



Treatment sequencing for pancreatic neuroendocrine tumors: daring to challenge the status quo

The incidence of pancreatic neuroendocrine tumors (pNETs) continues to increase, prompting renewed interest in the pathophysiology and treatment of this disease (1). These rare tumors are biologically distinct from pancreatic ductal carcinoma (PDAC) and account for less than 3% of pancreatic cancers. While the prognosis of patients with pNET in general is more favorable than PDAC, there is wide variation in phenotype and survival outcomes between patients. Surgical resection has been the mainstay of therapy, but recently, a plethora of clinical trials have identified novel therapies that improve symptom free survival and delay disease progression.

Treatment sequencing has been widely explored in most all solid tumors. For example, there is strong evidence for the addition of radiotherapy and chemotherapy to surgery in the treatment of localized PDAC, with many advocating for delivery of these treatments neoadjuvantly to maximize receipt of therapy and improve outcomes. However, there is little data to guide arguments for treatment sequencing in pNET, and until recently, adjuvant therapeutic options were limited. Our improved understanding of the molecular pathways involved in the tumorigenesis of pNETs has resulted in the development of novel therapies which have greatly expanded the options for treatment sequencing in patients with locally advanced and metastatic pNETs.

Therapeutic decisions surrounding the optimal sequence of treatments in patients with pNET must first be centered on the tumor. Tumor grade as defined by the World Health Organization (WHO) carries both prognostic and predictive significance (2). Both tumor differentiation and tumor proliferation are important harbingers of tumor biology. The differentiation of highly proliferative well-differentiated tumors (G3-NET) and poorly differentiated carcinomas (NEC) is an important one that has prompted debate on optimal management of these high-grade tumors (3). In general, NECs are associated with shorter recurrence-free survival and overall survival even after curative resection (3). This begs the question, would patients with NEC, even those with apparently localized disease, benefit from systemic therapy first? Could we spare those at highest risk for distant failure a non-curative resection that confers little benefit?

Knowing the extent of disease and the surgeon's ability to provide complete tumor extirpation is also critical to achieving optimal outcomes. The development of the radiographic isotope Gallium-68 (^{68}Ga) DOTATATE for use in positron emission tomography (PET) has significantly improved visualization of NETs. Accurate delineation of the extent of disease now allows for improved surgical planning and a more informed discussion of treatment sequencing especially in patients with metastatic or locally advanced tumors (4). ^{68}Ga - DOTATATE PET can also allow for predicting and assessing treatment response. In addition, in patients with synchronous liver metastases where pancreatectomy would require a biliary enteric anastomosis, the order of surgical therapies may be very important. A biliary enteric anastomosis will allow bacteria access to the liver and thereby increase the risk for liver abscess after liver directed therapy (5). The implications of identifying and treating liver metastasis prior to pancreatic resection may encourage the sequencing of other therapies, including liver directed treatments and/or systemic therapy prior to surgical resection of the primary tumor in the pancreas. The role of peptide receptor radionuclide therapy (PRRT) and other targeted therapies as a neoadjuvant strategy is also being investigated (6).

While no clear guidelines exist to support the best sequence of treatments in patients with pNET, the current advances in molecular research inch towards a more personalized approach to the multimodality therapy of pNETs. This focused series comprehensively reviews the pathophysiology, tumorigenesis, available clinical trials, and approved therapies for patients with pNETs. A deeper understanding of these factors is necessary to enhance our efforts to improve patient outcomes through the application of more innovative treatment sequencing. While patients with a localized, resectable tumor may go straight to surgery, those with locally advanced or synchronous metastatic disease may benefit from the delivery of a more complicated series of treatments which are somewhat personalized to the patient and the molecular/proliferative profile of their tumor.

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