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Clinical Practice Guidelines – Gastrointestinal Disease Site

Guideline Title:	Treatment of Borderline Resectable and Locally Advanced Pancreatic Cancer	**Date:**	**(O):** **(R):**	May 1, 2013
Tumor Group:	G. I. Disease Site Group	**Page:**		1 of 23
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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).			

Introduction:

Cancer of the pancreas is the fourth leading cause of cancer-related death in men and women, Canada, with an estimated 5-year survival of approximately 8% according to the latest data (1). The majority of exocrine pancreatic cancers are adenocarcinomas (85% - 95%). Typically patients present after the age of 50 years and the risk increases with each subsequent decade. Many patients present with symptoms of advanced disease such as obstructive jaundice, epigastric or back pain, weight loss and anorexia. Unfortunately, due to the late onset of symptoms, most patients with this malignancy will present with metastatic disease (2). Thus, the primary therapeutic goal in the majority of patients with adenocarcinoma of the pancreas will be of palliative intent (maintain or enhance quality of life and potentially improve survival).

The only potentially curative treatment is surgical excision of the primary tumor and regional lymph nodes. Only 15% of patients are considered to have ***resectable*** disease at diagnosis. Furthermore, the median survival for this cohort is only 18 months as many will develop local, regional or systemic recurrence of their disease (2,3). Twenty-five percent of patients with adenocarcinoma of the pancreas have surgically unresectable disease but no evidence of distant metastases, and are referred to as ***locally advanced pancreatic cancers (LAPC)***. Currently, there is no consensus on how to best manage these tumors and there is a desperate need of new research protocols to add to the limited existing body of literature on the treatment of LAPC. The oncology community awaits the results of clinical trials exploring neoadjuvant therapies that may 'downstage' these cancers, allowing them to become amenable to surgical resection and potential cure. Furthermore, the emerging classification of ***borderline resectable*** disease adds equipoise to the best management of these tumors. In the interim, the need arises for a treatment plan using a multidisciplinary approach for patients presenting with borderline resectable and LAPC, which was the impetus for the creation of this guideline.

Questions:

1. How is surgical resectability defined for patients with pancreatic cancer?

2. What are the optimal treatment options for patients with borderline resectable or locally advanced pancreatic cancer?

Target Population:

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

Supporting Evidence:

Surgical Resectability Criteria

Adenocarcinoma of the pancreas most frequently originates in the head of the pancreas, with approximately 15-20% occurring in the body and tail. Tumors of the body and tail of the pancreas have historically been associated with a poorer prognosis due to late presentation. Resectable tumors of the head of the pancreas usually require a surgical pancreatoduodenectomy (or Whipple procedure) while those of the body and tail undergo a distal pancreatectomy and splenectomy (4,5). LAPC are tumors deemed to be surgically unresectable, but have no radiological evidence of distant metastatic spread. Historically, due to the poor prognosis of these tumors, those patients diagnosed with LAPC were often grouped into studies with patients who had metastatic disease. Recent advances in imaging and surgical techniques, however, have revealed a subgroup of patients in the locally advanced category identified as 'borderline resectable', which theoretically may benefit from a neoadjuvant (treatment prior to surgery) approach. A widespread lack of consistency in what constitutes resectability of pancreatic cancer has made a consensus on the role of multimodality treatment problematic (6).

A conference held by the American Hepato-Pancreato-Biliary Association (AHPBA) in cooperation with the Society of Surgical Oncology (SSO), the Society for Surgery of the Alimentary Tract (SSAT), the University of Texas M. D. Anderson Cancer Center, and the Gastrointestinal Symposium Steering Committee (GSSC) has aimed to address this issue by developing consensus statements on the definitions of resectable and borderline resectable pancreas cancer (7). First used at the M. D. Anderson Cancer Center in Texas, this anatomy-driven approach allows an objective, computed tomography (CT)-based diagnostic classification, in conjunction with the most current American Joint Committee on Cancer (AJCC) staging system, to aid in determining local tumor resectability (8).

- Resectable Tumors – are those tumors considered localized and which demonstrate the following:
  - 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 – are those tumors that include the following:
  - 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.

The 2013 consensus-based guideline National Comprehensive Cancer Network (NCCN) defined **unresectability** (locally advanced and metastatic pancreatic cancer) has having the following characteristics (82):

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

To clarify for the purposes of this guideline, **locally advanced pancreatic cancer** will be defined as unresectable pancreatic cancer (as per the NCCN definition above) with no evidence of distant metastases.

Pre-treatment Staging

Radiological Staging

According to the 2013 Eastern Canadian Cancer Consensus, the preferred pre-operative imaging modality for the regional staging of pancreatic cancer is a triphasic CT scan. Endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) can be complementary to CT when the potential for resectability is unclear. Though not routine, laparoscopy and/or positron emission tomography (PET) may also be used to rule out metastatic disease (9).

Biopsy

Controversy continues to exist as to whether obtaining a cytologic or tissue diagnosis of pancreatic cancer prior to surgery is necessary. The advantages of this approach include pathological proof of malignancy and its type, which may aid in the determination of the optimal neoadjuvant treatment course, while excluding non-malignant pathologies. The disadvantages

Note: Review AJCC Pancreas Cancer Staging Poster in the Appendix

include the risk of seeding which in turn reduce the likelihood of obtaining a complete surgical resection, risk of procedural complications, and the elevation of healthcare costs (10,11). The latest guidelines from both NCCN and the European Society of Medical Oncologists (ESMO) suggest that a biopsy be performed in all cases of locally advanced unresectable pancreatic cancer as well as for those cases where preoperative or neoadjuvant therapy is planned (78,82).

