

Poorly Differentiated Carcinomas of the Foregut (Gastric, Duodenal and Pancreatic)

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Introduction

Poorly differentiated endocrine carcinomas (PDEC) of the gastrointestinal tract are rare tumors. A PDEC is defined as 'a malignant epithelial tumor composed of highly atypical, small- to intermediate-sized tumor cells growing in the form of large, ill-defined aggregates, often with necrosis and prominent angioinvasion and/or perineural invasion' [1]. In the older literature, these tumors have been variously described as high-grade neuroendocrine carcinomas, small-cell carcinomas, oat cell carcinomas, undifferentiated carcinomas or anaplastic carcinomas. When applying the WHO criteria for PDEC, care should be taken to separate PDEC from mixed exocrine-endocrine tumors and exocrine tumors containing only small numbers of endocrine cells. Separation of PDEC from mixed exocrine-endocrine tumors is not always

clear in the older literature. Due to the rarity of gastrointestinal PDEC, comprehensive studies are still lacking on the epidemiology, clinical presentation, genetic alterations, histopathology, natural history and treatment of these tumors. Our knowledge of gastrointestinal PDEC is therefore limited and mainly based on a small series of patients and case reports.

Primary small cell carcinoma of the stomach was first described in 1976 [2]. So far, more than 100 cases of gastric small cell carcinomas have been reported [3]. PDECs of the stomach account for approximately 6% of gastric endocrine tumors [4]. Males are more frequently affected than females (M:F ratio 3:1) and the mean age at diagnosis is 64 years [3, 5]. Most patients have regional or distant metastases at presentation and lack hormone overproduction syndrome. The clinical outcome is poor, with death due to tumor disease within 12 months of the di-

agnosis in about half of the patients [3, 4]. Primary tumors are evenly distributed in the stomach and present as single lesions with an average size of 4.2–6.3 cm [3, 6]. Histopathological features of gastric PDEC include small- to intermediate-sized tumor cells growing in solid sheets, prominent angioinvasion, deep wall invasion and lymph node/distant metastases [6]. Tumor cells are strongly positive for cytosolic markers of neuroendocrine differentiation (NSE, PGP9.5) but show weak or absent positivity for chromogranin A or hormonal products [4]. Gastric PDECs frequently contain an adenocarcinomatous or squamous component in addition to the endocrine component [3]. Surgical treatment with removal of the entire tumor is seldom possible. Patients can be treated according to the so-called Mayo program (streptozotocin + 5-FU alternated with adriamycin) or with a combination of cisplatin + etoposide [7–9].

PDECs of the duodenum are rare tumors with less than 30 cases reported in the literature [10, 11]. Duodenal PDECs are primarily located in the ampulla of Vater [10] and account for 2–3% of the ampullar tumors [11]. The mean age of patients is 70 years with a male preponderance (M:F ratio 3:1). Most patients present with jaundice and abdominal pain. Regional and/or distant metastases are usually present at diagnosis and a majority of patients die from tumor disease. The primary tumor present as a single lesion with a mean size of 2.5 cm. Half the tumors are associated with adenomas in the adjacent mucosa [11]. The histopathological features of ampullar PDEC include separation into two groups, large-cell neuroendocrine carcinomas and small-cell neuroendocrine carcinomas. A majority of tumors of both types stain positive for synaptophysin and chromogranin A [11]. Surgical treatment that has been employed includes endoscopic resection, local excision and pancreaticoduodenal resection [7]. Effective response has been obtained with adjuvant chemotherapy, e.g. with a combination of 5-FU, TNF and interferon [12].

PDECs of the pancreas are rare tumors with less than 50 cases reported in the literature [13]. PDECs of the pancreas account for 1% of all malignant pancreatic tumors and 2–3% of pancreatic endocrine tumors [14–17]. Elderly patients are primarily affected with a male preponderance (M:F ratio 4:1) [13]. Presenting symptoms include jaundice, weight loss, abdominal pain and hepatomegaly. Symptoms due to hormone overproduction are rare, although cases with Cushing's syndrome [18] and carcinoid syndrome [19] have been reported. Pancreatic PDECs are predominantly located in the pancreatic head, measure 4 cm in diameter and typically invade adjacent

organs or metastasized at the time of diagnosis. The outcome is generally poor and most patients die within 2 years of diagnosis. However, curative resection with long survival has been reported in individual patients [13]. Histopathological features of pancreatic PDEC include small- to intermediate-sized tumor cells growing diffusely or in irregular nests, often with extensive necrosis and high mitotic rate. Tumor cells are positive for synaptophysin and PGP9.5 but chromogranin A staining is usually negative or only focally positive [17].

