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Adenocarcinoma of the Pancreas

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Cancer Care Alberta

Clinical Practice Guideline GI-006 – Version 10
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Background

Adenocarcinoma of the pancreas is associated with a poor prognosis. Even after resection of small tumours without regional lymph node involvement, five-year survival rates remain low at around 20 percent.[1]

The diagnosis of pancreas cancer may be preceded by non-specific symptoms (e.g.: fatigue, anorexia, weight loss, dull epigatric pain). Early satiety, malabsorption, steatorrhea, glucose intolerance, and jaundice (from extra-hepatic biliary obstruction) may also occur.

Risk factors include age, male gender, chronic pancreatitis, diabetes mellitus type 2, germline mutations in *P_{16}* and *BRCA2*, and a familial predisposition (e.g.: multiple endocrine neoplasia type 1, hereditary non-polyposis colon cancer). A referral to genetics should be discussed with patients with a personal history of pancreatic adenocarcinoma at any age AND two or more close relatives with breast, ovarian, or pancreatic cancer at any age. There is a dose-response relationship with smoking[2] and an association with processed meat consumption.

Although disease confined to the pancreas may be amenable to a pancreaticoduodenectomy or distal pancreatectomy, involvement of the celiac axis or superior mesenteric artery, venous occlusion at the confluence of the superior mesenteric and portal veins, or metastatic disease represents unequivocally unresectable disease. Direct extension to the duodenum, bile duct, or peri-pancreatic tissue with or without isolated involvement of the superior mesenteric vein or portal vein may still be amenable to resection.

This guideline was developed to outline the management recommendations for patients with pancreatic cancer (adenocarcinoma). For specific recommendations for the management of malignant biliary obstruction, please refer to the Malignant Biliary Obstruction clinical practice guideline.

Guideline Questions

- What are the recommendations for the diagnostic workup of adult patients with adenocarcinoma of the pancreas?
- What are the treatment recommendations for adult patients with potentially curable adenocarcinoma of the pancreas?
- What are the management recommendations for adult patients with unresectable cancer of the pancreas?

Search Strategy

The Pubmed database was searched using the following search strategy: (("adenocarcinoma"[MeSH Terms] OR "adenocarcinoma"[All Fields]) AND ("pancreas"[MeSH Terms] OR "pancreas"[All Fields]))

AND (Clinical Trial[ptyp] AND ("2017/11/01"[PDAT] : "2019/12/31"[PDAT])). Only phase II or greater clinical trials published in English were included.

Target Population

The recommendations outlined in this guideline apply to adults over the age of 18 years with pancreatic cancer. Different principles may apply to pediatric patients.

Recommendations

Suggested Diagnostic Work-Up

For patients with a family history suggestive of hereditary pancreatic cancer, consider referral to the Hereditary Cancer Clinic for pancreatic cancer susceptibility screening. A family history suggestive of hereditary pancreatic cancer includes:

1. A personal history of pancreatic adenocarcinoma at any age AND
    i. Two or more close relatives with breast/ ovarian/ pancreatic cancer at any age.
    ii. Family history suggestive of Lynch syndrome (two or more close relatives with endometrial cancer and/or colon cancer).
    iii. Ashkenazi Jewish heritage.

2. Personal history of pancreatic adenocarcinoma plus another primary cancer diagnosis.

3. Relative with known cancer predisposition syndrome (i.e. BRCA1 or BRCA2 mutation, Lynch syndrome, moderate risk cancer predisposition gene such as ATM, PALB2).

A CT scan of the chest, abdomen, and pelvis can distinguish between resectable and unresectable disease. An MRI of the abdomen (and other tests, as clinically indicated) may be used as supplemental investigations. Bone scans can be done for patients suspected of having bone metastases. A CA19-9 should be performed as a baseline laboratory test. If surgery is performed, the CA 19-9 should be performed post-operatively. While on neoadjuvant or palliative systemic treatment, CT chest abdomen pelvis should be done every 2-3 months. Consider IgG4 levels, if autoimmune pancreatitis is on the differential diagnosis. For patients not undergoing upfront surgery, tissue biopsy should be performed via endoscopic ultrasound, ERCP, or CT guidance.