When indicated, a fine needle aspiration (FNA) biopsy of a pancreatic mass can be accomplished either percutaneously under CT-guidance or via endoscopic ultrasound. Few studies have compared these two sampling techniques. However, one prospective, randomized crossover trial comparing endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) with CT or ultrasound (US)-guided FNA in diagnosing pancreatic cancer, found no statistical difference between either approaches (12). Several theoretical advantages are offered by the EUS-FNA technique, which include reduction in the risk of needle-tract seeding, shorter distance to the mass, the ability to continuously visualize the needle tip and to identify vascular structures with Doppler ultrasound (11). A meta-analysis of 33 studies has demonstrated that EUS-FNA is a safe and highly accurate diagnostic technique to confirm the diagnosis of pancreatic cancer (13). However, when EUS is unavailable or inappropriate, a CT-guided biopsy may be an acceptable alternative.

Tumor Markers

Tumor marker serum carbohydrate antigen (CA19-9) has been found to be elevated in 75%-85% of patients with pancreatic cancer, but it has also been found to be elevated in patients with pancreatitis (14,15). Therefore, it is not reliable in screening or diagnosis alone, but can be useful for monitoring the effect of treatment. Carcinoembryonic antigen (CEA), commonly seen in gastrointestinal malignancies, has been found to be elevated in 40%-45% of patients with pancreatic cancer, and may also be useful for the monitoring of treatment response (14). Prior to treatment, CA 19-9 and CEA levels should be obtained, as well as baseline laboratory investigations such as complete blood count, electrolytes, liver and renal function.

Therapeutic Options

A multidisciplinary approach in the management of patients with pancreatic adenocarcinoma is crucial in identifying the most appropriate therapeutic options. Management of patients with pancreatic cancer include professionals from medical and radiation oncology, surgery, interventional radiology, gastroenterology, pathology, nutrition and palliative care. Both patient related [age, comorbid status, performance status (PS)] and disease dependent (presence of jaundice, steatorrhea, anorexia) factors play a role in the treatment of this disease.

Biliary Decompression

Patients often present with serious symptoms such as obstructive jaundice consistent with tumor compression of the biliary duct, which is consistent with tumors located in the head of the pancreas. Blockage of the biliary duct results in hyperbilirubinemia and its associated sequelae. Although biliary stenting is controversial in patients who are eligible for immediate surgery, evidence suggests it may be appropriate for those patients requiring neoadjuvant therapy, especially when chemotherapeutic agents require normalization of liver function (16,17).

Neoadjuvant Therapy

Neoadjuvant therapy has become more popular in all areas of oncology practice today. It has found favor among oncologists for use in the treatment of locally advanced cancers, as it may enable these tumors to become amenable to resection. Use of neoadjuvant treatment with chemotherapy alone, or in combination with radiation in LAPC, has several theoretically perceived benefits over that of adjuvant (post-surgery) therapy, especially for appropriate patients with locally advanced disease (18). These include:

- Increased compliance
    - Patients will be more likely to receive all components of their multimodality treatment plan. Consistently, studies have shown that a significant proportion of patients were unable to receive the adjuvant (post-operative) therapy in their original treatment plan, due to potentially lengthy recovery from such extensive surgery;
- More effective drug delivery
    - Neoadjuvant therapy is administered when the oxygen supply to the tumor site has not been affected by surgical intervention, and therefore at its optimum and believed to provide the most effective cell kill;
- Avoidance of surgery in early relapsers
    - A neoadjuvant approach allows an observation period for patients who have occult disease and/or unresponsive rapidly progressing disease. Thus, those patients would be excluded from the unnecessary morbidity of surgical resection;
- Downstaging of tumor
    - Patients could have their disease downstaged to resectable status with neoadjuvant therapy.

Potential disadvantages of neoadjuvant therapy include:

- requirement for preoperative biopsy and subsequent risk of tumor seeding;
- chemotherapy and/or radiation toxicities which may require further delay to surgical resection;
- potential for increase in post-operative complications;
- lack of response to neoadjuvant treatment resulting in disease progression may deem the patient to be ineligible for surgery (though probability of surgery being curative in the setting of a quick progression is low) (9).

Recently, neoadjuvant therapy has been frequently used in an attempt to downstage, surgically resect, and potentially cure some patients with borderline resectable pancreatic tumors. Patients with LAPC, however, were considered to be incurable and believed to have microscopic metastases, despite no radiological evidence of metastases. Treatment regimens frequently revealed poor response rates, high toxicity, and inability to change the natural history of the disease (19). However, recent data suggests that neoadjuvant therapy and subsequent surgical resection may offer improved progression free survival (PFS) and provide a small subset of patients with LAPC the same survival benefit as those patients with resectable disease (20).

Systemic therapy options for the treatment of pancreatic cancer include mainly chemotherapy. There remains a paucity of new, novel targeted agents coming into clinical practice over the past few years. Pancreatic cancer is known to have several genetic aberrations in signaling

pathways such as K-ras (occurring in 75%-90% of cases), Hedgehog, aurora kinase, SMAD4 and p16; however, none of these have been validated for clinical decision making thus far (82).

Chemotherapy with Gemcitabine

For over 15 years, gemcitabine has been the cornerstone of chemotherapy treatment for patients with advanced pancreatic cancer, with a modest superiority demonstrated over fluorouracil (5FU), resulting in median survival durations of 5.65 months versus 4.41 months, respectively (p = .0025) (21). Since that time, many trials have attempted to improve upon this benefit by combining gemcitabine with other cytotoxic agents, including platinum analogs (cisplatin, oxaliplatin), fluoropyrimidines (5FU, capecitabine), irinotecan, docetaxel, as well as, several molecular targeting agents (erlotinib, cetuximab, bevacizumab, axitinib, sorafenib) with limited success.

