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Commentary

On the origin of "indolent" and "aggressive" non-functioning pancreatic neuroendocrine tumour: genetically unrelated or close relative?

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In the present issue of *Digestive and Liver Disease*, M. Falconi's team raises interesting questions in its article "The Size of Well Differentiated Pancreatic Neuroendocrine Tumors Correlates with Ki67 Proliferative Index and is not Associated with Age" [1].

If a conservative management of asymptomatic, small sporadic or syndromic non-functioning pancreatic neuroendocrine tumours (NF-PanNET) is now widely accepted [2,3], this raises several questions regarding the long-term natural history of these lesions and the definition of their malignancy. Indeed, it remains to be determined whether NF-PanNET with an "indolent" or an "aggressive" behaviour, since they cannot formally be called "benign" and "malignant", have a different, genetically unrelated, carcinogenesis or if their progression follows the "*adenoma- carcinoma sequence*". For example, in thyroid nodules, it appears that benign nodules carry a molecular signature that differs from carcinoma, providing evidence that benign and malignant nodules have an independent origin [4]. Answering this question for NF-PanNET would have important clinical consequences.

If age is not correlated with tumour size or with the Ki67 index as stated in Partelli's article and the risk of "malignancy" is not time-related, one could hypothesise that "indolent" NF-PanNET are genetically unrelated to "aggressive" tumours. Consequently, long-term careful management of these lesions should be considered, especially in young patients, since their long-life expectancy will unlikely increase the risk of malignant transformation. The consideration of age in the clinical management of patients with NF-PanNET remains controversial, even if in the available literature, age is rarely associated with tumour recurrence [5–7]. These questions also remain unresolved for other pancreatic neoplasms such as intraductal papillary mucinous neoplasm (IPMN) of the pancreas, in which "*adenoma-carcinoma sequence*" is well documented. For example, IPMNs in young patients show different epithelial subtypes from those in older patients, with a more favourable prognosis [8]. Furthermore, the high postoperative mortality of pancreatic surgery of up to 9% and the functional consequences of pancreatic resection should be considered in the benefit-risk balance of prophylactic pancreatic surgery [9,10].

From a clinical point of view, various clinical, radiological or pathological criteria have been proposed to tailor the management of NF-PanNET, including incidental finding, size (with various proposed cut-off), ductal dilatation, and Ki-67. However, even if preoperatively, taken separately, none of them can perfectly identify aggressive NF-PanNET. Indeed, clinical, radiological or pathological criteria might soon become outdated or at least completed by genetic or molecular markers. For example, genomic patterns of small PanNETs associated with a different risk for liver metastases have recently been identified [11,12]. Pea et al. reported three genomic patterns of small PNETs with a different risk for distant spreading. While some criteria, such as Ki-67 and ATL status, can be easily determined in routine practice, the assessment of more complex genomic assessment (chromosomal rearrangement) is not yet feasible [11]. These preliminary data are encouraging, even if their predictive value remains imperfect. Moreover, PanNET are not a homogeneous group of tumours, various tumorigenesis pathways may exist. Nonetheless, it is likely that the overall combination of molecular/genetic markers and clinical features will improve the management of PanNETs in the near future.

In a population with a long-life expectancy, "*failure is not an option*". What should be the next step? Surgeons should, as their

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medical counterparts, have access to international prospective, randomised [13] or translational research [14] on PanNETs to better understand their long-term natural history and make available a high-quality tumour biobank for research. Indeed, the *Prospective Evaluation of Asymptomatic Small Pancreatic Endocrine Neoplasms* (ASPEN) *study* (https://www.aspen-study.com) is the first step in achieving this.

Conflict of interest

None declared.

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