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EDITORIAL

Pancreas neuroendocrine tumors - not so rare or benign

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms characterized by a common embryonic origin but with a highly variable clinical outcome. Their incidence has notably increased in the last 30 years, which is no doubt influenced by their being incidental finding in imaging studies performed for other reasons, and is currently around 5 cases per 100,000 population/year. Pancreas NETs (P-NETs) represent approximately 10% of their total (around 0.5 cases per 100,000 population/year), reaching 33% in the Spanish registry (1). A small proportion are associated with hereditary syndromes, primarily with MEN-1.

Historically, most P-NETs were functional, and were recognized from the manifestations of hormone hyperproduction. Today non-functioning P-NETs are much more common (68-85%). In these chromogranin A and pancreatic polypeptide measurement is recommended.

Confusion has long reigned regarding gastro-enteropancreatic (GEP) NET nomenclature and its diagnostic and therapeutic approach.

In the last times, imaging technology (CT, MRI) has greatly improved, EUS is routinely used for lesions biopsy, and the potential to perform PET-CT scans with somatostatin receptor-related radiotracers, has been added to somatostatin receptor scintigraphy. PET-CT with radiotracers is useful for the staging of well to moderately-differentiated NETs (80%), whereas PET-CT with metabolic tracers (FDG) is used for the less common undifferentiated tumors that rarely express somatostatin receptors.

In 2010, the WHO updated their classification and adapted the validated staging system of the European Neuroendocrine Tumor Society (ENETS), which emphasizes cell proliferation as measured by the mitotic count and Ki67 index. Thus, GEP-NETs are now classified into three categories: grade 1 (< 2 mitoses and Ki67 ≤ 2%), grade 2 (2-20 mitoses and Ki67 = 3-20%), and grade 3 (> 20 mitoses or Ki67 > 20%). The addition of differentiation degree (well or poorly differentiated), which was the key categorization factor in the WHO guidelines 2000, is recommended. Apart from these histologic factors (mitosis, Ki67, differentiation), P-NET prognosis is influenced by other factors: tumor size and neighboring organ involvement, lymphatic involvemont, vascular invasion, and presence of distant metastases (location and number). Two TNM classification systems (ENETS 2006 and UICC 2010) are currently used, which display minimal differences and are mostly overlapped. Routine use of either classification, together with the grading system, is now considered a key factor for the management of these patients (2). Both factors (TNM and differentiation) represent the most significant survival predictors. Approximately 50-60% of P-NETs are diagnosed with distant metastatic disease.

Surgical resection is the treatment of choice for G1-2 P-NETs whenever clinically and technically feasible, even for locally advanced or metastatic tumors. Enucleation is a well accepted technique for G1 tumors < 2 cm with a lower risk of endocrine/exocrine dysfunction, although controversy remains on whether these tumors should or should not be resected. G1 tumors > 2 cm and G2 tumors should be managed with the same oncologic principles that apply to pancreatic adenocarcinoma. Laparoscopic surgery is considered an acceptable option whenever technically and oncologically feasible.

For cases not amenable to surgery effective loco-regional therapy (radiofrequency, arterial embolization, somatostatin-analog peptides labeled with radionuclides, and radioembolization) or systemic therapy (somatostatin analogs, systemic chemotherapy with the addition of temozolamide-capecitabine to classic regimens, targeted therapies including everolimus or sunitinib) options are available. In these patients management must be approached by a multidisciplinary team to provide an optimal therapy sequence. Liver transplantation may be indicated for highly selected cases.

In the manuscript by J.A. Cienfuegos et al. included in this issue of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)* (3) a retrospective review is made of a significant national single-institution experience on a series of 79 patients undergoing surgery for P-NET throughout 21 years. This is a highly heterogeneous series reflecting current P-NET epidemiology: most are non-functioning (73.4%), sporadic (96.2%) lesions, and a significant proportion is recognized as an incidental finding (44.3%). There is only one G3 lesion, consistent with the trend against operating undifferentiated tumors except for selected cases, although 20 cases (25.3%) have insufficient data for assigning a pathology grade. It includes neoplasms highly variable in size (0.3-23 cm) and site (head 24, body 16, tail 39), of which 21 had liver metastases at diagnosis (10 subsequently operated upon with 6 R0). Their effort at TNM reclassification according to current guidelines, as strongly recommended, is highly commendable. However, their stage pooling for the mortality analysis is striking, with significant differences being obtained when tumors invading neighboring structures but N0 M0 (ENETS IIIA) are grouped together with N1 (IIIB) and M1 (IV) tumors. Metastatic tumors are supposed to have clearly worse outcomes, and such pooling seems clinically irrelevant. In fact, stage-specific Kaplan-Meier curves reflect equal 10-year survival rates for stages I, II and III. Furthermore, tumor recurrence is said to have

occurred in 13 of 79 patients (16.4%), but nevertheless at least 15 cases of 21 with liver metastases had persisting tumors (except for the 6 R0 cases among the 10 operated upon patients).

The mortality analysis according to functional status is misleading since half of functioning tumors are insulinomas (usually more benign) and no TNM or grade is specified for either group, which is no doubt a confounder (not cleared since a multivariate analysis was not feasible). It is also stated that mortality rates were higher for NF-P-NETs, when the statistical analysis indicates the opposite ($p = 0.052$). Furthermore, vascular invasion is said to be associated with poorer prognosis when evidence suggests otherwise ($p = 0.186$). Curiously, survival was not compared between G1 and G2.

Confusing is also their statement on the 5-year survival analysis according to ENETS TNM, distinguishing between a favorable prognosis group (stages I y II) and a poorer prognosis group (stages III and IV). However, figures for stage III (100%) are identical to those for stages I and II (90.5% and 100%, respectively), and clearly better than for stage IV (69.6%).

Table II lists 16 R2 cases. However, in their results all 21 patients with liver metastases are seemingly considered R2.

From a statistical standpoint the simultaneous use of central measures (mean and median values) and dispersion measures (SD, range) instead of only one type for each item (mean and SD or median and IQR) is also striking, as is the use of mortality rate per 1,000 person-years rather than endpoints more familiar in the oncology setting (median survival, overall survival, DFS).

The superiority of laparoscopic surgery (shorter stay, no mortality, no pancreatic fistula) seems to be inferred, but this is likely not the scenario to even suggest it since open surgery includes all cephalic duodenopancreatectomies (with higher risk) and virtually all enucleations (6 out of 7, with the associated higher fistula rate).

While lymphatic involvement is said in the discussion to not entail a poorer prognosis, such evidence is not shown in the text or tables. The majority of the current literature (2) supports a prognostic value for lymphatic metastasis (as well as the lymph node ratio) and therefore recommends lymphadenectomy for such tumors.

Finally, the resection of incidental tumors < 2 cm in size is justified with some references reporting lymphatic metastasis (25%), or even systemic metastasis (13%), in a significant number of these tumors. Other papers from highly prestigious institutions, where the opposite is concluded (2), remain to be mentioned; conservative management seems to be a safe option, but this is still controversial.

Despite these limitations I consider their review praiseworthy, and warmly congratulate the authors on the effort in their data collection and analysis doubtless entailed.

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