Well-Differentiated Duodenal Tumor/Carcinoma (Excluding Gastrinomas)

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Introduction

Duodenal neuroendocrine tumors (NETs) are located in the duodenum and may or may not be associated with a functional clinical syndrome. The term duodenal NET includes all duodenal tumors with neuroendocrine (NE) features as determined by histological/immunohistochemical methods including positivity for NET cytosolic markers [neuron-specific enolase (NSE), PGP 9.5] or secretory vesicle proteins [chromogranin A (CgA), synaptophysin] and also frequently the presence of specific gastrointestinal (GI) hormones [1–6]. The term duodenal NET in this paper refers to tumors included in different studies classified as: duodenal carcinoid; duodenal gastrointestinalpancreatic (GEP) tumor; duodenal pancreatic endocrine tumor (PET); duodenal gastrinoma; duodenal somatostatinoma; gangliocytic parangangioma; ampullary carcinoid or somatostatinoma; argentaffin carcinoid producing serotonin of the duodenum; psammomatus somatostatinoma; duodenal neuroendocrine carcinoma, poorly differentiated and small-cell neuroendocrine carcinoma of the duodenum [4]. The latter will be covered in the paper on poorly differentiated tumors and thus only referred to here. The clinical and management aspect of duodenal gastrinomas are included in the ‘Endocrine tumors of the pancreas – gastrinoma’ section and duodenal gastrinomas will only be consider in this section in comparison with the other duodenal NETs.

Epidemiology and Clinico-Pathological Features

Minimal Consensus Statement on Epidemiology

Duodenal NETs comprise 1.8% of all carcinoid tumors in the ERG Group (1950–1969); 2–3% of the Third NCS Survey (1969–1971); 1.9% of the early SEER Registry (1973–1991); 3.8% of the Late SEER Registry (1992–1999), and 2.8% of the PAN-SEER Registry (1973–1999) [3, 7, 8]. Primary duodenal neoplasms occur in 0.03–0.05% of all autopsies [9]. Duodenal NETs comprise 1–3% of all primary duodenal tumors [2].
Clinicopathological Features – General

In other studies, duodenal NETs were classified generally into five different tumor types [1]. These included duodenal gastrinomas; somatostatinomas; nonfunctional duodenal NETs which were not associated with a clinical syndrome but often demonstrated hormones with immunohistochemistry including serotonin and calcitonin; duodenal gangliocytic parangangiomas, and poorly differentiated neuroendocrine carcinomas [1, 4]. Many studies also differentiated ampulla of Vater or periampullary NETs because numerous studies demonstrated they differed from other duodenal NETs clinically, histologically and in their growth behaviors [10–15]. Ampullary NETs are frequently associated with von Recklinghausen’s disease and often show somatostatin immunoreactivity, but almost never produce the clinical features of the somatostatinoma syndrome [4, 6, 10, 13, 16–20].

In older studies reporting on the 5 types of duodenal NETs, duodenal gastrinomas were the most frequent (mean 48.3% of all duodenal NETs, range 27–58%, 9 series) [4, 6, 10, 11, 21–27]; followed by somatostatinomas (mean 43 ± 6%, range 23–75%, 9 series) [4]; nonfunctional serotonin-containing tumors (mean 27.6 ± 7.2%, 6 series) [4]; nonfunctional calcitonin-containing NETs (mean 9 ± 2.5%, 4 series) [4], and finally rare gangliocytic parangangiomas or neuroendocrine carcinomas.

More than 90% of all duodenal NETs arise in the first and second part of the duodenum [4, 21, 22, 24, 26]. This has been well studied for duodenal gastrinomas [5, 6, 10, 21, 22, 24, 25, 27, 28] where 58% arise in D1, 33% arise in D2, 5% in D3 and 4% in D4 [29–33]. Approximately 20% (mean 18 ± 5%, 6 series) of duodenal NETs occur in the periampullary region [4].

