Emerging Approaches in the Management of Patients with Neuroendocrine Liver Metastasis: Role of Liver-Directed and Systemic Therapies

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Neuroendocrine tumors (NETs) are rare neoplasms arising from cells of the neuroendocrine system in a multitude of anatomic locations, and representing a wide range of histologies. Compared with other malignancies from the same organ (eg, pancreatic NET vs pancreatic ductal adenocarcinoma), NETs are often indolent in both biology and disease progression. However, metastasis will develop in almost 40% of patients with NETs during the course of their disease, most commonly to the liver.[1] In contrast to other malignancies, in a proportion of patients with neuroendocrine liver metastasis (NELM) disabling clinical symptoms can develop secondary to the production of specific biogenic amines and polypeptide hormones. Therefore, treatment of patients with NELM is focused on optimizing quality of life through reduction of such hormone-related symptoms, and improving survival in patients with disease amenable to liver-directed therapy, including hepatic resection, thermal ablation, and intra-arterial therapy (IAT).[2-8] To date, hepatic resection remains the only potentially curative option for patients with NELM, with 5-year survival after hepatectomy ranging from 60% to 80% in recent series.[6-11] Until recent reports of the use of somatostatin analogues in neuroendocrine tumors of mid-gut origin, and sunitinib and everolimus in patients with advanced pancreatic NETs (PNETs), there has been little success in the use of systemic therapy to treat patients with advanced NELM, with historic responses ranging from 15% to 20%.[12-15] As these systemic agents are not curative, there is still considerable interest in the use of liver-directed therapy to increase patient survival and address hormonally related symptoms. In addition to surgery, IAT has emerged as an alternative liver-directed approach to treat patients with NELM. We review the management of patients with NELM with an emphasis on clarifying the relative roles of surgery, IAT, as well as emerging systemic therapeutic agents. To accomplish this, we performed an extensive literature search in PubMed using medical subject headings (ie, neuroendocrine, carcinoid, liver metastasis, hepatic metastases, hepatectomy, liver resection, transplantation, intra-arterial therapy, radiation therapy, chemotherapy) to identify relevant articles for inclusion.

Patient evaluation

Classification of neuroendocrine tumors

Neuroendocrine tumors encompass a diverse set of rare neoplasms arising most commonly throughout the gastrointestinal tract and bronchopulmonary tree. Pancreatic NETs originate in the endocrine tissues of the pancreas, and carcinoid tumors arise in neuroendocrine cells in the bronchopulmonary tree, small intestine, appendix, rectum, and thymus. These tumors can vary in degree of differentiation and hormonal secretion. Within the gastrointestinal tract, NETs most commonly arise in the small bowel (42%), rectum (27%), appendix (5%), and stomach (9%).[1] The potential for metastatic disease is dependent on location and cell of origin. An analysis of Surveillance, Epidemiology, and End Results data in the 1990s suggested that NETs of pancreatic origin have the greatest potential for distant metastasis, and the lowest incidence was observed for bronchopulmonary and rectum sites.[1]

In 2000, under the auspices of the WHO, an NET classification system was proposed that had 3 distinct categories: well-differentiated tumors with benign or uncertain behavior, well-differentiated carcinoma with malignant characteristics, and poorly differentiated carcinoma.[16-18] Since 2000, this classification system has been updated, with the most recent changes made in 2010. The 2010 WHO classification takes into account the anatomic location of origin, specific amine or hormonal production, mitotic activity, and the proliferative index

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Abbreviations and Acronyms

IAT = intra-arterial therapy
NELM = neuroendocrine liver metastasis
NET = neuroendocrine tumors
OLT = orthotopic liver transplantation
PFS = progression-free survival
PNET = pancreatic neuroendocrine tumor
RFA = radiofrequency ablation
TACE = transarterial chemoembolization
Y-90 = Yttrium-90

as defined by Ki-67 (Table 1).[19] Components of this version of the WHO system classification were partially incorporated into the 7th edition of the American Joint Committee on Cancer staging manual, as well as into the recent National Comprehensive Cancer Network practice guidelines.[20,21] However, it is important to note that the 7th edition of the American Joint Committee on Cancer classification system has applied the TNM staging system of pancreatic adenocarcinoma to PNETs without considering mitotic count, Ki-67 staining, or hormonal production, which are essential components of the WHO 2010 classification schema.

Presentation

Patients with NELM are diverse in their clinical presentation. Overall, approximately two thirds of patients report symptoms that are attributable to their primary or hepatic metastasis.[8] Depending on the hormonal functional status of the cancer, the patient might exhibit some of the hallmark syndromes associated with varied primary NET histologies (eg, carcinoid syndrome from carcinoid primaries, hypoglycemic episodes from insulinomas, necrolytic migratory erythema from glucagonomas, etc). In the largest study to date, of 753 patients with NELM undergoing surgical management (resection ± ablation) or IAT, Mayo and colleagues reported that between 25% and 50% of patients presented with hormonally related symptoms.[8] The degree of symptoms is often directly related to the extent of hepatic disease burden and ultimately can lead to both a decreased quality of life and worse long-term survival.[1,3-6] Aside from hormonal symptoms, patients with synchronous primary and hepatic disease can present with symptoms from the primary tumor, with abdominal cramping often being the initial symptom.[7]

Among patients with NELM, it is estimated that close to 50% of patients will present with synchronous liver metastasis, and in the other half of patients, metachronous liver disease will develop during the course of their life.[2,7] Regardless of presentation, patients often seek and benefit from hepatic cytoreduction for relief of their hormonal or other symptoms.[22] Sarmiento and colleagues reported that hepatic cytoreduction of 90% reduced endocrine-related symptoms in 90% of patients.[6] Cytoreduction, in addition to alleviating symptoms, might also be associated with improved long-term survival, although the data are retrospective and need to be interpreted with caution.[6,22,23] In addition, the degree of hepatic cytoreduction necessary to achieve symptomatic relief is not based on any prospective, randomized data, largely due to the rarity of patients with NELM eligible for surgical management.

Liver-directed therapy

Surgery: resection and ablation

Resection of the both the primary NET and the hepatic disease remains the mainstay of treatment for patients with NELM. Patients with untreated hepatic metastasis have a 5-year survival rate in the range of 20% to 40%.[2,3,24] The relatively long 5-year survival rate among

Table 1. World Health Organization Classification of Gastrointestinal and Pancreatic Neuroendocrine Tumors

Behavior	Metastasis	Size, cm	Muscularis propria invasion	Differentiation	Angio-invasion	Ki-67, %	Hormonal index
WHO criteria, gastrointestinal							
Benign	−	≤1	−	Well	−	<2	−
Benign/low-grade malignant	−	1−2	−	Well	±	<2	−
Low-grade malignant	+	>2	+	Well	+	2−20	+
High-grade malignant	+	Any	+	Poorly	+	>20	−
WHO criteria, pancreas							
Benign	−	≤1	−	Well	−	<2	−
Benign/low-grade malignant	−	1−2	−	Well	±	<2	±
Low-grade malignant	+	>4	+	Well	+	2−20	±
High-grade malignant	+	Any	+	Poorly	+	>20	−