Gemcitabine doublets

In recent years, several meta-analyses have been performed comparing gemcitabine to gemcitabine-based combination therapies in the treatment of locally advanced and metastatic pancreatic cancer. These meta-analyses have consistently shown an overall survival (OS) benefit for gemcitabine-based combination chemotherapy compared to treatment with gemcitabine alone, albeit toxicities were also more frequent (22-31). Four of the most current meta-analyses divided the gemcitabine-based combinations into subgroups for analysis: gemcitabine plus fluoropyrimidines, gemcitabine plus platinum, gemcitabine plus irinotecan, gemcitabine plus other cytotoxic agents, and gemcitabine plus targeting agents (28-31).

One analysis of 18 randomized controlled trials (RCTs) compared gemcitabine with gemcitabine-based doublets. Patients (n=4237) were subdivided into 5 subgroups, which included gemcitabine/capecitabine (GEMCAP), gemcitabine/cisplatin (GEMDDP), gemcitabine/5-fluorouracil (GEMFU), gemcitabine/irinotecan (GEMIRI), and gemcitabine/oxaliplatin (GEMOX) (28). The results of this subgroup analysis included:

- Compared with gemcitabine alone, gemcitabine-based cytotoxic doublet chemotherapy reduced the risk of death by 9% in 6-month OS (risk ratio, 0.91, 95% CI: 0.85-0.97, p = 0.005). While for 1-year OS, doublet therapy reduced the risk of death by 4% (risk ratio, 0.96, 955 CI: 0.93-0.99, p = 0.02).
- The five separate subgroups were evaluated for 6-month OS. Only GEMCAP and GEMOX significantly reduced the risk of death by 15% (risk ratio, 0.85, 95% CI: 0.73-0.99, p = 0.04) and 20% (risk ratio, 0.80, 955 CI: 0.70-0.91, p = 0.001), respectively. The other three regimens did not significantly improve OS. For 1-year OS, the sub-group analysis has shown that GEMOX potentially reduced the risk of death by 7% (risk ratio, 0.93, 95% CI: 0.87-1.00, p = 0.05), while the remaining four regimens did not show a survival benefit.
- Subgroup analysis divided patients into a good PS group [Karnofski Performance Status (KPS) = 90-100, Eastern Cooperative Oncology Group (ECOG) 0-1] or a poor PS group (KPS = 60-80, ECOG 2), with four trials providing data on these two groups. Patients with advanced pancreatic cancer, who had a poor PS were at increased risk of death with gemcitabine-based cytotoxic doublets chemotherapy.

Another meta-analysis reviewed 35 trials dividing a total of 9979 patients, into the following subgroups: gemcitabine/fluoropyrimidine (capecitabine or 5-FU), gemcitabine/platinum (cisplatin or oxaliplatin), gemcitabine/camptothecin (irinotecan or exatecan), gemcitabine/other agents (pemetrexed or docetaxel), and gemcitabine/targeted therapy (29). The results were:

- Gemcitabine-based combination therapy, again was associated with significantly better OS (odds ratio, 1.15; 95% CI, 1.03-1.28; p = 0.011) than gemcitabine alone. Gemcitabine-based combination also had favorable progression free survival (PFS) compared to gemcitabine alone (odds ratio, 1.27; 95% CI, 1.14-1.42; p < 0.001). A similar advantage for gemcitabine-based combination was observed in terms of overall response rate (ORR) (odds ratio, 1.58; 95% CI, 1.31-1.91; p < 0.001) with no significant heterogeneity (p = 0.79);
- Gemcitabine versus gemcitabine/fluoropyrimidine – Analysis showed a significant improvement in OS (odds ratio, 1.33; 95% CI, 1.08-1.64; p = 0.007), PFS (odds ratio, 1.53; 95% CI, 1.24-1.88; p = 0.000), and ORR (odds ratio, 1.47; 95% CI; 1.04-2.07; p = 0.03) when gemcitabine was combined with fluoropyrimidine. The odds ratio for 1-year survival in the gemcitabine/fluoropyrimidine group as compared to gemcitabine alone was 1.08 (95% CI, 0.82-1.43; p = 0.58);
- Gemcitabine versus gemcitabine/platinum – Subgroup analysis comparing gemcitabine/oxaliplatin versus gemcitabine alone showed a statistically significant benefit for both OS (odds ratio, 1.33; 95% CI, 1.05-1.69; p = 0.019) and PFS (odds ratio, 1.38; 95% CI, 1.08-1.76; p = 0.011) in the combination arm. However, the comparison of gemcitabine/cisplatin with gemcitabine alone showed no survival benefit. No difference was found for 1-year survival between gemcitabine/platinum versus gemcitabine alone, but there was a significant improvement in OS in the gemcitabine/oxaliplatin group in the subgroup analysis (odds ratio, 1.40; 95% CI, 1.02-1.93; p = 0.04);
- Gemcitabine versus gemcitabine/other agents – The analysis indicated that OS in both the pemetrexed and docetaxel combination groups were lower than the gemcitabine alone group, though the ORR analysis showed therapeutic benefit of the combinations.
- Gemcitabine versus gemcitabine/targeted therapy – The analysis included nine trials of gemcitabine and molecular targeted agents, but only gemcitabine/erlotinib (a tyrosine kinase inhibitor) combination has shown a significant improvement in OS.

In 2012, another gemcitabine versus gemcitabine combination meta-analysis was undertaken in locally advanced or metastatic pancreatic cancer. Twenty-six studies with a total of 8808 patients were included and subdivided the gemcitabine combinations into 4 groups: platinum, fluoropyrimidine, camptothecin, and targeted agents. It found that patients treated with gemcitabine monotherapy had significantly lower ORR (objective response rate) (risk ratio, 0.72; 95% CI: 0.63-0.83; p < 0.001], and lower 1-year OS (risk ratio, 0.90; 95% CI: 0.82-0.99; p = 0.04). Gemcitabine monotherapy caused fewer complications, including fewer grade 3-4 toxicities including vomiting, diarrhea, neutropenia, anemia and thrombocytopenia compared with gemcitabine combination therapies. The data of median PFS and OS in every study were extracted and assessed by a paired *t*-test. The results showed that only gemcitabine plus fluoropyrimidine significantly increased the median PFS (3.480 versus 4.520; p = 0.045) and median OS (6.95 versus 7.84 months) (30).