Duodenal NETs are generally small with a mean size of 1.2–1.5 cm in seven series [4] and >75% are <2 cm in diameter [4, 5, 10, 11, 24, 25, 28]. Duodenal NETs are usually limited to the submucosal or mucosa; however, they are associated with regional lymph node metastases in 40–60% [1, 4, 30, 34–36]. Liver metastases generally occur in <10% of all patients with duodenal NETs (mean 9 ± 6%, 5 series) [4].

Duodenal NETs are generally single lesions with multiple tumors detected in only 9 ± 3% (5 series) [4, 11, 21, 24–26]. Multiple tumors should lead to a suspicion of multiple endocrine neoplasia type 1 (MEN1). MEN1 occurs in 6 ± 2.5% of all patients with duodenal NETs (mean, 8 series) [4, 6, 10, 21–23, 25–27]. However, MEN1 occurs in 20–30% of all patients with duodenal NETs with Zollinger-Ellison syndrome [34, 37–39].

Duodenal gangliocytic parangangiomas generally occur in the periampullary region [1, 12, 26, 40, 41]. These tumors may be large and invade the muscularis propria, but generally pursue a benign course [4, 11, 15, 42].

A WHO classification has recently been proposed for duodenal/jejunal NETs that will allow a better comparison to NETs in other locations [1]. This classification is summarized in the specific section below with a few other important points covered in the general clinicopathological section above.

Minimal Consensus Statement on Clinicopathological Features – Specific

Classification

1 Well-differentiated neuroendocrine tumor (carcinoid) (50–75%). (Percentage of all duodenal NETs. Modified from Kloppel et al. [1].)

Benign: nonfunctioning, confined to mucosa-submucosa, nonangioinvasive, ≤1 cm in size.

– Gastrin-producing tumor (upper part of the duodenum)
  – Serotonin (5-HT)-producing tumor
  – Gangliocytic parangangioma (any size and extension, periampullary)

Benign or low-grade malignant (uncertain malignant potential): confined to mucosa-submucosa, with or without angioinvasion, or >1 cm in size

– Functioning gastrin-producing tumor (gastrinoma), sporadic or MEN-associated
  – Nonfunctioning somatostatin-producing tumor (ampullary region) with or without
  – Neurofibromatosis type 1 nonfunctioning serotonin-producing tumor

2 Well-differentiated neuroendocrine carcinoma (malignant carcinoma) [25–50%]

Low-grade malignant: invasion of the muscularis propria and beyond or metastases

– Functioning gastrin-producing carcinoma (gastrinoma), sporadic or MEN-associated
  – Nonfunctioning somatostatin-producing carcinoma (ampullary region) with or without
  – Neurofibromatosis type 1 nonfunctioning serotonin-producing tumor

3 Poorly differentiated neuroendocrine carcinoma [<1–3%]

– High-grade malignant

Clinicopathological Features

Although >95% of duodenal NETs synthesize GI peptides/amines, 90% are not associated with a functional syndrome. In the 10% that cause a functional syndrome the relative frequency is: ZES (10%) > carcinoid syndrome (4%) > other (<1%). Duodenal NETs occur in greatest frequency in the proximal duodenum and 40–60% have lymph node metastases. 20% of duodenal NETs occur in the periampullary region and these differ from other duodenal NETs in their biological behavior and also with respect to clinical, histological and immunohistochemical features.

Jensen et al.
**Prognosis and Survival**

Duodenal NETs characteristically metastasize first to proximal lymph nodes and infrequently (<10%) to the liver or distant sites. For all patients with well-differentiated duodenal NETs (carcinoid) the 5-year survival rate is 80–85% [28, 43], whereas for patients with well-differentiated duodenal carcinomas or variant duodenal carcinoid it is significantly (p<0.01) less at 72% [28].

