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Clinical Practice Guidelines – Gastrointestinal Disease Site

Guideline Title:	Treatment of Borderline Resectable and Locally Advanced Pancreatic Cancer - **Summary**	**Date:**	**(O):** **(R):**	May 1, 2013
Tumor Group:	G. I. Disease Site Group	**Page:**		1 of 7
Issuing Authority:	Dr. Jehan Siddiqui Clinical Chief, Cancer Care Program	**Date Signed:**		June 24, 2014
Adapted From:	Up To Date "Initial chemotherapy and radiation for nonmetastatic locally advanced unresectable, borderline resectable, and potentially resectable exocrine pancreatic cancer", March 2014 (85).			

Target Population:

These recommendations apply to patients diagnosed with borderline resectable or locally advanced pancreatic cancer (LAPC).

Recommendations:

The following recommendations of the Eastern Health G. I. Disease Site Group apply to patients with radiographical and/or pathological confirmed borderline resectable or locally advanced pancreatic cancer:

- The American Hepato-Pancreato-Biliary Association (AHPBA) in cooperation with the Society of Surgical Oncology (SSO), and the Society for Surgery of the Alimentary Tract (SSAT) definition of borderline resectable pancreatic cancer and the National Comprehensive Cancer Network (NCCN) definition of 'unresectability' of locally advanced pancreatic cancer are acceptable for use in this guideline;
- The preferred pre-operative imaging modality for regional staging is the triphasic CT scan. If resectability remains in question, endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) can be complementary to CT. Laparoscopy and positron emission tomography (PET) may also be used selectively to rule out metastatic disease;
- All patients with borderline resectable or LAPC who are eligible for neoadjuvant therapy should undergo a reasonable attempt to obtain a tissue biopsy. The GI group recognizes the theoretical risk associated with peritoneal seeding; therefore, a EUS is recommended to reduce this risk, as well as to increase diagnostic yield and safety. If EUS is unavailable, a CT-guided biopsy may be an acceptable alternative;
- Pre-treatment serum carbohydrate antigen (CA 19-9) and carcinoembryonic antigen (CEA) levels, as well as baseline laboratory investigations including complete blood count, electrolytes, liver and renal function tests should be performed;
- Appropriate management of obstructive jaundice (i.e. biliary decompression) is required prior to commencing neoadjuvant treatment;

- All patients should enroll in a clinical trial whenever possible. In the absence of which, patients should be added to a national or international registry where one exists;
- All patients should be discussed in a multidisciplinary tumor board which includes representatives from medical oncology, hepatobiliary surgery, radiation oncology and radiology;
- Classification of disease as either borderline or locally advanced unresectable should occur prior to initiation of treatment. Controversy exists as to whether neoadjuvant therapy and potential surgical resection can achieve cure in patients diagnosed with LAPC. However, in the present setting where no standardized treatment approach exists for this patient population, patients deemed appropriate by a multidisciplinary tumor board may be offered similar treatment options as that of the borderline resectable population;
- The GI group acknowledges that no international consensus exists on the treatment of patients presenting with borderline resectable or locally advanced unresectable pancreatic cancer. However, the GI working group has elected to create a Cancer Care guideline to recognize the growing body of literature regarding the neoadjuvant management of this unique patient population:
    - Patients with an Eastern Cooperative Oncology Group (ECOG) score of 0-1, appropriate laboratory values and minimal comorbidities will be offered a combination chemotherapy regimen, consisting of fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) chemotherapy. Patients will be reassessed at a multidisciplinary tumor board before and during treatment to evaluate resectability. This recommendation is based on limited, retrospective evidence.
    - Patients unsuitable for FOLFIRINOX chemotherapy will be offered single agent gemcitabine or a gemcitabine doublet. The latter option is based on an extrapolation from clinical trials consisting of LAPC and metastatic pancreatic cancer patient populations. There is insufficient evidence to offer nab-paclitaxel plus gemcitabine at this time.
    - Given the results of the LAP 07 clinical trial, chemoradiation therapy (CRT) will not be offered routinely to patients undergoing neoadjuvant therapy for pancreatic cancer, but may be discussed on a case by case basis within a multidisciplinary tumor board setting. Furthermore, erlotinib will not be offered based on the results of this study as well and the questionable clinical significance of erlotinib observed within the NCIC CTG PA.3 clinical trial.
- Patients who exhibit a tumor response following neoadjuvant treatment should be reassessed for surgical resection. Tumor reassessment may include CT scan, CA19-9, CEA and a potential laparotomy as per the consensus of the multidisciplinary tumor board;
- Option of adjuvant therapy will be at the discretion of the medical oncologist.

