinoid) tumors [1]. Patients with PC from a pancreatic NET source may undergo combinations of streptozotocin and either doxorubicin or 5-FU or temozolamide-based therapy but results in patients with PC are unknown.

Minimal Consensus Statements on Medical Therapy

Patients with symptomatic intestinal occlusion or subocclusion require a number of standard measures: low-residue diet, use of antispasmodics and other analgesics but careful use of opiate medications (corticosteroid, antiemetic, anticholinergic). Most of the patients receive somatostatin analogue therapy either for carcinoid syndrome and/or to reduce intestinal secretion and symptoms related to PC [41–43]. In frank occlusion, nil per os with nasogastric suction is usually necessary; antisecretory drugs may help by decreasing the volume distal to the site(s) of obstruction. Few patients with frank occlusion benefit from endoscopic-radiological or surgical procedures such as gastrostomy or internal bypass [1, 44]. Notably, some patients receiving somatostatin analogues may have their occlusive symptoms increased under treatment [41–43]. The efficacy of other treatments such as peptide receptor radionuclide therapy for patients with PC has not yet been reported. Novel chemotherapeutic strategies using targeted therapies may hold promise in the future.

Follow-Up

In patients with well-differentiated GEP-NET, follow-up including clinical and biological examination is required every 3 months for the first 2 years and then every 6 months. Patients who had undergone chemotherapy or those who had had aggressive procedures could have a shorter evaluation every 3 months. Minimal biological examination includes serum chromogranin A and urinary 5-HIAA (if increased prior to initial therapy). CT scan of thorax and abdomen and other imaging examinations are indicated every 3–6 months after multidisciplinary discussions, taking into account major points including age, tumor origin, TNM stage, tumor differentiation and behavior, and previous and planned treatments.

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