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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

# The Chicago Consensus on Peritoneal Surface Malignancies: Management of Neuroendocrine Tumors

**Chicago Consensus Working Group**

Chicago, IL

**ABSTRACT** The Chicago Consensus Working Group provides multidisciplinary recommendations for the management of neuroendocrine tumors specifically related to the management of peritoneal surface malignancy. These guidelines are developed with input from leading experts including surgical oncologists, medical oncologists, pathologists, radiologists, palliative care physicians, and pharmacists. These guidelines recognize and address the emerging need for increased awareness in the appropriate management of peritoneal surface disease. They are not intended to replace the quest for higher levels of evidence.

## NEUROENDOCRINE TUMORS WITH PERITONEAL METASTASES

This article provides multidisciplinary recommendations for the management of peritoneal surface malignancies of neuroendocrine origin and constitutes 1 article in a series composed by the Chicago Consensus Working Group for the Management of Peritoneal Surface Malignancies.[1–10] Information regarding formation of the Chicago Consensus Group and explanation of the working group's consensus methodology is discussed elsewhere.[1,2]

The collaborators for the Chicago Consensus Working Group are listed in the acknowledgments.

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### *Principles of Surgery*

The incidence of peritoneal metastasis in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is estimated at approximately 20%. Most of these metastases originate from primary tumors in the midgut. Other sites of metastasis, such as liver and the lymph nodes, are frequently present in these patients.[11] Depending on the origin of the primary tumor, metastatic disease can be associated with 5-year survival rates of less than 50%.[12] Hepatic metastatic involvement and tumor grade are the most important prognostic factors.[13]

Because peritoneal metastases are not common in patients with GEP-NETs, insufficient data regarding surgical treatment are available. Most of the evidence is from level 2 and level 3 published articles, and recommendations are commonly extrapolated from studies of patients with GEP-NETs and liver metastases rather than peritoneal metastases.

Complete surgical excision of both the primary and metastatic disease remains the only potential curative option for patients with metastatic GEP-NETs. However, NETs are also one of the few tumor types in which debulking operations are recommended for patients with metastatic disease; several large retrospective studies showed that these procedures improve symptoms related to hormone hypersecretion and survival.[14–16] (See *Peritoneal Metastasis from Neuroendocrine Tumor Management Pathway*, Fig. 1).

Previous data suggested that cytoreduction surgery resulting in a 90% decrease in tumor volume is associated with improved overall survival.[16,17] Recently, however, this cytoreduction threshold has been lowered to 70% because several studies have shown that a survival benefit can be achieved at that level of cytoreduction.[15,18,19]

Primary tumor resection should be performed during cytoreductive surgery for GEP-NETs whenever possible (Fig. 1). Whether primary tumor resection has a role in the