Supporting Evidence:

Neoadjuvant FOLFIRINOX has become a viable option for gemcitabine, as the primary chemotherapy regimen of choice for patients with a good PS, in many centers in the United States for the treatment of borderline resectable and locally advanced pancreatic cancer (1). The basis for this treatment option includes evidence that the FOLFIRINOX regimen may be the superior option in terms of progression-free survival (PFS), overall survival (OS) and surgical resectability rates versus gemcitabine alone (2-14). Alternative chemotherapy options could include single agent gemcitabine or a gemcitabine doublet (15-25). Neither nabpaclitaxel nor erlotinib will be offered in combination with gemcitabine at this time (26-29).

Much controversey exists as to whether radiation therapy provides additional benefit to that of chemotherapy alone, in the settings of borderline resectable and locally advanced pancreatic cancers. Recent evidence, however, suggests that neoadjuvant CRT does not provide additional benefit, in terms of PFS and OS, over neoadjuvant chemotherapy alone (29). Therefore, for LAPC, the standard of care should remain neoadjuvant chemotherapy, with CRT being an option if tumor control is achieved.

Qualifying Statements:

Definitions of resectable tumors, borderline resectable tumors and unresectable tumors as accepted by the G .I. Disease Site Group, are as follows:

- Resectable Tumors (30) – are those considered localized and should demonstrate:
  - No distant metastases;
  - No radiographic evidence of superior mesenteric vein (SMV) and portal vein (PV) abutment, distortion, tumor thrombus, or venous encasement;
  - Clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA).

- Borderline Resectable Tumors (30) – are those that include:
  - No distant metastases.
  - Venous involvement of the SMV/PV demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/PV but without 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 the area of vessel involvement, allowing for safe resection and reconstruction.
  - Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
  - Tumor abutment of the SMA not to exceed > 180° of the circumference of the vessel wall.

- Unresectable Tumors (31) – are locally advanced and metastatic pancreatic cancers with the following characteristics:
  - Head of the pancreas lesion*
    - Greater than 180° SMA encasement, any celiac abutment
    - Unreconstructible SMV/portal occlusion
    - Aortic invasion or encasement
    - Distant metastases (for metastatic pancreatic cancer)
  - Body of the pancreas*
    - SMA or celiac encasement greater than 180°
    - Unreconstructible SMV/portal occlusion
    - Aortic invasion
    - Distant metastases (for metastatic pancreatic cancer)
  - Tail of the pancreas*
    - SMA or celiac encasement greater than 180°
    - Distant metastases (for metastatic pancreatic cancer)

Note: Review AJCC Pancreas Cancer Staging Poster in the Appendix

- Nodal Status
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable.

Disclaimer:

These guidelines are a statement of consensus of the Eastern Health Gastrointestinal Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

Contact Information:

For more information on this guideline, please contact Dr. Melanie Seal MD FRCPC, Dr. H. Bliss Murphy Cancer Center, St. John's, NL; Telephone 709-777-7802. For the complete guideline on this topic or for access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

Literature Support:

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Appendix:

American Joint Committee on Cancer

Pancreas Cancer Staging*

7th EDITION

Definitions

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ1**
- T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
- T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
- T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

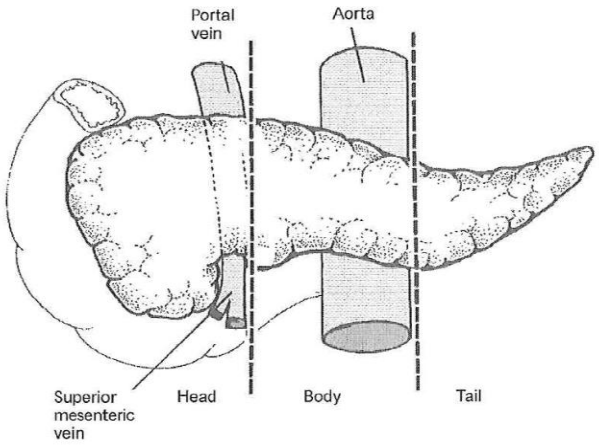
Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1



Tumors of the head of the pancreas are those arising to the right of the superior mesenteric-portal vein confluence.

Notes

* Endocrine AND exocrine tumors are now staged by a single pancreatic staging system.

** Also includes the "PanIntIII" classification.

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