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The Diagnosis and Management of Neuroendocrine Carcinoma of Unknown Primary

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1. Introduction

In 1907, the pathologist Siegfried Oberndorfer first coined the term “carcinoid” to describe neoplasms located in the submucosa of the ileum (Oberndorfer 1907). These small intestinal neoplasms were typically small and often multifocal. Their borders were well circumscribed. Although he initially erroneously asserted that carcinoid tumors did not metastasize, he later recognized their malignant potential.

One hundred years after Oberndorfer’s initial description of carcinoid tumors, the preferred term for these neoplasms is neuroendocrine tumors (NETs). Compared with other neoplasms, NETs are rare. However, the incidence of NETs is increasing, occurring in 5.25 individuals per 100,000 persons per year in the United States (Yao, Hassan et al. 2008). Neuroendocrine tumors most commonly arise from the gastrointestinal (GI) tract and bronchopulmonary (BP) tree. Histologically, NETs vary from well differentiated to poorly differentiated and are characterized by expression of neuroendocrine markers like chromogranin A and synaptophysin. Uptake of tracer using somatostatin receptor scintigraphy is also common in well differentiated tumors.

Hormone production occurs in a minority of patients, but can cause a range of clinical syndromes, including: hypoglycemia (insulin), recurrent ulcers/diarrhea (gastrin), glucose intolerance (glucagon), watery diarrhea (vasointestinal peptide), and diarrhea, flushing, palpitations, right-sided heart valve dysfunction (serotonin). Poorly differentiated NETs are rare but can arise in nearly any location. They are associated with a poor prognosis and have a high predilection for metastases. As such, systemic chemotherapy (with a small cell lung cancer regimen) is the mainstay of therapy. Treatment for localized well differentiated tumors is surgical. Patients with advanced disease may benefit from treatment to control hormone-mediated symptoms and/or disease progression. Treatment options are evolving and include somatostatin analogs, liver-directed approaches, systemic chemotherapy, peptide receptor radionuclide therapy, interferon, and newer targeted agents (e.g. sunitinib and everolimus). The recent approval of everolimus and sunitinib in pancreatic NET specifically highlights the importance of identifying the primary site. Despite extensive

evaluation, some patients are diagnosed with neuroendocrine carcinoma of unknown primary, presenting a major therapeutic challenge in the face of therapies that are increasingly disease- and site-specific.

2. Epidemiology

Patients with neuroendocrine carcinoma of unknown primary present unique clinical challenges. In a recent epidemiological study, a primary tumor site was not identified in up to 4,752 (13%) of 35,618 patients with NETs (Yao, Hassan et al. 2008).

3. Diagnostic methods used to identify the primary site

Currently, there are no clear recommendations for how best to identify the primary site in patients with advanced neuroendocrine carcinoma and an elusive primary site.

3.1 Rationale for identifying the primary site

The value of identifying the primary site depends largely on the tumor's differentiation and grade. Recognizing the fact that randomized trials are lacking, patients with advanced extra-pulmonary poorly differentiated or high grade (e.g. small or large cell) NETs are typically treated with a small cell lung cancer chemotherapy regimen. In contrast, identification of the primary site in patients with well differentiated (low and intermediate grade) NETs may directly influence treatment decisions and prognosis. Well differentiated NETs of the midgut are often associated with symptoms consistent with traditional carcinoid syndrome and may cause bleeding and obstruction from the primary tumor and regional adenopathy/fibrosis but tend to be relatively indolent. In contrast, rectal tumors do not typically cause hormone-mediated symptoms.

Some systemic treatments have selective use in NETs of known primary sites. Octreotide has been proven to improve outcomes in midgut carcinoids (Rinke, Muller et al. 2009), whereas the molecularly targeted agents sunitinib and everolimus are indicated for treatment of pancreatic NETs specifically (Raymond, Dahan et al. 2011; Yao, Shah et al. 2011). Furthermore, pancreatic NETs tend to be more sensitive to chemotherapy than carcinoids (Nakakura, Venook et al. 2007). Within carcinoid tumors, emerging data suggests that tumors of bronchial and thymic origin may be particularly sensitive to temozolomide (Ekeblad, Sundin et al. 2007). Therefore, identification of the primary site may assist in prioritizing systemic treatment options and may shed light on the role of surgical intervention in a given patient (especially in the setting of resectable metastatic disease).

3.2 Methods for identifying the primary site

Imaging identifies most pancreatic NET primaries. In a recent study, computed tomography (CT) identified the majority of pancreatic NETs (84% [n=231]) (Khashab, Yong et al. 2011). This sensitivity was greater in nonfunctional pancreatic NETs (92% [n=173]). In the same study, 56 patients had combined CT and endoscopic ultrasound (EUS) imaging; EUS detected 91% [n=22] of pancreatic NETs (i.e., insulinomas) not identified on CT. Therefore, as most pancreatic NET primaries are found with CT, EUS, or hormone marker tests, the

pancreas is unlikely to account for a large fraction of NETs of unknown primary once the appropriate work-up has been done.

