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Review

Conservative management and parenchyma-sparing resections of pancreatic neuroendocrine tumors: Literature review

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ABSTRACT

Background: Pancreatic neuroendocrine tumors (pNETs) are uncommon entities. pNETs are often small, slow growing, clinically silent neoplasms. However, they have an almost unpredictable biological behaviour with a not negligible malignant potential. Surgery still represents the treatment of choice, but the high morbidity associated to the enucleation or the formal pancreatectomy should be considered in the decision of the proper treatment.
Management of these neoplasms is still debated, and indications for a conservative observational approach and for parenchyma sparing resections are not yet standardized.
Method: We review the state of art on the indications for the conservative management of pNETs. Searches on MEDLINE database were performed to identify articles reporting prognostic systems, biochemical screening, observational management, medical treatment and surgical strategies for pNETs.
Discussion: Currently, an accurate 'wait-and-see' policy is recommended by the European Neuroendocrine Tumor Society (ENETS) only for non-functioning pNETs (NF-pNETs) <2 cm.
A biochemical screening, based on sampling of serum levels of pancreatic polypeptide (PP) and chromogranin A, can address to early conservative surgery for MEN-1 associated NF-pNETs <2 cm to prevent their malignant transformation.
The subtotal (80%) distal pancreatectomy first proposed by Thompson, often with the enucleation of possible pancreatic head tumors, still represents a good compromise between oncological radicality and prevention of pancreatic endocrine/exocrine insufficiency caused by standard radical resections for the treatment of inherited syndromes associated with NF-pNETs >2 cm and symptomatic F-pNETs of any size.
Conclusion: More studies are needed to further clarify and predict the biologic behaviour of pNETs and increase the indications for conservative observational management and parenchyma sparing pancreas resections.

1. Introduction

Pancreatic neuroendocrine tumors (pNETs) are rare neoplasms accounting for 1–2% of all pancreatic cancers [1].

pNETs are clinically divided into functioning (F-pNETs) and non-functioning (NF-pNETs) depending on the presence or less of a functional syndrome due to hormones incretion [2].

F-pNETs can secrete various hormones (including gastrin, insulin and glucagon), whereas NF-pNETs secrete other inert

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substances (like PP, chromogranin A, and neuron-specific enolase) or synthesize but do not secrete hormones, so by definition they lack of a hormone hyper-secretion syndrome [3].

They can be sporadic or associated with inherited syndromes such as multiple endocrine neoplasia type 1 (MEN-1), Von Hipple-Lindau (VHL) disease and Neurofibromatosis type 1 (NF-1) [4].

Recently, the significantly increased detection of incidental NF-pNETs seems related to the widespread use of advanced imaging techniques [5].

The European Neuroendocrine Tumor Society (ENETS) proposed a classification system for pNETs that embeds tumor-node-metastases (TNM) staging and pathological grading of the proliferative rate of tumor cells. This classification is accurate to assess a prognostic malignant risk for pNETs [6].

On the contrary, as pNETs may often have a mainly indolent course, some controversies remain about their management.

Radical resections, such as pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), are associated with a high incidence of exocrine and endocrine insufficiency. In addition, a not negligible morbidity and mortality, especially caused by postoperative pancreatic fistulas, is often reported.

In this setting, with the aim of avoiding postoperative life-threatening complications, conservative resections (enucleation or atypical resection) are performed more and more frequently.

The conservative 'wait and see' management and the parenchyma-sparing techniques, when indicated, can both reduce the risk of pancreas failure and the incidence of tumor recurrence/malignant progression [7].

Here, we review the state of art of the indications for a conservative management of pNETs.

2. Material and methods

The preliminary phase of the study was conducted to identify relevant data. Searches on MEDLINE database were performed to identify articles published until February 2015, which reported prognostic systems, biochemical screening, observational management, medical treatment and surgical strategies for pNETs. All the references founded were reviewed for the acquisition of additional data. The review was performed after the exclusion of duplicates and articles with low grade of evidence.

The grade of evidence of the articles was classified into high and low grade by using the following method: if a multivariate analysis was performed to explore the statistically significant difference between conservative approach and radical standard pancreatectomy, the article was classified as high grade; if only a univariate analysis was performed the article was classified as lowgrade.