A 2013 Italian meta-analysis of thirty-four trials with a total of 10,660 patients, again investigated the efficacy and safety of gemcitabine-based combination regimens as compared to gemcitabine alone in the management of locally advanced and metastatic pancreatic cancer. A subgroup analysis described a significant OS advantage only for fluoropyrimidine-based schedules. Interestingly, the remaining other subgroups did not reach a significant OS advantage, with the exceptions of the platinum and irinotecan-based schedules, even when a survival trend was revealed in favor of combination therapy. To further clarify the benefit due to the addition of fluoropyrimidines or platinum to gemcitabine, these two subgroups were further

divided comparing cisplatin versus oxaliplatin and oral versus intravenous (IV) administration of fluoropyrimidines. A significant hazard ratio (HR) of 0.86 in favor of oxaliplatin and orally administered fluoropyrimidines was found, while cisplatin and IV fluoropyrimidine administration failed to reach statistical benefit (31).

A new phase III randomized trial (MPACT), released at ASCO in 2013, looked at 861 patients with metastatic pancreatic cancer with a Karnofsky PS of ≥ 70 who received either nab-paclitaxel plus gemcitabine or gemcitabine alone (32). Nab-paclitaxel/gemcitabine was found to be superior to gemcitabine alone in median OS 8.5 versus 6.7 months, respectively (hazard ratio 0.72; 95% CI, 0.617 – 0.835; p = 0.000015); median PFS 5.5 versus 3.7 months, respectively (HR 0.69; 95%CI, 0.581 – 0.821; p = 0.000024); and ORR was 23% vs 7% (p = 1.1 x 10^{-10}) by RECIST. Importantly, the combination nab-paclitaxel/gemcitabine arm had a very acceptable toxicity profile compared to gemcitabine alone, and also appears to have been well tolerated by a subgroup of patients with a poorer PS (KS 70-80 vs 90-100). This new regimen has recently received FDA approval in the United States for the treatment of metastatic pancreatic cancer.

Gemcitabine and erlotinib
Erlotinib is a tyrosine kinase inhibitor of epidermal growth factor receptors (EGFR) which is believed to interfere with the growth of pancreatic cancer while improving the anticancer effects of gemcitabine (33). Despite many trials investigating the combination of molecular targeted agents and gemcitabine, only erlotinib has shown a statistically significant survival advantage when given in addition to gemcitabine for unresectable, locally advanced, or metastatic pancreatic cancer (33,34). In a double-blind phase III trial, 569 patients with unresectable, locally advanced, or metastatic pancreatic cancer were randomly assigned to receive either gemcitabine plus erlotinib or gemcitabine plus placebo. Based on intent-to-treat analysis, OS was significantly prolonged on the erlotinib/gemcitabine arm with a median 6.24 months vs 5.91 months, with an HR of 0.82 (95% CI, 0.69 to 0.99; p=.038) (34). Most notable adverse events associated with the addition of erlotinib to gemcitabine included rash and an increase in interstitial lung disease (ILD)-like symptoms.

Gemcitabine and cisplatin in familial pancreatic cancers
The combination of gemcitabine and cisplatin has not shown a significant survival benefit, over gemcitabine alone, in several phase III trials or any of the meta-analyses reviewed for this guideline (28-31,35,36). However, patients who are BRCA mutation carriers with a personal and/or familial history of breast and ovarian cancers, as well as, some patients with a family history of pancreatic cancer, are known to have disease that is sensitive to a platinum agent (37-40). The 2013 NCCN guidelines on pancreatic adenocarcinoma has recommended that gemcitabine and cisplatin may be a good option, in those select patients with disease characterized by hereditary risk factors, such as BRCA or PALB2 mutations (84).

Chemotherapy without Gemcitabine
FOLFIRINOX
The results of a pivotal French trial were released in 2011, which compared a combination chemotherapy regimen consisting of fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) to the standard of gemcitabine as first-line therapy for patients with metastatic cancer of the pancreas (41). Only those patients with a good PS (ECOG score of 0 - 1) were

eligible for this trial. The FOLFIRINOX arm revealed a 11.1 month OS compared to 6.8 months in the gemcitabine arm (HR for death was 0.57; 95% CI, 0.45 to 0.73; p<0.001), with a median PFS of 6.4 months versus 3.3 months, respectively (HR 0.47; 95% CI, 0.37 to 0.59; p<0.001). In the FOLFIRINOX arm, the ORR was 31.6% and only 9.4% in the gemcitabine arm (p<0.001). The 1-year survival rate in the FOLFIRINOX arm was 48.4% in comparison to 20.6% in the gemcitabine arm. Not surprisingly, the incidence of treatment-related grade 3 and 4 adverse events, such as neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy were higher in the FOLFIRINOX arm. However, fewer patients had a degradation in their quality of life with the FOLFIRINOX (31%) compared to those in the gemcitabine arm (66%) at 6 months (42). As a result of this study, FOLFIRINOX has become the standard in the treatment of metastatic pancreatic cancer for patients with a good PS (43).

A 2012 Canadian medicoeconomic analysis did a comparison in the metastatic setting of first-line FOLFIRINOX followed by second-line gemcitabine therapy to first-line gemcitabine therapy followed by second-line platin-based chemotherapy. It revealed that using FOLFIRINOX in the first-line setting produced more life years and quality-adjusted life years than gemcitabine (44).

A phase II French study from eleven hospitals used FOLFIRINOX first-line in 77 patients with LAPC, followed by external beam radiotherapy for 62% of the patient population, and found a partial response rate of 30% while 53% of patients had stable disease (45). It reported a manageable toxicity profile and led to secondary potentially curative surgery for approximately one third of the population. Conversely, concerns were raised about the high toxicity rates associated with this chemotherapy regimen. One US retrospective analysis found that significant grade 3 and 4 toxicities led to a discontinuation of treatment in a third of their studies' patients with advanced pancreatic cancer, however at least 9% of their study population were ECOG > 1(46).

