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11255 Editorial

Pancreatic neuroendocrine tumors — Bridging knowledge gaps for better outcomes

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Patients' values and preferences are a core element of the clinical decision-making process. However, in practice, their effective implementation is only possible when the probabilities of different clinical outcomes, and the costs and effectiveness of available therapeutic options are known in detail. As physicians, we know that, when evaluating patients with neoplasms, both aspects are rarely straightforward.

Pancreatic neuroendocrine tumors (pNETs), a group of well-differentiated epithelial neoplasms with heterogeneous clinical and pathological features, represent a paradigm of such complex scenarios. Although most cases are sporadic, more than 10 % (1) result from germline mutations responsible for hereditary syndromes, including multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau syndrome, neurofibromatosis type 1, tuberous sclerosis, and mutations in DNA repair genes. Recognizing this hereditary background is relevant not only because of its impact on prognosis and treatment but also for its implications in identifying at-risk relatives.

Some lesions, classified as functioning, have the capacity to secrete insulin, gastrin, somatostatin, serotonin, glucagon, or vasoactive intestinal peptide into systemic circulation. These hormones evade negative feedback mechanisms and give rise to characteristic endocrine syndromes in which surgery is generally considered the first-line treatment for localized disease. The majority of pNETs do not cause endocrine symptoms and are often discovered incidentally through imaging studies performed for other reasons. These non-functioning lesions are generally characterized by indolent behavior and have a better prognosis when compared to pancreatic ductal adenocarcinoma; however, a significant proportion follows a less favorable clinical course than their functioning counterparts (2).

Currently, prognosis estimation and treatment recommendations are primarily based on tumor stage and grade, defined by mitotic count and the Ki-67 proliferation index (3). Non-functioning lesions larger than 20 mm in diameter, especially high grade ones, carry a significant risk of regional lymphatic invasion and metastasis. Therefore, clinical practice guidelines from the European Neuroendocrine Tumor Society (ENETS) (4), the North American Neuroendocrine Tumor Society (NANETS) (5), and the National Comprehensive Cancer Network (NCCN) (6) recommend surgical resection in all these cases. However, pancreatic surgery still carries a significant risk of complications (7). As such, these same guidelines consider active surveillance a possible alternative for selected low-grade tumors smaller than 2 cm without dilation of the main pancreatic duct—particularly in older patients, in clinical contexts where surgery is associated with increased morbidity or mortality, and especially for tumors located in the pancreatic head.

Nonetheless, the limitations of our current conceptual framework are evident. A large prospective international study found that almost 20 % of resected tumors smaller than 2 cm exhibited aggressive features (8), defined as Ki-67 over 20 %, perineural invasion, microvascular invasion, and nodal or distant metastases. A recent meta-analysis found lymph node involvement in more than 11 % of patients who underwent surgery (9), and a retrospective analysis of a large U.S. population-based database reported that surgery provided no clear prognostic benefit over observation for tumors smaller than 10 mm, but could improve survival in patients with larger

neoplasms (10). Furthermore, tumor grading—usually estimated from samples obtained via endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) or fine-needle biopsy (EUS-FNB)—also has important limitations. It has been reported that this assessment is feasible using EUS-FNA in fewer than 30 % of lesions smaller than 2 cm (11), and although a recent meta-analysis found an overall concordance between EUS-FNA/FNB and surgical specimens exceeding 80 %, significant variability was observed across studies, ranging from 53.8 % to 97.1 % (12).

Follow-up of patients also presents significant challenges. Available biomarkers, such as chromogranin A (13), have low sensitivity for detecting tumor progression, and routine imaging modalities, including gallium-based PET scans (14), may fail to detect early lymphatic or peritoneal invasion. Moreover, real-world clinical practice has shown that not all patients are able to adhere to recommended follow-up schedules (15), which may result in missed opportunities for potentially curative treatment.

The dynamic interplay between neoplastic cells and the immune system follows complex patterns, in which the emergence of new somatic mutations or epigenetic changes—whether spontaneous or treatment-induced—along with other poorly understood variables, can drastically alter tumor behavior and render it unpredictable. Lessons learned from the study of other complex and chaotic systems—such as the significant advances in climate modeling over recent decades—demonstrate that reliable predictions can only be achieved through integrative analyses that account for the nonlinear interactions and interdependencies among a large number of relevant variables. However, predictive modeling in oncology remains far from these structured approaches. Currently, recommendations made by multidisciplinary NET boards rely on static, morphology-based criteria that fail to capture the dynamic and multifactorial nature of tumor progression, and—even when statistically associated with clinical outcomes—do not allow for individualized patient prognoses.

Fortunately, after decades of stagnation, new technologies are poised to revolutionize our ability to predict the behavior of these neoplasms, ushering in a new era of precision medicine. Advances in genetics have underscored the prognostic significance of somatic mutations—particularly in the DAXX and ATRX genes—as well as alternative lengthening of telomeres (ALT), all of which is associated with an increased risk of

lymphovascular invasion, metastasis, and reduced overall survival (16). Although not widely recommended as standard clinical practice, the most recent ENETS guidelines already include the detection of these alterations as an additional factor in the evaluation of non-surgical treatment options. Emerging tools such as liquid biopsy—and especially the development of the NETest, a panel of 51 blood-based RNA markers—provide a novel approach to diagnostic and prognostic assessment. These tools overcome the limitations of accessibility and representativeness inherent to tissue sampling, demonstrating over 84 % accuracy in distinguishing stable from progressive disease, and more than 93 % accuracy in predicting treatment response (17)—including response to peptide receptor radionuclide therapy (PRRT) (18).

The exponential progress of artificial intelligence over the past decade has driven the emergence of radiomics, a field based on mathematical approaches that enable the quantitative analysis of the vast amount of information encoded in imaging studies—information that previously went unnoticed by the human eye. Early retrospective studies have shown its potential to predict disease-free survival (19), and an integrated nomogram, combined with a new computational pathology model, promises to improve our ability to predict the risk of liver metastases following curative-intent surgery (20).

The complexity and risks associated with pancreatic surgery compel us to provide patients with pNETs with accurate estimates regarding the behavior of their disease, along with follow-up tools capable of capturing its dynamic progression. At present, this remains an unmet clinical need. Although current evidence on the role of liquid biopsy and radiomics is still preliminary, their transformative potential is undeniable. Acknowledging the limitations of our current decision-making framework—and understanding that any progress toward truly personalized medicine will require the development of entirely new predictive methodologies—is a step in the right direction.

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