Journal of Visceral Surgery (2018) xxx, xxx—xxx

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REVIEW

Preoperative imaging and pathologic classification for pancreatic neuroendocrine tumors

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KEYWORDS
Neuroendocrine tumor;
Pancreatic resection;
Classification;
Grade;
Molecular imaging

Summary The management of patients with pancreatic neuroendocrine tumor (PNET), whether hormonally secretory or not, is multidisciplinary and often multimodal. Surgical treatment plays a central role because complete resection is the only potentially curative treatment. The choice of the therapeutic plan for a PNET requires precise localization of the primary tumor (which may sometimes be multiple in case of genetic predisposition), confirmation of the diagnosis of PNET, a search for metastases (mainly hepatic), and identification of the main histoprognostic factors. This update focuses on the WHO 2017 histological classification and recent innovations in the preoperative assessment of PNET using conventional and isotopic imaging. The aim is to not only allow the mapping of primary and metastatic lesions but also to predict tumor aggressiveness.

Introduction

Pancreatic neuroendocrine tumors (PNET) are rare, with a calculated incidence of less than 0.5 cases per 100,000 people, based on US registry data (SEER database) between 2000 and 2012 [1]. PNETs are hormonally secretory in 15% of cases, are associated with lymph node metastases in 20—40%, and hepatic metastases (HM) are present in 10—60% of cases depending on the study population (exclusively surgical or non-surgical series) [2,3]. HM are often synchronous, multiple, bilobar, variable in size, and unresectable from the outset in three-quarters of cases [4]. The median survival for PNET is generally between 3 and 4 years, but these tumors vary in their aggressiveness. The principal factors of poor prognosis are tumor differentiation, the presence of HM, and unresectability of the primary tumor [1,2,5] (Table 1).

The management of patients with PNET is multidisciplinary and often multimodal [6,7]. Complete surgical tumor resection is currently the only potentially curative treatment and its possibility must always be discussed [6,7]. More

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https://doi.org/10.1016/j.jviscsurg.2017.12.008
1878-7886/

Table 1 Global survival for pancreatic neuroendocrine tumors as a function of their main prognostic criteria.

Criteria	Median survival Months (extremes)	References
Tumor grade	G1-G2	51–60 [2],
	G3	7–7.5 [53]
Stage	Localized	100 (68–148) [53]
	Locally advanced	69 (52–86)
	Metastatic	17 (14–19)
Functional hormone secretion	Non-functional	26 (23–30) [53]
	Functional (except for benign insulinoma)	54 (37–74)
Surgery	Resection of primary tumor with no evidence of distant metastasis	136 [2]
	Non-resection of primary tumor with no evidence of distant metastasis	19

exceptionally, surgery can also be discussed for unresectable disease in an effort to control hormonal hypersecretion, to prevent or treat local complications of the primary tumor, or to limit the disease to the liver by resecting the primary tumor [2,4,6,7]. Surgery treatment of PNET, and especially the surgical resection of HM, can be preceded or associated with tumor destruction by medical or radiological treatments, which can, in rare cases, make initially unresectable disease resectable. This possibility must be systematically discussed at each re-evaluation in the Multidisciplinary tumor conference or RENATEN Network (Réseau national de prise en charge des tumeurs [neuro-]endocrines malignes rares sporadiques et héréditaires) [6–8].

The first part of this review focuses on the World Health Organization (WHO) 2017 histological classification and the main innovations in conventional and isotopic imaging for preoperative assessment of PNET. Imaging must not only specify the number and location of both primary and metastatic lesions but also, if possible, provide information on the aggressiveness of these lesions. The second part of this study reviews the operative indications and the various surgical techniques (place of parenchyma-sparing surgery) with regard to the primary pancreatic lesion, and the role of ''wait and see'' surveillance for certain ''small'' (≤ 2 cm) PNETs.

Histological classification of PNET

The WHO classification (2010 and 2017) of digestive NET is based on two criteria: histological differentiation and cell proliferation index. Tumor grade is defined in three categories (G1, G2, G3) [9] (Table 2). Tumor grade is one of the major prognostic factors for NET. Median survival for NETs at all locations for G1, G2, and G3 tumors is respectively > 16 years, > 8 years, and 10 months [1].

Pathologic interpretation of tissue specimens should be re-read within the framework of the TENPATH expert network (Réseau national de référence anatomopathologique de prise en charge des tumeurs neuroendocrines malignes rares sporadiques et héréditaires) (available at http://www.sfendocrino.org/category/9), and double reading of pathology slides is essential for:

- PNETs considered to be ''poorly differentiated'', especially when the Ki-67 index is less than 50%;
- for PNETs considered as ''well differentiated'', but with a Ki-67 index between 20 and 50%;
- in case of suspicion of PNET of incomplete immunohistochemical phenotype;
- in case of suspicion of mixed tumor including carcinoma with a neuroendocrine component [7].

Tumor differentiation

Tumor differentiation is evaluated by pathological examination that classifies PNET as well- or poorly-differentiated. Well-differentiated PNETs may present heterogeneous architectures but cells have a neuroendocrine morphology; they classically express the corresponding markers (chromogranin A and synaptophysin) and do not have major cytonuclear atypia [9].

Poorly differentiated tumors, also called neuroendocrine carcinomas (NEC), may consist of large or small cells. The cells of large-cell NECs have abundant cytoplasm and a strongly atypical nucleus. The cells of small-cell NECs have very little cytoplasm and a less-atypical nucleus. Mixed adenocarcinoma neuro-endocrine carcinoma (MANEC) is a rare entity in the 2010 classification, and is renamed MiNEN (Mixed neuroendocrine-non-neuroendocrine neoplasm) in the 2017 classification. These tumors include both a neuroendocrine component and an adenocarcinoma-type exocrine or acinar-cell component.

Histoprognostic grade

Histoprognostic grade is determined by the Ki-67 proliferation index (percentage of cells labeled with MIB-1 antibody measured on 2000 cells in the highest cell density areas) and the mitotic index (number of mitoses per 10 high-power fields). These two factors enable classification of NETs into three grades (G1, G2, G3). The highest count of either Ki-67 or mitoses defines the tumor grade [10].

The 2017 classification now also recognizes well-differentiated G3 NETs, which generally have an Ki-67 index between 20% and 50% [11]. This improved characterization of G3 tumors has therapeutic implications. While the standard therapy for poorly differentiated PNETs remains platinum-based systemic chemotherapy, targeted therapies using Everolimus or Sunitinib have been shown effectiveness for well- and moderately-differentiated G3 PNETs, regardless of the value of Ki-67. There may even be a role for surgery in well-differentiated G3 NETs [12–14].

The evaluation of cell proliferation of NETs by Ki-67, may exhibit ''spatiotemporal'' heterogeneity, with HM, especially metachronous HM, showing a higher Ki-67 index

Please cite this article in press as: Deguelte S, et al. Preoperative imaging and pathologic classification for pancreatic neuroendocrine tumors. Journal of Visceral Surgery (2018), https://doi.org/10.1016/j.jviscsurg.2017.12.008