A US report on the multi-institutional experience looked at the tolerance and effectiveness of using FOLFIRINOX in the treatment of pancreatic adenocarcinoma (47). It revealed that despite the high rate of toxicity and the need for required dose modifications, FOLFIRINOX was still clinically effective in both the locally advanced and metastatic setting, with more than 70% of patients having, at least, stable disease on treatment. Several small institutional-based studies have been carried out which involved using a modified FOLFIRINOX regimen, either by dose reductions or removing the bolus 5FU component , and adding prophylaxis growth factor support (48-52). All agreed that FOLFIRNOX, even with modifications, still provided a positive response and improved tolerability of toxicities.

Based on the experience of using FOLFIRINOX in the metastatic setting, many institutions, such as those associated with NCCN, have extrapolated the data as the basis for using FOLFIRINOX to treat patients with locally advanced disease as well (84).

Chemoradiation Therapy (CRT)

In the treatment of inoperable pancreatic cancer, chemotherapy has shown a proven benefit but the role of radiation therapy remains controversial. CRT had previously demonstrated a superior benefit over best supportive care alone but CRT has also been shown to be superior to radiation therapy (RT) alone albeit with more toxicities. Two meta-analyses, one of which was a Cochrane review, were carried out comparing CRT to RT alone. Both analyses found a

significant overall survival benefit with the addition of a chemo-radiosensitizer, such as 5-fluorouracil or gemcitabine, to the radiation therapy (53,54).

Much of the controversy, however, occurs when the benefit of CRT is compared to chemotherapy alone in treating this disease. For many years, the standard therapy for locally advanced disease was a combination of radiotherapy, consisting of a total dose of 40 to 54 Gy, and 5-fluorouracil chemotherapy. A French FFCD/SFRO trial compared CRT (60 Gy with cisplatin and continuous 48-hour infusional 5-FU) followed by maintenance gemcitabine versus gemcitabine alone (55). It reported a shorter OS and more toxicities for the CRT arm compared to gemcitabine alone. These results were also supported by one of the afore mentioned meta-analyses, which also failed to find a survival benefit for CRT over chemotherapy alone (52). A 2009 systematic review looking at CRT management in LAPC reviewed five studies, which compared CRT to chemotherapy alone, and found that there were no significant difference in OS between either group but more toxicity in the CRT arm (56). However, the investigators noted that three of the five studies were published in the 1980's with older radiation technology, and that the results had significant heterogeneity.

A 2010 Italian systematic review looked at the resectability rates and survival for those patients, with primarily unresectable LAPC, who had received neoadjuvant CRT (57). Thirteen studies (published from 2000 onward) were reviewed (n=510) with a surgical resection rate of 8.3 – 64.2% (median, 26.5%) reported. Of those patients who underwent surgical resection, an R0 (microscopic margins clear of tumor) resection was achieved by 57.1% – 100% (median, 87.5%). In this analysis, median survival ranged from 9 to 23 months (median, 13.3 months) compared to survival data of 8.6 to 13 months in the literature for concurrent CRT alone. For those patients with unresectable disease at presentation, the median survival after surgical resection ranged from 16.4 to 32.3 months (median, 23.6). The authors concluded that this analysis confirms the activity of neoadjuvant CRT and recommended that patients with unresectable pancreatic cancer without disease progression after CRT, should be considered for radical surgery.

A recent 2010 German systematic review and meta-analysis included a total of 111 studies (n = 4394 patients) from 1996 to 2009. It reviewed the response and surgical resection percentages for patients who presented with resectable and locally advanced non-resectable pancreatic cancer, and then underwent neoadjuvent treatment, with most receiving both chemotherapy and radiation therapy (20). The findings suggest that the median survival for patients with resectable disease who received neoadjuvant treatment (23.3 months) was very similar to that observed for patients who had surgical resection first followed by adjuvant chemotherapy (range 20.1 – 23.6 months). However, of the patients who presented with locally advanced non-resectable disease, 46.9% were able to undergo surgical resection after neoadjuvant treatment, and 69.9% of those were resected successfully. This translates into a resectability rate of 33.2% for patients, after neoadjuvant therapy, who were initially unresectable. This group also experienced a comparable rate of R0 resections as the initially resectable group. A R0 resection is defined as a complete surgical resection with no microscopic residual tumor as per the pathology findings. The literature suggests that for patients who present with locally advanced unresectable pancreatic cancer, the median survival is 6 to 11 months. In this analysis patients who were not surgically resected post-neoadjuvant treatment had a median survival of 10.2 months. While 33.2% of patients who had undergone resection post-neoadjuvant treatment had an estimated median survival of 20.5 months, which falls within the range of patients who

received primary surgical resection and adjuvant therapy. Therefore, the authors recommended that patients with locally advanced non-resectable pancreatic cancer should be provided neoadjuvant therapy and subsequently re-evaluated for surgical resection.

Two more recent German studies (not included in the afore mentioned meta-analyses) have investigated neoadjuvant CRT in the locally advanced setting and reported a surgical resection rate of 31.7% and 26%, respectively after CRT (58,59). Tinkl et al reported that median tumor-specific survival was 29 months and OS was 25 months (58). Also patients with an R0 resection had a 3 year disease-specific survival rate of 51% versus 0% for those with positive margins (p=0.008). The rate of lymph nodes containing disease also decreased from 50% on staging imaging to 32% post-neoadjuvant therapy at time of resection. Habermehl et al reported a R0 resection rate of 39.2% and a significant median OS of 22.1 months for the resected group compared to 11.9 months for the non-resected group (59).