For patients with duodenal NETs associated with Zollinger-Ellison syndrome the 5-year survival is >90% [30, 35, 36]. The 5-year survival with different tumor extent with duodenal NETs is thought to be similar to all GI foregut NETs which is 80–95% for local disease, 65–75% with regional involvement only and 20–40% for the 5–10% of patients with liver or distant disease [8, 27, 43]. Invasion of the duodenal NET into the muscularis mucosa, increased primary tumor size, and increased mitotic activity correlate with the occurrence of metastatic disease or aggressive growth [5, 10, 11, 25]. Ampullary NETs are reported to share different growth patterns than do nonampullary duodenal NETs. Two studies report [10, 13] that there was no relationship between these tumors and the development of metastases with primary tumor size.

**Clinical Presentation**

The mean age of presentation is in the 6th decade (range 15–91 years) and there is a slight male predominance (65 ± 5%, 9 series) [4]. Because 90% of duodenal NETs are not associated with a functional clinical syndrome, either symptoms due to the tumor itself or the discovery of the tumor by chance (usually at upper GI endoscopy) lead to the diagnosis. The most common presenting symptoms are pain (37 ± 8%, range 9–64%, 6 series), jaundice (18 ± 4%, range 7–32%), nausea/vomiting (4 ± 8%, bleeding (21 ± 3%), anemia (21 ± 3%, range 1–28), diarrhea (4%) and duodenal obstruction (1%) [5, 10, 24, 25, 43, 44]. Symptoms due to ZES are present in 10 ± 3% of all patients with duodenal NETs followed by carcinoid syndrome in 4 ± 2%, and rarely due to Cushing’s syndrome, acromegaly due to a GRF-secreting tumor, somatostatinoma syndrome, insulinoma, glucagonoma or due to the development of polycythemia rubra vera [4, 16, 18, 19, 44–46]. An increasing percentage of duodenal NETs are being diagnosed in asymptomatic patients during a UGI endoscopy (up to 33%).

The most common nonspecific symptom that led to the endoscopy was dyspepsia [10]. Periampullary NETs more frequently present with jaundice (50–60 vs. 7–15%) and also more frequently cause pain, nausea, diarrhea or vomiting [10, 11, 13, 15]. Periampullary NETs are more frequently associated with von Recklinghausen’s disease (18%) and the presence of somatostatinoma immunoreactivity (25–100%); however, a clinical somatostatinoma syndrome is very rare with these tumors [4, 6, 10, 11, 13, 47].

**Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests**

**Diagnostic Imaging – General**

Because duodenal NETs are generally small in size (mean 1.2–1.5 cm) (>75% <2 cm) [4, 5, 10, 11, 21, 22, 24, 25, 27, 28], they are frequently missed (80%) with conventional imaging studies (CT, MRI, ultrasound, angiography) [15, 29, 30, 33, 48–52]. Studies in duodenal gastrinomas demonstrate that conventional imaging studies detect ≤15% of gastrinomas <1 cm in diameter, 20–50% 1–3 cm in diameter and 95% >3 cm in diameter [48, 50, 53].

Although there are no systematic studies with all duodenal NETs, studies with somatostatin receptor scintigraphy (SRS) in duodenal gastrinomas show it is unlikely to be a more sensitive method to localize small duodenal primaries (<1 cm). SRS misses 50% of tumors <1 cm in diameter [30, 52, 54]. However, SRS will likely prove to be the most sensitive modality for detecting lymph node metastases, which occur in 40–60% of all patients with duodenal NETs [1, 4, 30, 34–36].

To detect the primary duodenal NET, UGI endoscopy with biopsy is the most sensitive modality with endoscopic ultrasound (EUS) used to confirm the diagnosis and locally stage the disease [55–59]. Some duodenal NETs such as gastrinomas may be primarily submucosal in location and these may be missed on both UGI endoscopy and/or EUS resulting in detection rates as low as 30–60% for duodenal gastrinomas causing ZES, which were diagnosed by hormone assays [60–62].

For full staging of duodenal NETs, helical CT is generally used [55, 56], although studies with gastrinomas suggest SRS may be more sensitive [52, 54, 63, 64].

In patients with advanced metastatic disease, bone metastases can develop especially in those with diffuse liver metastases. It is important they be sought because in other NETs their detection has been shown to generally change management [64–71]. Somatostatin receptor scintigraphy, bone scanning and MRI of the spine best detect them.