Epidemiology and Clinicopathological Features

Minimal Consensus Statements on Epidemiology and Clinicopathological Features

Epidemiology

Poorly differentiated endocrine carcinomas of the stomach, duodenum and pancreas are rare tumors accounting for less than 2% of gastric carcinomas and less than 3% of duodenal carcinomas. They are probably underestimated since they may resemble undifferentiated carcinomas. A positive staining for synaptophysin may be the only indicator of endocrine differentiation.

Clinicopathologic Staging

Poorly differentiated endocrine carcinomas belong to the WHO group 3 of highly malignant tumors, frequently of small cell type, displaying solid growth pattern, necrosis, high mitotic rate, high Ki67 indices and frequent accumulation of mutated p53. There is no information available on the average clinicopathologic staging of these tumors.

Prognosis and Survival

The prognosis for patients with poorly differentiated endocrine carcinomas is generally poor. Patients with treated metastatic disease have an expected survival time of 6–12 months [4].

Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests Including Pathology

Minimal Consensus Statements on Diagnostic Procedures

Imaging and Endoscopy

Stomach, Duodenum and Pancreas. CT, MRI, endoscopy with biopsy or EUS, FDG-PET. Comments: imaging procedure should be determined from the clinical situation. A minimal diagnostic procedure should include gastroscopy, CT or MRI [20, 21]. FDG-PET may be useful in the primary diagnosis and for staging. SRS is not recommended but should be evaluated in the clinical setting.

Biochemical Diagnosis

Stomach, Duodenum and Pancreas. Biochemical work-up should be performed at the time of diagnosis. NSE may be useful as a tumor marker [15]. Screening for chromogranin A and hormones is usually negative. Genetic testing is not indicated, except in cases with positive family history.

Histopathology

Stomach, Duodenum and Pancreas. HE, chromogranin A, synaptophysin, NSE, Ki67. Comments: histopathology is required for the diagnosis. Routine histopathology and immunohistochemical staining for general neuroendocrine markers should be performed. Staining for specific hormones is usually negative. Additional neuroendocrine and non-neuroendocrine markers may be useful in the differential diagnosis. Cytology with fine-needle aspiration is not recommended, but may be helpful in some instances.

Surgical and Cytoreductive Therapy

Minimal Consensus Statements on Surgery and Cytoreductive Therapy

Curative Surgery

Stomach. Partial or total gastrectomy with lymph node dissection as recommended for adenocarcinomas.

Duodenum. Pancreatico-duodenal resection (Whipple's procedure) for larger tumors. Duodenal resection for tumors located in the distal duodenum.

Pancreas. Pancreatic resection or pancreatico-duodenal resection (Whipple's procedure).

Comments. Curative surgery should be attempted in localized disease [7, 22]. Debulking surgery and surgery for liver metastases are not recommended.

Cytoreductive Therapy

Stomach, Duodenum, Pancreas. Cytoreductive therapy is generally not recommended, but TACE may be indicated in selected patients.

Medical Therapy

Minimal Consensus Statements on Medical Therapy

Stomach, Duodenum, Pancreas. Systemic chemotherapy with cisplatin and etoposide

Comment. Systemic chemotherapy is indicated in inoperable disease, provided the patient has adequate organ function and performance status. Combined treatment with cisplatin/carboplatin and etoposide has been reported to induce remission in 55–80% of patients with response duration of 8–11 months [9, 23–25]. Chemotherapy may be considered in selected cases as adjuvant treatment; however, there are no data available to corroborate this opinion and studies are thus required. Somatostatin analogue treatment or interferon therapy is not recommended.

Follow-Up

Minimal Consensus Statements on Follow-Up during and after Treatment

Stomach, Duodenum, Pancreas. All patients should be closely followed every 2–3 months with US, CT and MRT or other radiological methods depending on the affected organ. PRRT may be considered if SRS is strongly positive. Biochemical markers positive at diagnosis should be followed.

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