Induction Chemotherapy and CRT

For the past twenty years, the M. D. Anderson Cancer Center in the US has switched from the standard neoadjuvant CRT in treating patients with LAPC, to using an 'induction chemotherapy' (IC) treatment strategy. It consisted of the initial administration of 2-3 months of chemotherapy alone, followed by CRT. The rationale for this strategy was based on the early propensity of pancreatic adenocarcinoma to metastasize, even for those who had undergone surgical resection, reflected in the dismal 5-year OS rate.

In 2007, a retrospective study was published of 323 patients with locally advanced, unresectable pancreatic cancer, treated at that center, 76 of whom had received IC/CRT, while the remaining patients received CRT alone (60). The IC part of the regimen consisted of 74% of patients receiving a combination of gemcitabine and cisplatin with the remaining 15% receiving gemcitabine alone for a median of 2.5 months. The CRT regimen for both groups consisted of 85% of patients receiving the median radiation dose of 30 Gy in 10 fractions over two weeks, while 11% of patients received a more standard dose of 45 Gy in 25 fractions with a 5.4 Gy boost to a total of 50.4 Gy over five to six weeks. The chemotherapy used in the CRT regimen for both groups consisted of either 5-FU (41%), gemcitabine (39%) or capecitabine (20%). For all patients, the median OS was 9 months and PFS was 5 months, with the 2-year estimated OS and PFS rates were 9% and 5%, respectively. In the CRT group, the median OS was 8.5 months and PFS was 4.2 months, and in the IC/CRT group, the median OS was 11.9 months and PFS was 6.4 months, (both $p<0.001$). No difference was seen however in the pattern of disease failure in either group. The authors concluded that IC followed by CRT was a promising strategy for treatment of LAPC.

A French retrospective analysis, released the same year, looked at the survival of 181 patients with LAPC, enrolled in the prospective phase II and III GERCOR trials, who received 3 months of IC and then either received CRT or continued with chemotherapy alone (61). The median OS and PFS for all patients were 11.4 months and 6.3 months, respectively. Metastatic disease was detected in 29.3% of patients after 3 months of IC and weren't eligible for CRT. Out of the remaining 128 patients who had no disease progression and eligible for CRT, Group A with 72 patients (56%) received CRT, while Group B with 56 patients (44%) continued with chemotherapy alone. The two groups were balanced for PS, sex, age and type of chemotherapy as well as for IC results. For Groups A and B, the median PFS was 10.8 and 7.4 months,

(p=0.005) and median OS was 15.0 and 11.7 months (p=0.0009), respectively. The conclusion was that CRT after IC could significantly prolong survival in patients with LAPC.

An American phase II nonrandomized trial, reported on 25 patients who received 6 cycles of gemcitabine and cisplatin induction chemotherapy, followed by CRT with capecitabine for those without metastases (62). Twelve patients (48%) were able to receive all 6 cycles of IC and CRT and were shown to have a median survival of 17 months. In 2009, a French systematic review included all three of these studies and reported that, together, these studies provided enough evidence to suggest that IC before CRT improves survival in LAPC, supported by level C evidence (55). A UK multi-centre retrospective analysis (2010) looked at the outcomes of 48 patients with unresectable LAPC treated with CRT plus or minus IC (63). Forty-one of the 48 patients received IC while the remaining 7 received upfront CRT. All patients received CRT ranging from 45 Gy – 50.4 Gy. Five patients (8.3%) did not complete the intended CRT treatment due to related toxicities and one case of recurrent stent blockage. No grade 3/4 non-hematological toxicities were reported for the 43 patients who completed the CRT treatment regimen. The ORR and stable disease rate was 81.3%. The median OS was 17 months (range 5-66 months). In subgroup analysis, a trend toward improved survival was seen in patients who completed the intended treatment as opposed to those who didn't (17.1 months vs 11.0 months, p=0.06), and in patients who were able to undergo surgical resection post-neoadjuvant treatment (27 months vs 16 months, p=0.023). The authors suggested that this data confirms that IC followed by gemcitabine-based CRT was effective and that it was possible to administer with acceptable toxicity.

In 2012, a group from the Massachusetts General Hospital published an analysis of 70 patients with unresectable or borderline resectable LAPC, treated with CRT (50.4 Gy and either 5-FU, or capecitabine) (64). Forty patients received CRT alone, while the remaining 30 patients received neoadjuvant IC (typically gemcitabine), for a median of 4 months prior to CRT. Patients were only offered CRT if no radiological disease progression was evident after IC. The median follow-up was 14.2 months (range, 3-57 months). After completion of CRT, both groups experienced a 20% surgical resection rate. However, compared to CRT alone, the IC/CRT demonstrated a improved median OS (18.7 vs 12.4 months; p=0.02) and PFS (11.4 vs 6.7 months; p=0.02). On multivariate analysis, receiving IC (HR 0.49; 95% CI, 0.28-0.87; p=0.02) and surgical resection (HR 0.38; 95% CI, 0.17-0.85; P=0.02) were associated with increased OS benefit.

Uncontrolled studies of FOLFIRINOX in LAPC have demonstrated that 'downstaging' of pancreatic cancer may be achieved in some patients resulting in an R0 resection (45,47,50). Studies were then carried out using FOLFIRINOX as 'induction chemotherapy' prior to CRT for patients with borderline resectable or LAPC. A retrospective analysis was performed at the Medical College of Wisconsin using FOLFIRINOX as IC followed by CRT to improve resectability of borderline resectable pancreatic cancer (65). Twelve patients were treated with a median of 4 cycles, and proceeded to CRT with gemcitabine (8 patients) or capecitabine (4 patients) and a total of 50.4 Gy radiation. One patient did not complete CRT due to toxicities. At the completion of all neoadjuvant treatment, 7 (58%) out of 12 patients underwent resection and all 7 had a R0 with only 1 patient having lymph node metastases. At a median follow-up of 13 months, the median OS had not yet been met.