Various diagnostic methods have been explored for detecting the primary site in the context of nonpancreatic, well differentiated NETs, which typically arise in the foregut, midgut or hindgut (i.e., carcinoid tumors). Published studies focusing on the diagnostic work-up are almost always limited by a small sample size. In particular, CT, somatostatin receptor scintigraphy, enteroclysis, capsule endoscopy, and magnetic resonance imaging enteroclysis have all been found to have some utility for identifying the primary tumor (Picus, Glazer et al. 1984; Sugimoto, Lorelius et al. 1995; Bader, Semelka et al. 2001; van Tuyl, Kuipers et al. 2004; Johanssen, Boivin et al. 2006). Recently, the sensitivity of diagnostic methods for locating primary tumors in a larger number of patients with well differentiated NET liver metastases was reported by Wang et al. (Wang, Parekh et al. 2010). Computed tomography (35% [n=78]) and somatostatin receptor scintigraphy (26% [n=42]) were not sensitive in detecting the primary sites. For patients with colonic NETs, colonoscopy detected most primary tumors (87% [n=15]).

In the study by Wang et al., 15 patients with NET liver metastases and unknown primary tumor underwent surgical exploration, 7 of which were laparoscopic. The primary tumor was located in most (87%) patients (Wang, Parekh et al. 2010). All identified tumors were in the small intestine. They were small in diameter (1.4 cm), and more than half (54%) were multifocal. Another study also found that surgical exploration successfully localized and resected occult primary NETs in 17 of 22 (77%) patients (Boudreaux, Putty et al. 2005). Based on these data, for patients with well differentiated (low and intermediate grade) unknown primary tumors and NET liver metastases, a multidisciplinary team assessment for possible surgical exploration and resection of occult primary tumors should be considered. Before surgery, a CT scan, somatostatin receptor scintigraphy, and upper/lower endoscopy should be done (Wang, Parekh et al. 2010). EUS may be of value in identifying the location of an insulinoma (Khashab, Yong et al. 2011).

Immunohistochemical analyses using various markers are also emerging as potentially powerful tools for identification of the primary site for NETs. Expression of PAX8 or ISL1 is suggestive of a pancreatic primary tumor (Schmitt, Riniker et al. 2008; Haynes, Sangoi et al. 2011). Although CK7 and CK20 have been reported to be specific for BP- and GI-NETs, respectively (Cai, Banner et al. 2001), these findings were not corroborated by a larger study (Chu, Wu et al. 2000). TTF expression appears to be specific for BP-NETs (Agoff, Lamps et al. 2000; Oliveira, Tazelaar et al. 2001; Du, Goldstraw et al. 2004; Saqi, Alexis et al. 2005; Lin, Saad et al. 2007; Srivastava and Hornick 2009); however, its sensitivity is low and variable (Matoso, Singh et al. 2009). CDX2 is specific for GI-NETs, but it also has low and variable sensitivity and is not a good marker for pancreatic NETs (Saqi, Alexis et al. 2005; Lin, Saad et al. 2007; Srivastava and Hornick 2009). NKX2.2 is a highly sensitive and specific marker for GI-NETs, including NETs of the stomach, duodenum, ampulla of Vater, pancreas, ileum, and colon (Wang, Gallego-Arteche et al. 2009; Wang, Iezza et al. 2010). In the future, use of a panel of markers may be particularly informative (Srivastava and Hornick 2009).

Chromosomal abnormality and molecular gene profiling may have an increasing role in identifying tumor type. Jiao et al. recently reported that mutations of DAXX/ATRX, MEN1, and mTOR pathway genes are frequent in pancreatic NETs (Jiao, Shi et al. 2011).

Cunningham et al. suggest that chromosome 18 aberrations are common in both sporadic and familial ileal NETs (Cunningham, Diaz de Stahl et al. 2011). Recently, Erlander et al. recently reported on the use of a 92-gene real-time PCR assay for tumor classification used to compare the gene expression profile of an unknown sample to that of known tumors in a reference database (Erlander, Ma et al. 2011). This reference database includes NETs, such as small intestinal, BP, and pancreatic NETs. While these advances related to chromosome and gene profiling hold promise for the identification of unknown primary NETs, additional work is needed before these techniques can become standard of care.