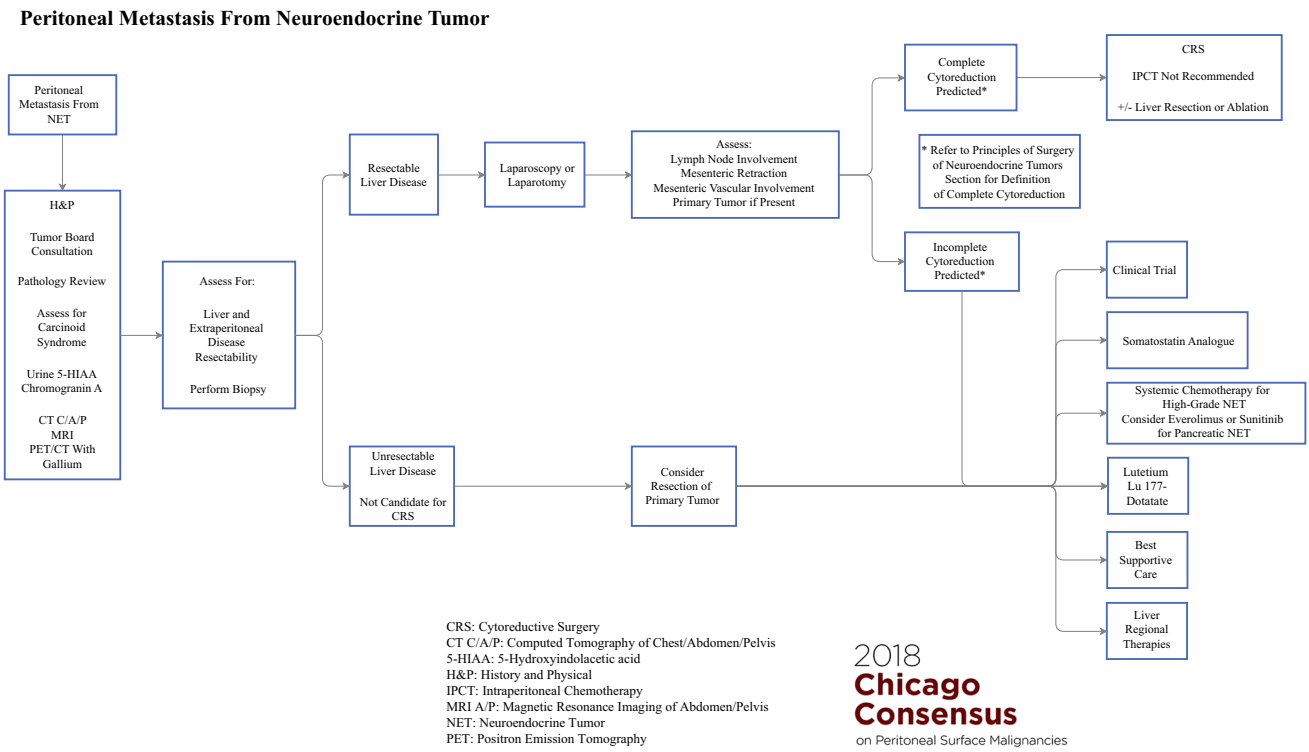


**FIG. 1** Peritoneal metastasis from neuroendocrine tumor management pathway

setting of unresectable distant disease is controversial, but increasing evidence supports this strategy. Several studies have shown improved survival for patients with unresectable distant disease undergoing primary tumor resection.[20,21]

*Principles of Systemic Therapy*

Medical management of stage IV GEP-NET is primarily effective at controlling tumor growth, with objective response rates to systemic treatments rarely occurring in more than 30% of patients.[22,23] The NETTER-1 trial, comparing 177 Lu-DOTA0-Tyr3-octreotate with octreotide long-acting release (LAR), has shown a clear benefit of one systemic therapy over another in the setting of metastatic NET.[24] No trials have specifically examined the efficacy of systemic therapy for peritoneal metastases. Therefore, no current guidelines indicate which systemic therapy should be used first. The following evidence supports using systemic therapies when surgical cytoreduction is not possible or not desired.

*Octreotide LAR* The PROMID study compared octreotide LAR at a dose of 30 mg every 28 days with placebo in 85 patients with well-differentiated metastatic midgut NETs. The authors reported a median progression-free survival (PFS) of 14.3 months in the group randomized to receive octreotide LAR, as compared with 6 months in the placebo group.[22] Similarly, the CLARINET study reported a significant improvement in PFS in patients treated with lanreotide (median PFS not reached) compared with placebo (median PFS of 18 months).[25]

*Everolimus* The RADIANT-3 trial prospectively randomized 410 patients with advanced, low-grade, or intermediate-grade pancreatic NETs to receive everolimus 10 mg daily or placebo. The median PFS for patients receiving everolimus was 11 months, as compared with 4.6 months in the placebo group.[12] The objective response rate was 5%. Although 92% of patients in this study had liver metastases, no data were available for study drug efficacy according to liver tumor burden or peritoneal disease.[12]

The RADIANT-4 trial prospectively analyzed the efficacy of everolimus administered at a dose of 10 mg daily in 205 patients with advanced, progressive, well-differentiated, nonfunctional NETs of lung or gastrointestinal origin (excluding pancreas). The median PFS for patients randomized to receive everolimus was 11 months, as compared with 3.9 months in the placebo group. The objective response rate was 2% for everolimus.[26]

*Sunitinib* Sunitinib was evaluated in 171 patients with advanced, well-differentiated pancreatic NETs. Median PFS was 11.4 months in the sunitinib group and

5.5 months in the placebo group.[27] In this study, 95% of patients had liver metastases and the objective response rate was 9.3% in the sunitinib group, but no data were provided for study drug efficacy according to liver or peritoneal tumor burden.

## 177 LU-DOTA0-TYR3-OCTREOTATE

The NETTER-1 trial prospectively studied the benefit of lutetium Lu 177-dotatate in patients with progressive, well-differentiated, metastatic midgut NETs. The study included 229 patients, 116 in the Lu 177-dotatate group (Lu 177-dotatate plus 30 mg intramuscular octreotide LAR) and 113 in the control group (60 mg intramuscular octreotide LAR). The median PFS was not reached in the Lu 177-dotatate group and was 8.4 months in the octreotide LAR group. The objective response rate was 18% in the Lu 177-dotatate group and was 3% in the control group, with 1 patient having a complete response. Adverse events that led to withdrawal from the trial occurred in 6% of patients in the Lu 177-dotatate group and 9% in the control group. The most common adverse events among patients in the treatment group were nausea (59%) and vomiting (47%). It should be noted that most patients had metastases to the liver or lymph nodes. However 7% of the patients did have peritoneal metastasis (7 in the treatment group and 10 in the control group).[24]

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