Another American retrospective study at the Miami University, analyzed 18 patients with borderline resectable or unresectable LAPC (66). Patients, had a median age of 57.5 years and

had ECOG PS of 0-1, and all were given FOLFIRINOX as induction chemotherapy (median of 8 cycles each). Dose modifications were performed as needed and were similar to those described in the ACCORD-11 trial (42). The results showed 7(39%) of the 18 patients became resectable by radiological criteria; 5 had R0 resections, 1 had an R1 resection (defined as complete resection with no grossly visible tumor as defined by the surgeon, but margins are microscopically positive according to the pathologist), and 1 had unresectable disease. The remaining 11 of the 18 patients, who remained unresectable after FOLFIRINOX therapy, 3 went on to have R0 resection after CRT (gemcitabine and 50.4 Gy/28 fractions), which resulted in a overall R0 resection rate of 44% (95% CI, 22% - 69%). The median follow-up was 13.4 months with a 1-year PFS of 83% (95% CI, 59% - 96%) and the 1-year OS of 100% (95% CI, 85% - 100%). Grade 3 - 4 toxicities included neutropenia (22%), neutropenic fever (17%), thrombocytopenia (11%), fatigue (11%), and diarrhea (11%).

Another American retrospective institutional experience from the Massachusetts General Hospital Cancer Centre looked at 22 patients with LAPC, who began FOLFIRINOX as IC (67). The median age was 63 years and a ECOG PS score of 0-1. Interestingly, the continuous infusion 5FU dose used was half of that used in the ACCORD-11 trial and the above mentioned Miami University study. Dosing modifications were determined by the individual treating oncologist. CRT regimen consisted, mainly, of fluoropyrimidine and 54Gy/28 fractions. Only 2 of the 22 patients did not receive CRT. Twelve patients went to the operating room post treatment and 5 (23%) underwent R0 resections (three of whom developed distant recurrence at 5 months), and the remaining 7 had surgically unresectable disease (6 of these had intraoperative radiation therapy plus or minus palliative surgery). The ORR was 27.3% and median PFS was 11.7 months (95% CI, 8.3-21.8 months) with 14 of the 22 patients developing local or distant progression. OS was not calculated. A total of 32% (or 7/22) patients required an emergency room visit or hospitalization. Four patients developed grade 3 or 4 neuropenia, but there were no cases of febrile neutropenia. The use of FOLFIRINOX was associated with a conversion to resectability in > 20% of patients. The authors of this study believe the tolerability and higher R0 resection rate seen in the previous American retrospective study by Hosein et al (66) may be attributed to its inclusion of borderline resectable patients.

Recently, the Medical College of Wisconsin Pancreatic Cancer Program carried out a study of 18 patients diagnosed with borderline resectable, biopsy-proven pancreatic adenocarcinoma who were treated neoadjuvantly with FOLFIRINOX, followed by gemcitabine- or capecitabine-based CRT (68). The results revealed 12 of the 18 patients were able to undergo pancreatectomy, all of which had negative (R0) margins. Interestingly, analysis of secondary outcomes revealed a low overall incidence of grade 3 or 4 therapy-induced toxicities. This was believed to be due to a treatment plan which included aggressive antiemetic support, planned hydration, routine use of pegylated filgrastim, and dose reductions when necessary, as well as stringent patient selection criteria.

Induction Chemotherapy and CRT versus neoadjuvant chemotherapy alone

Recently, the results of the randomized phase III LAP 07 clinical trial, reported at the 2013 ASCO annual meeting has helped to provide some clarity to the use of CRT after IC (69). It compared CRT (54 Gy plus capecitabine) vs chemotherapy (2 additional months of gemcitabine) in 269 pts with LAPC, who had disease control after 4 months of IC with gemcitabine plus or minus erlotinib (patients in the gemcitabine/erlotinib arm continued to receive erlotinib as maintenance therapy). After a median follow-up of 36 months, no significant

difference was seen in the median OS of either arm (CRT 15.2 months vs. chemotherapy 16.4 months) (HR 1.03; p=0.8295) nor in the median PFS (CRT 12.5 months vs chemotherapy 11.8 months) (HR 0.9; p=0.2161). Therefore, futility was declared at the second interim analysis. Erlotinib was not found to be beneficial either in terms of median OS [11.9 months for gemcitabine/erlotinib arm vs 13.6 months for the gemcitabine alone arm (HR 1.19; p=0.093)], though it did increase toxicity. The authors declared that for LAPC, the standard of care should remain chemotherapy, with CRT being an option after tumor control with chemotherapy.

The most recent UpToDate clinical practice guideline for the treatment of both borderline resectable and LAPC suggests that the preference is for the enrollment of eligible patients to a clinical trial, especially since controversy still exists on optimal management of these patients (85). However, when such trials are unavailable or patients are ineligible, this guideline recommends the use of neoadjuvant IC, with or without CRT (with capecitabine or infusional 5FU), followed by re-evaluation of surgical resection. The IC options are FOLFIRINOX for those with a good PS, or nab-paclitaxel plus gemcitabine using extropolated data from the MPACT metastatic pancreatic cancer study (32), while the standard remains single-agent gemcitabine.

Radiological Re-evaluation

Most studies have used CT scan, as well as, CA19-9 and CEA levels, to aid in determining which patients are able to undergo surgical resection, following neoadjuvant treatment. However institutions, such as the MD Anderson Cancer Center, with its extensive experience in the surgical resection of pancreatic cancers have found a great deal of disparity between post-treatment diagnostic imaging and pathological findings. A recent analysis performed at MD Anderson found that only 12% of patients (n=129) with borderline resectable cancers had a tumor size reduction according to RECIST (or Response Evaluation Criteria in Solid Tumors) following neoadjuvant therapy, and only 1 patient had tumor downstaging which met a radiographic definition of potentially resectable. However, R0 resection was achieved in 66% of all the patients (70,71). Hence, radiological evidence of downstaging is not required post neoadjuvant therapy, at MD Anderson Cancer Center, as a requirement for surgical eligibility.