4. Treatment and outcome

Tumor grade is of paramount importance in determining the treatment and outcome for patients with neuroendocrine carcinoma of unknown primary (Stoyianni, Pentheroudakis et al. 2011). As such, a precise determination of grade is essential. Additional tissue should be obtained if the initial sample is inadequate. Current data support that measures of proliferation rate are critical in determining grade (i.e., Ki67 index and mitotic counts). Therefore, grade is a standard feature of pathology reports describing NETs and forms the basis of the most recent NET pathology guidelines (Klimstra, Modlin et al. 2010).

4.1 Treatment of well differentiated (low and intermediate grade) unknown primary NETs

For patients with well differentiated (low and intermediate grade) NET liver metastases and an unknown primary tumor, a multidisciplinary evaluation for possible surgical exploration and resection of occult primary tumors should be considered. Interestingly, Dr. Oberndorfer's initial description of carcinoids included 6 patients with tumors arising from the ileum (Oberndorfer 1907). Over 100 years later, the jejunum/ileum remains one of the most common sites from which GI-NETs arise (Modlin, Shapiro et al. 2004). Despite their small size, NETs of the small intestine cause a characteristic fibrosis of the mesentery, leading to bowel obstruction, ischemia, or perforation in approximately one-third of patients (Makridis, Oberg et al. 1990; Boudreaux, Putty et al. 2005). Thus, the accepted standard of treatment for locoregional disease is resection of the small intestinal primary tumor and regional lymph nodes/fibrosis.

For a limited number of patients with liver metastases, hepatic resection appears to improve survival (Chen, Hardacre et al. 1998; Norton, Fraker et al. 2006). If complete resection of metastases is feasible, this should be considered. However, most patients are not candidates for liver resection because of extensive disease. For these patients, resection of the primary tumor could be beneficial. Two studies reported that resection of the midgut carcinoid primary tumor may be associated with improved outcome, even in the setting of unresectable liver metastases (Hellman, Lundstrom et al. 2002; Givi, Pommier et al. 2006). For carefully selected patients with unresectable NET liver metastases, some recommend that the primary tumor be localized and resected, even in asymptomatic patients (Boudreaux, Putty et al. 2005; Givi, Pommier et al. 2006; Wang, Parekh et al. 2010).

If surgery is not deemed prudent, patients with unknown primaries should be treated similarly as if they have advanced well differentiated NETs, assuming a pancreatic primary has been excluded (Nakakura, Venook et al. 2007; Stoyianni, Pentheroudakis et al. 2011). In

particular, treatment with somatostatin receptor analog therapy (i.e., octreotide) should be considered, especially for those with carcinoid syndrome. The results from the PROMID study suggest that octreotide has an antitumor effect in midgut carcinoids in addition to controlling hormone-mediated symptoms--the indication for which it has FDA approval (Rinke, Muller et al. 2009). In this placebo-controlled, double-blind, prospective study, patients treated with octreotide had a 14.3 month median time to progression compared to 6 months in the placebo group (Rinke, Muller et al. 2009). Of note, the primary site was unknown in 21 patients, and these patients were considered eligible for the study; however, NETs of the lung, pancreas, and other sites were excluded. Importantly, the optimal timing of treatment in patients with nonfunctional tumors (i.e., at diagnosis or after documented disease progression) and the value specifically in unknown primary tumors remains somewhat uncertain.

Unfortunately, aside from octreotide, systemic treatment options are extremely limited for advanced, nonpancreatic, well differentiated NETs (Chan and Kulke 2011; Strosberg, Cheema et al. 2011). Interferon is associated with stability and biochemical control in some cases, but radiographic responses are rare. There are little data to support cytotoxic chemotherapy in well differentiated NETs, although streptozotocin-based regimens may have limited activity at the expense of toxicity (Nakakura, Venook et al. 2007). Temozolamide-based regimens have emerged as potentially active in pancreatic and poorly differentiated NETs (Strosberg, Fine et al. 2011; Welin, Sorbye et al. 2011). Nevertheless, many believe that cytotoxic chemotherapy should be an option for patients who have failed other therapies, recognizing that no standard regimen exists (Boudreaux, Klimstra et al. 2010). Additional treatments are needed, and enrollment on clinical trials is encouraged.

Emerging data suggest that vascular endothelial growth factor (VEGF) and mTOR are valid targets for therapy in pancreatic NETs, as evidenced by the recent approval of sunitinib and everolimus in this disease (Raymond, Dahan et al. 2011; Yao, Shah et al. 2011). The value of these agents in well differentiated NETs arising outside of the pancreas is uncertain. In the RADIANT-2 study, patients with progressive nonpancreatic well differentiated NETs and a history of carcinoid syndrome were randomized to receive everolimus or placebo. While a trend towards improved progressive free survival was seen with the mTOR inhibitor, the results were not statistically significant, hence the agent is not approved for this indication. Phase III trials with a VEGF inhibitor have not been completed in carcinoid, although SWOG-0518 is ongoing (bevacizumab plus octreotide LAR vs. placebo plus octreotide LAR).

