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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*, Pr Falconi's team raises interesting questions in its article “The Size of Well Differentiated Pancreatic Neuroendocrine Tumours 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 not 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**, taken separately, none of them can perfectly identify aggressive NF-PanNET. Consequently, 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]. 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 medical counterparts, **propose** international prospective, randomised [13] or translational research [14] on PanNETs to better understand their long-term natural history and make available high-quality tumour biobanks for research. The *Prospective*

Evaluation of Asymptomatic Small Pancreatic Endocrine Neoplasms (ASPEN) study (<https://www.aspen-study.com>) is the first step **in achieving this.**

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