Adjuvant Therapy

There is no evidence available at present to determine if there is a role for the use of adjuvant chemotherapy, following neoadjuvant therapy and surgical resection. Since it is common for patients to experience a delay in recovery from the extensive surgery, any benefit from additional chemotherapy postoperatively would be questionable. Due to the morbidities associated with the overall treatment regimen, further treatment post surgery would be decided upon a case-by-case basis at the discretion of the medical oncologist and the patient.

Future Treatment Strategies

- Nab-paclitaxel plus Gemcitabine Chemotherapy Regimen – As a result of the MPACT clinical trial (32), FDA approval has been granted for the use of this regimen in the metastatic setting of pancreatic cancer. However, there may also be a future role for this regimen, as induction chemotherapy in borderline resectable or LAPC, especially for those patients whose PS may fall just short of the desired ECOG score of 0-1, preferred for undergoing the FOLFIRINOX regimen. More research is necessary however before this regimen could be considered in the treatment of borderline resectable or LAPC.
- Stereotactic Body Radiotherapy (SBRT) – Several phase II trials have looked at the feasibility of using SBRT, consisting of 1 – 3 fractions (20 Gy to 30 Gy per fraction) prior to, or in the

middle of, a first cycle of a chemotherapy regimen (usually gemcitabine) for patients with LAPC (72-78). Since the vast majority of patients with LAPC will go on to develop distant metastases, this alternative attempts to provide good local control, without exposing patients to the toxicities associated with a longer course of conventional radiation therapy. The results indicate that SBRT appears to provide good local control, though with an increase in duodenal toxicity (ie. ulceration, perforation). However, data from a large randomized head-to-head comparison would be necessary to determine if SBRT was an effective option.

- Intra-arterial Chemotherapy – The use of continuous infusional chemotherapy via an arterial access for the treatment of pancreatic cancer was developed as an attempt to increase survival rates. In 2012, a meta-analysis was carried out on several small randomized control trials, comparing the regional intra-arterial chemotherapy (RIAC) method to standard systemic chemotherapy in the treatment of advanced pancreatic cancer (79). It concluded that regional intra-arterial chemotherapy is more effective, with a median survival of 5-21 months for RIAC and 2.7-14 for the standard method of administering chemotherapy, as well as a higher clinical benefit of 78.06% vs 29.37%, respectively. Fewer complications and toxicities were also noted with the use of RIAC compared to the standard method as well. However, the authors admitted that this analysis was limited by the relatively small number of patients and risk of bias due to the failure to include unpublished data. Larger and more rigid methodological trials are required to confirm these findings.

Upcoming Clinical Trials

There are 5 clinical trials presently listed under the U.S. National Institutes of Health, which are about to recruit or are in the process of recruiting. Each of these are investigating the use of neoadjuvant FOLFIRINOX with or without radiation therapy (NCT01771146, NCT01661088, NCT01992705, NCT01821612, NCT01760694).

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 AHPBA/SSAT/SSO definition of borderline resectable pancreatic cancer, and the 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, EUS or MRI can be complementary to CT. Laparoscopy and PET may also be used selectively to rule out metastatic disease;
- All patients with borderline resectable or locally advanced pancreatic cancer 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 CA 19-9 and 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 ECOG score of 0-1, appropriate laboratory values and minimal comorbidities will be offered 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;
    - Given the results of the LAP 07 clinical trial, 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 laparoscopy as per the consensus of the multidisciplinary tumor board;
- Option of adjuvant therapy will be at the discretion of the medical oncologist.

Search Strategy:

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, using keywords “pancreatic neoplasms” AND “antineoplastic treatment”, as well as an extensive manual search of the reference lists of available literature articles. Guideline searches were also carried out on the websites of the world’s most highly respected cancer organizations and agencies. All selected literature articles and source guidelines were in English and dated after the year 2004 (unless the selection was an earlier landmark study) up to May 2013. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Six source guidelines were identified, had conformed to our search criteria and were selected due to currency, quality of content and/or were Canadian in origin (80-85).

The six identified source guidelines were put through the ADAPTE process (86) with an AGREE II assessment (87), and the Up To Date guideline "Initial chemotherapy and radiation for nonmetastatic locally advanced unresectable, borderline resectable, and potentially resectable exocrine pancreatic cancer" was chosen to be adapted for use in our guideline (85). The guideline was selected as the optimal choice due to its applicability, quality, currency of content, and the interpretation of the evidence to determine treatment options.

There has been much debate but no consensus on the 'grading of evidence' in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.
No competing or conflicts of interest were declared.

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 these 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, Dr. H. Bliss Murphy Cancer Center, St. John's, NL; Telephone 709-777-7802. For access to any of our guidelines, please visit our Cancer Care Program website at www.easternhealth.ca

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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)

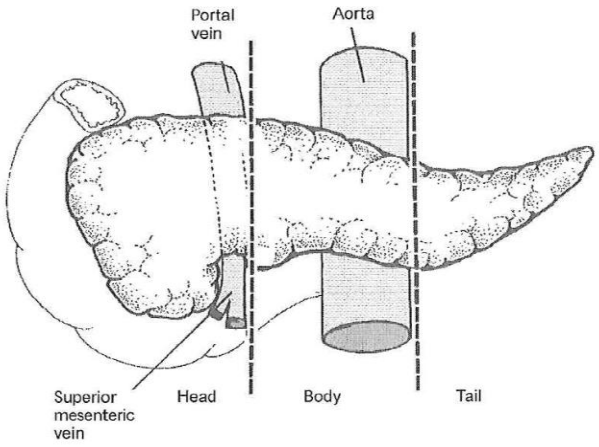
Regional Lymph Nodes (N)

- 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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