For patients with clinically significant progressive disease in the liver, liver directed therapy (e.g., arterial embolization, chemoembolization, radioembolization, or ablative therapy), may be considered although randomized trials are lacking (Nakakura, Venook et al. 2007). Accumulating data with peptide receptor radionuclide therapy (PRRT) suggest that this modality might hold promise for patients with advanced NETs (Bodei, Pepe et al. 2010).

4.2 Treatment of poorly differentiated (high grade) NETs of unknown primary

For patients with poorly differentiated (high grade) neuroendocrine carcinoma of unknown primary, chemotherapy with a small cell lung cancer regimen (i.e., platinum-based therapy, such as etoposide and cisplatin) should be considered (Nakakura, Venook et al. 2007;

Stoyianni, Pentheroudakis et al. 2011). A study of etoposide and cisplatin in patients with poorly differentiated NETs had an objective response rate of 41.5%, an 8.9 month median progression-free survival, and 15 month median overall survival (Mintry, Baudin et al. 1999). Other regimens include carboplatin- and irinotecan- based combinations, which are also small cell lung cancer regimens (Strosberg, Coppola et al. 2010). These tumors carry a poor prognosis.

4.3 Outcome of well differentiated (low and intermediate grade) unknown primary tumors

Patients with well differentiated neuroendocrine carcinoma of unknown primary may exhibit a relatively indolent course similar to those with advanced well differentiated NETs arising from the GI tract and BP tree (Stoyianni, Pentheroudakis et al. 2011). In a study by Kirshborn et al., patients with advanced midgut NETs (i.e., arising from the jejunum, ileum, and cecum) and those with neuroendocrine carcinoma of unknown primary shared similar serotonin levels as assessed by urine 24 hours hydroxyindoleacetic acid and serotonin levels, as well as by serum and platelet serotonin levels (Kirshbom, Kherani et al. 1998). Moreover, patients with advanced midgut NETs and neuroendocrine carcinoma of unknown primary shared similar 10-year survival rates (28% and 22%, respectively).

In a larger study, Yao et al. analyzed the outcomes of nearly 36,000 patients with NETs and found that primary site was probably the most useful predictor of outcome for patients with well differentiated NETs (Yao, Hassan et al. 2008). Patients with a liver primary and localized disease (i.e., disease confined to the liver) had a 5-year survival rate of 43%; this compared favorably with a 5-year survival rate of 54% for patients with a jejunum/ileum primary and distant disease. Not surprisingly, for patients with a liver primary and distant disease (i.e., widely metastatic disease), the prognosis was poor with a 0% survival rate at 10-years.

4.4 Outcome of poorly differentiated (high grade) NETs of unknown primary

Patients with poorly differentiated (high grade) neuroendocrine carcinoma of unknown primary clinically resemble those with aggressive small cell lung cancer (Nakakura, Venook et al. 2007; Stoyianni, Pentheroudakis et al. 2011). That is, their disease frequently responds to platinum-based therapy but inevitably becomes refractory. These patients have a poor prognosis with a median survival typically less than 1 year.

5. Conclusion

The diagnosis and management of patients with neuroendocrine carcinoma of unknown primary is challenging. Tumor grade directs treatment and is prognostic. Patients with well differentiated (low and intermediate grade) NETs may benefit from identification of the primary site because it may influence prognosis, but also because the available treatments we have are increasingly site-specific (e.g. octreotide for midgut tumors, and chemotherapy, everolimus and sunitinib for pancreatic NETs). In some settings, the type and timing of surgical intervention may also be dictated by the primary site. In contrast, patients with

poorly differentiated (high grade) neuroendocrine carcinoma of unknown primary clinically resemble those with aggressive small cell lung cancer: Patients with advanced high grade tumors tend to experience an aggressive course (regardless of primary site). As such, they should be assessed for possible treatment with a small cell lung cancer regimen (i.e., platinum- or irinotecan-based chemotherapy regimens).

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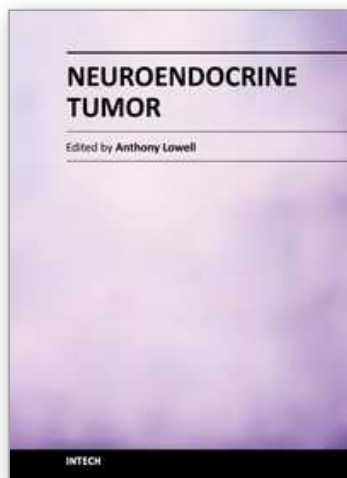
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