Consensus Statement

Keynote: Neuroendocrine Tumours

A. What is the role of mTOR inhibitors combined with octreotide in the treatment of advanced low and intermediate grade neuroendocrine tumours?
   - Treatment with everolimus and octreotide LAR may be considered in patients with a history of symptoms consistent with carcinoid and documented progressive disease (Level I)³.
   - Correcting for the informative sensoring bias, a 5.5 month progression free survival benefit was seen (Level I)³.

B. What is the role of Octreotide LAR in the treatment of asymptomatic advanced low and intermediate grade midgut neuroendocrine tumours?
   - The PROMID study² showed a time to progression benefit for patients with metastatic low- and intermediate- grade midgut neuroendocrine tumours (Level I).
   - This data does not present a strong case for immediate introduction of octreotide LAR therapy in these patients (Level III).
   - Patients who become symptomatic, demonstrate disease progression, or have a biochemical indication for therapy could be considered for octreotide LAR therapy. These patients should also be considered for multidisciplinary evaluation (Level III).
A. What is the role of everolimus and sunitinib in the treatment of advanced pancreatic neuroendocrine tumours?
   - Both agents have demonstrated a progression free survival benefit compared to placebo in a randomized phase III trial setting. The magnitude of benefit is similar for the two agents (Level I)\(^4,5\).
   - The optimal sequencing of these agents in reference to other treatment modalities has not been established (Level III).

B. What is the role of resection of the primary tumor in the setting in advanced neuroendocrine tumours?
   - These patients should be referred to an experienced surgical team, and reviewed in a multidisciplinary setting to define the most appropriate treatment options (Level III).
   - Resection of the primary tumour may provide clinical benefit (Level II-2).

C. What is the role of debulking surgery in the management of advanced neuroendocrine tumours?
   - Debulking performed by a specialized surgical team should be considered in a multidisciplinary setting for patients with metastatic disease. Resection may offer benefits in terms of palliation, reduction of serum serotonin metabolite levels, outcomes, and response to subsequent therapies (Level II-2).

D. What are the indications for radioisotope therapy in the management of neuroendocrine tumours?
   - Baseline octreotide and MIBG scans are required if radioisotope therapy is being considered (Level III).
   - Indications for therapy include progressive disease or progressive symptoms, regardless of whether or not tumours are functional or non-functional (Level III).
   - Prospective multicentre trials are required to better elucidate the indications for radioisotope therapy in this patient group (Level III).
Locally Advanced Pancreatic Tumors

A. What is the definition of borderline resectable pancreatic cancer?

- These patients should be referred to an experienced surgeon with expertise in the surgical management of pancreatic cancers to determine resectability status.
- We are in agreement with the consensus definition of borderline resectable pancreatic cancer sponsored by the American Hepato-Pancreato-Biliary Association, Society of Surgical Oncology and Society for Surgery of the Alimentary tract which includes the following features:
  - No evidence of distant metastases,
  - There may be venous involvement of the superior mesenteric vein (SMV)/portal vein due to tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but no encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to area of vessel involvement, allowing for safe resection and reconstruction.
  - There may be gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, but no extension to the celiac axis
  - The tumour may abut the superior mesenteric artery but does not exceed 180 degrees of the circumference of the vessel wall.

B. What is the role of systemic therapy in the management of locally advanced pancreatic cancer?

- In the absence of a clinical trial, patients with good performance status can be considered for gemcitabine +/- erlotinib (Level I)
- We encourage further investigation of FOLFIRINOX in this patient population

C. What is the role of combined chemoradiation in the management of locally advanced pancreatic cancer?

- There is no consistent evidence for benefit of chemoradiation over chemotherapy in patients with locally advanced pancreatic cancer (Level III).
- Chemoradiation could be considered in selected patients after discussion in a multidisciplinary setting (Level III).

D. What is the role of stereotactic radiation in the management of locally advanced pancreatic cancer?

- At present, there is no evidence to support the use of stereotactic radiation in the management of locally advanced pancreatic cancer.
Levels of Evidence

I Evidence from randomized controlled trial(s)
II-1 Evidence from controlled trial(s) without randomization
II-2 Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group
II-3 Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here
III Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

References
1. Canadian Task Force on Preventive Health Care: Levels of Evidence - Research Design Rating, 2003, pp Levels of evidence as defined by the Canadian Task Force on Preventive Health Care