**Minimal Consensus Statement on Diagnostic Procedures – Specific**

**Endoscopy**

UGI endoscopy with biopsy is the most sensitive method to detect and diagnose most duodenal NETs, followed by endoscopic ultrasound to locally stage the disease extent.

**Imaging and Nuclear Medicine**

Helical CT or MRI of the abdomen and somatostatin receptor scintigraphy should be used to fully assess disease extent and detect possible distant metastases. In patients with advanced disease, including especially patients with liver metastases, bone, somatostatin scanning and an MRI of the spine should be performed to seek bone metastases.

Well-Differentiated Duodenal Tumor/ Carcinoma (Excluding Gastrinomas)
**Pathology and Genetics**

**Histopathology – General**
Duodenal NETs demonstrate light microscopic features typical of GI NETs in having trabecular, acinar, ribbon or cribiform structures which are uniform, have few mitosis, little necrosis and are separated by stroma [1, 5, 23, 24]. On silver staining 75–80% of duodenal NETs are argyrophilic [5, 6, 23, 24], they are usually argentaffin negative (0–12% positive) [5, 6, 23], 75–100% show positivity for chromogranin A [4–6, 10, 27], 80–100% for neuron-specific enolase (NSE) [5, 6, 10, 28] and 91% for Leu-7 [6]. Greater than 85% of duodenal NETs synthesize GI peptides/amines and 40 ± 16% (7 series) synthesize >1 hormone/amine [4, 5]. Their relative frequency is: gastrinomas (48%) > somatostatinomas (43%) > nonfunctioning serotonin containing tumors (27%) > nonfunctioning calcitonin containing tumors (9%) > poorly differentiated carcinomas, gangliocytic paragangliomas [4]. Duodenal NETs uncommonly (<5%) produce insulin, PP, glucagon or ACTH.

Duodenal somatostatinomas tend to occur periamillary and histologically they frequently contain psammoma bodies (49–68%) [4, 6, 10, 25–28]. This is in contrast to other duodenal NETs, which uncommonly contain psammoma bodies (4.8%) [4, 11, 21, 24–28, 74].

Duodenal gangliocytic paragangliomas contain epithelial (with PP and somatostatin cells), ganglia, and spindle cells [4, 26, 75]. They characteristically contain gangliocytic differentiation and S-100 protein immunoreactive Schwann cells [26, 75]. They also show positive staining for NSE in 94–100%, PGP 9.5 in 100%, synaptophysin in 94–100%, S-100 in 90%, PP in 75–92%, serotonin in 48–69%, chromogranin in most series in 10–15% and infrequently (<1%) calcitonin, gastrin or ACTH [4, 40, 75, 76].

**Minimal Consensus Statement on Histopathology and Genetics – Specific [1]**

**Histopathology**
50–75% of duodenal NETs are well-differentiated, 25–50% well-differentiated carcinomas and <1–3% poorly differentiated carcinomas. All duodenal NETs should have routine histology with hematoxylin-eosin staining, as well as staining for chromogranin A, and synaptophysin. S-100 staining should be performed on suspected gangliocytic paragangliomas and gastrin, somatostatin and serotonin if the clinical setting is suggestive. Duodenal NETs should have a mitotic index determined by mitotic counting and a Ki-67 to assess proliferative rate. Cytology is not routinely recommended.

**Genetics**
Patients with a duodenal NET with MEN1, a family history suggestive of MEN1 or with multiple duodenal NETs should be considered for germline DNA testing for MEN1 (following genetic counseling).

