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Small pancreatic neuroendocrine tumours: observe and monitor or prompt surgical resection

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Over recent decades there has been a significant increase in the annual incidence of neuroendocrine tumors of the pancreas (PanNets), from 0.4 to 0.8 per 100,000 inhabitants, due to the more widespread use of more sensitive imaging techniques (cross-sectional and functional imaging)(1–3).

Given their heterogeneous biological nature and that 70-80 % are nonfunctional (NF-PanNETs), 50-70% of these tumors are diagnosed incidentally. Therefore, the issue of how to manage small tumors (< 2 cm in diameter) remains controversial (4–6).

Apart from all of these factors, we must also bear in mind the morbidity associated with pancreatic resections (30-40%) and the slow implantation of minimally invasive techniques, which have a very long learning curve (60-70 cases) (7)

FUNCTIONAL TUMORS

Given the limitations of space in editorials, here we will only deal with functional tumors (F-PanNETs; 20% of PanNETs): insulinomas (70%), glucagonomas (10%), gastrinomas and somatostatinomas (10%), vasoactive intestinal peptide (VIPoma); together with other less frequent types: cholecystokinin-producing tumors, serotonin, ectopic adrenocorticotrophic hormone (ACTH) (8).

The risk of malignancy for F-PanNETs is highly variable, ranging from 5-10% in insulinomas to 60-90% in gastrinomas, somatostinomas and glucagonomas (4, 5). European and American guidelines recommend the resection of localized functional tumors (stages T1-4, No-N1, M0) (3). Generally, 50-60% of these tumors are located in the tail of the pancreas with the exception of gastrinomas, and enucleations and parenchyma-sparing resections, central and distal pancreatectomies performed laparoscopically are recommended (7, 9)

NONFUNCTIONAL NEUROENDOCRINE TUMORS (NF-PanNETs)

NF-PanNETs are not associated with hormonal syndromes although they may secrete polypeptides or hormones and 75-90% are diagnosed incidentally (10–12).

The therapeutic recommendations for tumors < 2 cm are based on expert clinical guidelines, retrospective studies, systematic reviews and meta-analyses which compare surgical resections with watchful waiting and monitoring with imaging techniques (level 3 evidence)(4, 5, 13–16).

Retrospective studies suffer from limitations derived from the selection bias of the patients by tumor location (head vs tail of the pancreas), the surgical experience of the center and the lack of histologic prognostic factors in the watchful waiting and monitoring group (Ki-67 proliferation index, tumor grade, perineural and vascular invasion) (3).

Currently, two multicenter prospective trials are underway with the aim of clarifying the controversy caused by tumors < 2 cm in diameter.

The ASPEN trial (NCT 03084770) promoted by the European Neuroendocrine Tumor Society (ENETS) aims to compare watchful waiting and monitoring (every 6 months for the first two years and then annually up to 5 years) using computed tomography (CT), magnetic resonance imaging (MRI), 68 Gallium-labeled positron emission tomography/computed tomography (68 Gallium PET/CT) and or endoscopic ultrasonography (EUS) with surgical resection. The primary endpoint of the trial is progression-free survival and the study plans to recruit 1000 patients(17).

The second trial, the PANDORA trial (Netherlands Trial Register NL 6510), includes patients with NF-PanNETs < 2 cm, with no lymph node involvement who are to be followed for five years. The primary objective is to assess tumor growth > 0.5 cm/year and the second aim to determine the intervention rate due to surgery for tumor growth or the development of lymph node metastases (18).

In a recent interim analysis, the authors have described the preliminary results of 76 patients included in the trial (January 2017-February 2020): 68 (89%) patients experienced no increase in size during a 17-month follow-up (i.q.r. 8-15) while in 8 (11%) tumour growth was observed. It is worth noting that tumours with a malignant phenotype were excluded and that 6 of the eight patients in whom surgery was indicated refused the intervention (17).

PROGNOSTIC FACTORS

Most studies refer to a size of 2 cm to indicate the resection of NF-PanNETs (4, 5, 19). Bettini et al(20) and Sallinen et al(21) reported that even tumors smaller than 2 cm were associated with lymph node metastases in 14% and 10.6% of cases respectively. A clear association between tumor size and lymph node involvement has been reported. Tumors > 1.5 cm have a 4.7-fold greater risk of having lymph node metastases, an increased Ki-67 index, lymphovascular invasion and poor differentiation (grade 3 Ki labeling index > 20%) (3, 22). Furthermore, the incidence of the adenopathies is related to location of the tumor, with tumors in the head of the pancreas having more lymph node metastases.

In spite of this general recommendation, controversial outcomes have been reported which require several factors to be borne in mind when taking a decision in one direction or the other in tumors between 1.5 and 2 cm in diameter.

Finkelstein et al(15) in a meta-analysis of 11 studies (1607 patients being observed vs 1491 undergoing resection) and Assi et al (19) in an analysis of records from the National Cancer Database (1781 patients undergoing resection vs 223 with observation), found a higher overall 3- and 5-year survival rate in the patients undergoing resections vs those only being observed and monitored. In a study by Sharpe et al(23), in which 380 patients (National Cancer Database) with tumors of 2 cm or less were included, 71 (18.7%) were observed and 309 (81.3%) underwent resection. Univariate analysis revealed better results for the resection group (5-year OS 82.2% vs 34.3%; $p<0.001$).

In contrast, other authors such as Sadot and Partelli recommend watchful waiting and monitoring in NF-PanNETs of 1.5-2 cm as opposed to surgical resection (13, 24). However, it should be noted that the patients receiving surgery were significantly younger and that in the study by Sadot et al 25% of the observation group underwent surgery after a median of 30 months (13). Observation of early-stage did not lead to an increased locoregional metastases.

In the systematic review by Partelli et al)(24) on non-functioning tumours < 2cm, the results of 327 patients under observation and follow-up were compared with 213 resected patients. Only 14.1% of the patients in the observation group underwent surgery due to tumour growth, justifying the conservative approach in tumours < 2cm.

In spite of the contradictory data, unanimity exists that watchful waiting and monitoring in the terms described above are generally recommended in NF-PanNETs of < 2 cm (4, 5).

In tumors between 1-2 cm, the decision must be individualized on center resources and weighed against other criteria such as age of the patient, location of the tumor (head-body-tail), access to prolonged and intense follow-up (CTI, MRI, EUS), presence of regional adenopathies, appearance of symptoms, Ki-67 proliferation index, degree of differentiation, (G1-G3), surgical experience of the center (low morbidity < 15-20%), use of minimally invasive pancreatic parenchyma-sparing techniques, availability of endoscopists with experience in the transmural drainage of postoperative intrabdominal fluid collections and the preferences of the patient (4–7).

A wide consensus exists that tumors > 2 cm should be resected with disease-free margins (R0 resection, margin > 1 mm) (4, 5, 25). Disagreement exists with regard to lymphadenectomy, as some authors, unlike what has occurred with other tumors, have observed no increase in overall survival when the procedure is performed.

The resection of 11-15 lymph nodes with the tumor is recommended. This number may be difficult to reach in pancreatic parenchyma-sparing resections (enucleations and central pancreatectomies) or when splenic vessel-sparing techniques are used, and therefore we suggest that samples be taken from the areas around the hepatic artery, celiac trunk and splenic artery (4, 5). Figure 1 shows a decision algorithm based on the recommended guidelines.

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