3. Results

The widespread use and the improved accuracy of imaging have increased the detection of the incidental sporadic NF-pNETs [5].

These are often small indolent neoplasms and the incidence of malignancy among all incidental NF-pNETs smaller than 2 cm is 6% [8].

Reported low morbidity and virtual absent mortality rate in pNETs patients suggested that an extended survival can be expected without surgery. However, the biological behaviour of pNETs varies widely within patients, especially in those associated with inherited syndromes such as MEN-1.

Partelli et al. demonstrated that liver metastases occurred in 30% of patients with NF-pNETs and the risk of metastases is unacceptably high for NF-pNETs larger than 2 cm [9].

Moreover, the malignant progression of pNETs, mainly with liver metastases, is the major cause of death both in sporadic and inherited syndromes associated-pNETs with nearly half of metastatic pNETs patients dying before 50 years of age [10].

In 2010 the ENETS proposed a staging system that combines TNM classification with the grading evaluation of neuro-endocrine tumors assessed with mitotic rate and Ki67 index. The neoplasms can be assigned to one of the three grading categories: G1 if the proliferative index is $\leq$2%; G2 if the index is between 2 and 20%; G3 if > 20% [6]. This grading system is helpful and accurate for pNETs prognostication.

Currently, a wait-and-see policy is recommended by the ENETS guidelines for NF-pNETs <2 cm incidentally found, especially when, due to their location, an aggressive surgical approach is needed to remove these lesions [3].

A follow-up based on yearly imaging control while, with the first screening performed 6 months after the incidental diagnosis, seems to be reliable [11].

For the treatment of NF-pNETs >2 cm and symptomatic F-pNETs, radical surgical procedures, such as PD and DP, still remain the gold standard. The high risk of the resulting pancreatic endocrine/exocrine insufficiency after PD and DP (or any other radical pancreatic resection) has increased the use of parenchyma-sparing techniques such as enucleation and middle pancreatectomy (for lesions of the central portion of the gland) [12].

These limited resections are associated with a low risk of pancreatic endocrine/exocrine impairment, but they have a higher rate of pancreatic fistulas (PF) when compared with radical resections [13]. However, the clinical impact of PF resulting after limited resections is very low [14].

Therefore, the use of intraoperative ultrasonography (IOUS) is mandatory for parenchyma-sparing resections, especially for deep enucleation of pNETs distant $\leq$3 mm from the main pancreatic duct (MPD), which have a higher risk of post-operative PF [15].

At present, the only indication for these parenchyma-sparing procedures is limited for symptomatic F-pNETs <2 cm [16].

Further studies would be needed to clarify and predict the biologic behaviour of pNETs and make possible the use of limited resection for larger functioning and non-functioning sporadic pNETs.

The pNETs can be associated with inherited syndromes such as MEN-1, VHL disease and NF-1 [4].

MEN-1 is an autosomal dominant inherited disease consisting of mainly pNETs, parathyroid tumor and pituitary tumor [17,18].

MEN-1 is caused by inactivating mutations of the MEN-1 gene on the long arm of chromosome 11 (11q13) [19]. This gene encodes for menin and is involved in regulation of cell growth, apoptosis and DNA repair [20]. The second most common endocrinopathy in MEN-1, after parathyroid tumor, are pNETs. This endocrinopathy is classically characterized by numerous micro-adenomas distributed through the entire pancreatic parenchyma with few concomitant larger lesions [21]. MEN-1 associated pNETs have often an indolent course, although pancreatic malignancy with liver metastases is the first cause of premature death in MEN-1. Moreover, when pNETs related to MEN-1 are discovered for symptoms of hormone excess, 30–50% of patients already have liver metastases [22]. Akerstom G et al. proposed a biochemical screening for early detection of NF-pNETs in MEN-1 patients, decades before that a clinical syndrome of hormone excess has developed. For this reason in their center, high serum levels of pancreatic polypeptide (PP) and chromogranin A can address to early conservative surgery also for NF-pNETs <2 cm [10]. Owing to the high rate of pancreatic multicentric lesions in MEN-1, the treatment of choice for NF-pNETs results in a subtotal (80%) DP with enucleation of possible pancreatic head tumors. This procedure was first proposed by Norman Thompson in 1989, also associated with lymphadenectomy and duodenotomy, for the treatment of MEN-1 associated with the Zollinger–Ellison