**Surgical Therapy**

**Curative Surgery – General**
Potential curative resection is possible in most patients with duodenal NETs because only 9 ± 6% (5 series) have distant metastases at diagnosis with the remainder having either no metastases or a primary with lymph node metastases (40–60%) [1, 4, 5, 30, 34, 35, 44, 49]. Numerous surgical/endoscopic methods have been reported to be effective at removing duodenal NETs, including endoscopic removal by snare or stripping; laparoscopic removal; transduodenal local excision or aggressive resection by a pancreaticoduodenectomy using either a Whipple resection or a pylorus-sparing pancreaticoduodenectomy [15, 28, 49, 51, 60, 78–88]. The optimal method for removing duodenal NETs remains unclear because their natural history is still largely unknown. In addition, the long-term relative results of resection performed with endoscopy, laparoscopy, transduodenal local resection or by pancreaticoduodenectomy have not yet been determined. Finally, the sensitivity of available tumor imaging modalities in assessing local progression pre- or post-resection has not been determined, primarily because of the low frequency of these tumors [15, 44, 49, 60, 89].
Carcinoma (Excluding Gastrinomas)

Well-Differentiated Duodenal Tumor/ surgical resection may be required. Large duodenal NETs (i.e., 1 cm) or duodenal NETs of any size with lymph node metastases should be treated surgically with local resection (1st part duodenum), distal duodenectomy (4th part duodenum) or pancreaticoduodenectomy (frequently required in the 2nd and 3rd part of the duodenum). Treatment of intermediate size duodenal NETs (i.e., 1–2 cm) is controversial with some recommending endoscopic removal if no lymph node metastases are present on tumor localization studies (helical CT/MRI, endoscopic ultrasound), whereas others recommend surgical treatment of these NETs [15, 28, 44, 49, 60]. With ampullary NETs, a number of studies report no correlation between the NET size and the presence of malignancy [13–15, 42] and thus a pancreaticoduodenectomy is generally recommended for these tumors.

Palliative Surgery
In the uncommon patient with a duodenal NET who has hepatic metastases that are potentially resectable without distant metastases and no medical conditions markedly limiting life expectancy or increasing surgical risk, surgical resection and/or ablative therapy should be considered.

Medical Therapy

Minimal Consensus Statement on Medical Therapy

For the ≤10% of patients with functional hormonal syndromes due to a duodenal NET, appropriate specific therapy for the hormone excess state should be instituted. Specifically, treatment of the acid hypersecretion with proton pump inhibitors in patients with Zollinger-Ellison syndrome; treatment with somatostatin analogues for carcinoid syndrome, and treatment of ectopic Cushing’s syndrome medically or by adrenalectomy. For patients with advanced metastatic disease, alpha interferon can be attempted, however, experience is limited. For patients with progressive advanced metastatic disease or with symptomatic diffuse metastatic disease, the combination of streptozotocin and 5-fluorouracil/doxorubicin is recommended in tumors with a low to moderate proliferative rate. Cisplatin/carboplatin plus etoposide is recommended in such patients with poorly differentiated tumors (see relevant consensus paper). For patients with metastatic/ inoperable disease with no other options, peptide receptor radionuclide therapy (PRRT) should be considered if the octreoscan is positive. Although there is extensive experience with this therapy with other GI NETs, especially with lutetium-177- or yttrium-90-labeled somatostatin analogues [90–94], there is minimal experience specifically with duodenal NETs.

Follow-Up

Minimal Consensus Statement at Follow-Up

In patients with a nonfunctional duodenal NET completely removed at endoscopy, follow-up endoscopic examinations, abdominal ultrasound or CT and serum chromogranin A levels are recommended at 6, 24 and 36 months. In patients with postsurgical resection, helical CT, somatostatin receptor scintigraphy and serum chromogranin levels are recommended at 6 and 12 months, then yearly for at least 3 years. If any abnormalities are detected, endoscopic ultrasound should be performed. For patients with unresectable advanced metastatic disease, no treatment is given because the disease is not progressive or symptomatic, the patient should be re-evaluated at 3- to 6-month intervals by chromogranin A, helical CT and/or ultrasound and somatostatin receptor scintigraphy. For patients with metastatic/inoperable disease receiving antitumor treatment (chemotherapy, interferon-alpha, PRRT) follow-up needs to be dictated by the protocol used and expected toxicities.

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