Original Communications

Neuroendocrine carcinomas: Optimal surgery of peritoneal metastases (and associated intra-abdominal metastases)

Dominique Elias, MD, PhD,[a] Anaelle David, MD,[a] Isabelle Sourrouille, MD,[a] Charles Honoré, MD,[a] Diane Goéré, MD,[a] Frédéric Dumont, MD,[a] Annabelle Stoclin, MD,[b] *and* **Eric Baudin, MD,[c]**
Villejuif, France

Aim. *To report the results of complete cytoreductive surgery (CCRS) of peritoneal metastases from neuroendocrine tumor (NET) and to compare patients treated with or without hyperthermic intraperitoneal chemotherapy (HIPEC).*
Background. *Aggressive management of peritoneal metastases from NET (in most of the cases associated with other types of metastases) has not been addressed in the literature, but these metastases affect overall survival.*
Patients and methods. *From 1994 to 2012, 41 patients underwent CCRS, with HIPEC (*n *= 28) from 1994 to 2007 but without HIPEC (*n *= 13) from 2008 to 2012. Liver metastases were treated during the same operative procedure in 66% of the patients.*
Results. *Mortality was 2% and morbidity 56%. Overall survival at 5 and 10 years was 69% and 52%, respectively, and disease-free survival at 5 and 10 years was 17% and 6%, respectively. At 5 years, peritoneal metastases and liver metastases recurred in 47% and in 66% of cases, respectively. Overall survival was not different between patients treated with or without HIPEC, but disease-free survival was greater in the HIPEC group (*P *= .018), mainly because of fewer lung and bone metastases.*
Conclusion. *CCRS of peritoneal metastases from a NET is feasible in most of the patients and seems to increase survival rates. We were unable to determine whether adding HIPEC had a positive or a negative impact. (Surgery 2014;155:5-12.)*

From the Department of Surgery,[a] Intensive Care Unit,[b] and Neuroendocrine Oncologic Unit,[c] Gustave Roussy, Cancer Campus, Villejuif, France

Peritoneal metastases (PM) are considered a serious event in virtually all malignancies and usually portend a poor prognosis. The situation has been treated differently for PM related to neuroendocrine tumor (NET). Deemed infrequent, PM rarely are mentioned in series and generally are considered to exert no impact on overall survival (OS).[1-3] Furthermore, they are neglected frequently by surgeons who perform cytoreductive surgery directed at treating liver metastases. Conventional therapy consists in only treating obstruction of the gut and not resecting PM, and then eventually using hormonal therapy or systemic chemotherapy to treat distant residual disease.

Series reporting operatively treated patients with stage IV disease do not describe PM but simply mention that one third of the patients had intestinal obstruction.[1,3-5] In a preliminary study, we showed that PM was the direct cause of death in 40% of patients with NET in our center.[6]

The incidence of PM in patients with NET is approximately 17%, according to the following two large series: 17.5% among the 508 patients with gastrointestinal NET in the prospective French National Register[7] and 17% among the 603 consecutive small intestinal NET treated in Uppsala between 1985 and 2010[8]; these patients with PM comprise approximately 20% of all patients undergoing operative treatment.

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Reprint requests: Prof. Dominique Elias, MD, PhD, Gustave Roussy, 114 Rue Edouard Vaillant, 94805 Villejuif, France. E-mail: elias@igr.fr.

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NET-derived PM arise mainly from midgut tumors and usually are associated with other sites of distant metastases, notably liver metastases, and usually represent only a small part of the tumor load. Neglecting to treat PM but not liver metastases exposes patients to progressive peritoneal disease and the consequences of these PM. Death related to PM raises the question of treating PM with cytoreductive approaches as in other tumor types, whenever possible, but with the added difficulty of treating associated metastases (in the liver and lymph nodes) which also should be resected.

Since 1994, we have been treating NET-derived PM with complete cytoreductive surgery (CCRS) involving resection of other metastases whenever possible. During the first period (1994–2007), CCRS was combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in attempt to eradicate nonvisible residual foci of tumor on the peritoneum. Admittedly, HIPEC probably increases morbidity, and its impact by itself is unclear, making its use of unknown importance in patients undergoing an otherwise-extensive operation (PM, liver metastases, lymph nodes, primary). For this reason, we decided to perform CCRS alone without HIPEC during the second period (2008–2012). The aims of this study were to analyze the results of our use of CCRS to treat PM related to NETs and to determine whether adding HIPEC was beneficial.

PATIENTS AND METHODS

All patients who underwent macroscopically complete operative resection of well-differentiated, NET-derived PM between June 1994 and August 2012 in our institution were recorded prospectively and analyzed retrospectively. Histologic proof of PM was obtained, and the well-differentiated form was defined according to criteria published by the World Health Organization in 2000.[9]

Operative therapy was discussed systematically in multidisciplinary gastrointestinal tumor board meetings for patients in good general condition (World Health Organization performance status <2), and who had slow tumor growth under systemic treatment (but at least a 20% increase in tumor burden in the preceding in 12 months). The workup included a clinical examination; multiple endocrine laboratory tests; abdominal, pelvic, and thoracic computed tomography; ultrasonography; magnetic resonance imaging; bone scintigraphy; and somatostatin receptor scintigraphy. The concept of "optimal surgery" was proposed when the entire tumor burden (PM, primary tumor if present, liver metastases, ovaries and lymph node metastases) was deemed completely resectable or ablatable without creating a short gut syndrome.

There were two patient cohorts corresponding to two different periods. During the first period (1994–2007), all consecutive patients underwent CCRS of all visible PM followed by immediate HIPEC intraoperatively, whereas during the second period (2008–2012), all consecutive patients underwent CCRS alone without HIPEC.

The extent of peritoneal seeding was evaluated with the use of Sugarbaker's peritoneal index[10]: each of the 13 abdominal areas was allotted a score of between 0 and 3 points culminating in a total index ranging from 1 to 39. In this series, CCRS is defined as resection of all tumor deposits greater than 1 mm in diameter. Peritonectomies were performed according the principles described by Sugarbaker.[11] Liver metastases were treated during the same session with a partial hepatectomy, frequently and/or ultrasound-guided radiofrequency ablations.

Between 1994 and 2007, the protocol of HIPEC included intravenous infusion of 20 mg/m^2 of leucovorin followed by 400 mg/m^2 of 5-fluorouracil.[12,13] Then HIPEC was performed over 30 minutes at an intraperitoneal temperature of 43°C, with oxaliplatin alone or mixed with irinotecan, in 2 L/m^2 of 5% dextrose.[12] The doses of oxaliplatin were 460 mg/m^2 when given alone but 300 mg/m^2 when mixed with irinotecan (200 mg/m^2). Intraperitoneal oxaliplatin and irinotecan were chosen, because they have been demonstrated to be moderately effective in the treatment of NET[14-20] and because the tumor tissue concentration after HIPEC is 20-fold greater than when used intravenously.[12,13]

Postoperative morbidity was defined according to the Dindo-Clavien classification[21]: grade III, requiring operative, endoscopic, or radiologic intervention; grade IV, life- threatening complications, including central nervous system complications, requiring intensive care/intensive care unit management; and grade V, death of patient.

No somatostatin analog and no systemic chemotherapy was given in an adjuvant setting after an optimal procedure. Follow-up took place every 3 months during the first 2 years and every 6 months thereafter. Recurrent PM and recurrent liver metastases were defined according to radiologic criteria with the use of different techniques (abdominal ultrasonography, thoraco-abdomino-pelvic computed tomography, positron emission tomography, hepatic and abdominal magnetic resonance imaging, somatostatin receptor