Going above and beyond the pancreatic neuroendocrine tumor classification

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Over the last decades, significant progresses have been made in the diagnosis, understanding of pathophysiology and natural history and management of pancreatic neuroendocrine tumors (PanNETs). Nevertheless, the term of "*pancreatic neuroendocrine tumours*" encompasses a very large and heterogeneous group of tumours, that can be functional *i.e.* associated with clinical symptoms in relation with secreted peptides or non-functional, sporadic or from a genetic origin, indolent in the long-term or highly aggressive and shortly life- threatening. Facing such heterogeneous neoplasm/carcinoma, patients' management is highly challenging and as stated by Li and collaborators[1] in their comprehensive review, given the heterogeneity of these tumors, an individualized approach should be the goal.

In this issue of JCO Oncology Practice, Li and collaborators[1] nicely summarized current knowledge of the epidemiology, diagnostic evaluation, pathology assessment, and various treatment modality and strategy in the management of PanNETs, with a specific attention to ongoing controversies and trials. As they underline, several clinically relevant questions remain unanswered.

Radical resection is the only curative option for PanNETs but pancreatic surgery is associated with a significant morbidity and mortality. The mortality of pancreatectomies usually range from 1% to 4% in high-volume centers but increases above 10% when nationwide data are considered[2,3]. This should always be kept in mind when patients are selected for surgery, and the risk– benefit balance of the surgery has to be carefully weighted. Consequently, such resection should only be performed in expert and dedicated centers[4-6]. Surgery and especially patient selection for surgery has recently benefit a better knowledge of the natural history of < 2 cm, asymptomatic, non-functional PanNETs[7] and of the progress of diagnostic evaluation, including diffusion-weighted MRI and nuclear imaging with the development ^{68}Ga and a metabolic grading FDG PET/CT[8]. These recent progresses should not mask the lack of evidence, and it is important to note the absence of surgical randomized controlled study, while there is an increasing number of oncological randomized controlled trials published or ongoing. The lack of "*evidence-based surgery"* call for a larger implication of surgeons in true collaborative network.

Systemic therapies have made a great leap forward in recent years, with the publication of several randomized controlled studies some of them only dedicated to PanNET[9]. Additionally, as summarized in the present review, numerous trials are ongoing, increasing in a near future the armamentarium of treatment options for our patients. If several of these trials are driven by the industry, others are true academic trials, and interestingly trials addressing therapy sequencing such as SEQTOR trial (*Efficacy and Safety of Everolimus and (STZ-5FU) Given One Upfront the Other Upon Progression in Advanced PanNET***)** are also in progress. This is key to study patients having a long-life expectancy, for whom quality of life is key and can be altered by the sequence of treatment.

Up to now, available recommendations are mainly based on 2017 WHO histopronostic classification, regularly updated. There is no doubt, as in many other neoplasms, that genetic testing with next-generation sequencing, will in a near future help to tailor patient's treatment and avoid a one-size- fits-all strategy. This will be at some point included in clinical recommendations to better tailor panNET management and enabling the future of personalized medicine. Nevertheless, in order to accomplish such progresses, we need to build strong collaborative multidisciplinary network including basic scientist, genetician, surgeons, radiologists, interventional radiologist, gastroenterologist pancreatologist, pathologist, diabetologist, psychologist, nutritionist and oncologist.

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