All patients with pancreatic cancer should be referred to a registered dietician. Patients should be screened for pancreatic enzyme deficiency and initiate replacement if needed. Pancreatic enzyme replacement is typically prescribed at 500–2500 units of lipase per kilogram body weight per meal, up to 10 000 units of lipase per kilogram of body weight per day.[3]

Stage Information

Table 1. AJCC Cancer Staging System for Adenocarcinoma of the Pancreas and Ampulla, Eighth Edition.

Stage	Tumour Stage		Regional Lymph Node Involvement		Metastases	
Stage 0	T_{is}	Carcinoma *in situ*	N_0	None	M_0	Absent
Stage I_A	T_1	Tumour ≤ 2 cm in size and confined to pancreas	N_0	None	M_0	Absent
Stage I_B	T_2	Tumor >2 and ≤4 cm in greatest dimension	N_0	None	M_0	Absent
Stage II_A	T_3	Tumor >4 cm in greatest dimension	N_0	None	M_0	Absent
Stage II_B	T_1	Tumour ≤ 2 cm in size and confined to pancreas	N_1	1-3 nodes involved	M_0	Absent
	T_2	Tumor >2 and ≤4 cm in greatest dimension	N_1	1-3 nodes involved	M_0	Absent
	T_3	Tumor >4 cm in greatest dimension	N_1	1-3 nodes involved	M_0	Absent
Stage III	T_1	Tumour ≤ 2 cm in size and confined to pancreas	N_2	≥4 nodes involved	M_0	Absent
	T_2	Tumor >2 and ≤4 cm in greatest dimension	N_2	≥4 nodes involved	M_0	Absent
	T_3	Tumor >4 cm in greatest dimension	N_2	≥4 nodes involved	M_0	Absent
	T_4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size	Any		M_0	Absent
Stage IV	Any		Any		M_1	Present

Goals and Recommendations for *Potentially Curable* Adenocarcinoma of the Pancreas

1. To render the patient free of disease and to delay or prevent recurrence.
2. To improve the patient's quality of life.

Table 2. Treatment Recommendations for Potentially Curable Adenocarcinoma of the Pancreas.

Stage	Recommendations
Stage 0 $T_{is}N_0M_0$	• Perform Whipple pancreaticoduodenectomy or distal pancreatectomy to resect disease with macroscopically clear margins.
Resectable Disease Stage I_A $T_1N_0M_0$ Stage I_B $T_2N_0M_0$ Stage II_A $T_3N_0M_0$ Stage II_B $T_{1-3}N_1M_0$	• Perform Whipple pancreaticoduodenectomy or distal pancreatectomy to resect disease with macroscopically clear margins. Consider referral to a dietician. • Consider adjuvant treatment on a clinical trial, if available. • In the absence of medical or surgical contraindications, adjuvant chemotherapy should be offered after R0 or R1 resection of pancreatic adenocarcinoma. A discussion addressing patient preferences concerning the balance of toxicity and efficacy should guide the decision for adjuvant chemotherapy. If the patient accepts adjuvant therapy, ideally, it should be initiated within twelve weeks of surgery. Combination chemotherapy has been shown to be superior to single agent gemcitabine in randomized trials.[4, 5] Preferred regimens in the absence of concerns for toxicity or tolerance: • FOLFIRINOX for 12 cycles: The phase III Unicancer GI PRODIGE 24/CCTG PA.6 trial randomized patients with pancreatic ductal adenocarcinomas after R0 or R1 resection, WHO PS ≤1, with adequate hematologic and renal function, and no cardiac ischemia to receive modified FOLFIRINOX (oxaliplatin 85mg/m2, irinotecan 150 mg/m2 , leucovorin 400 mg/m2, and fluorouracil 2400 mg/m2 for 12 cycles) or gemcitabine (1000 mg/m2 on day 1, 8, and 15 every 4 weeks, for 6 cycles). The median overall survival was 54.4 months in the modified-FOLFIRINOX group and 35.0 months in the gemcitabine group (HR = 0.64, 95%CI: 0.48-0.86; p=0.003). Grade 3/4 adverse events occurred in 75.9% of patients in the modified-FOLFIRINOX group vs 48.6% of patients in the gemcitabine group.[4] (Evidence quality: high.) • Adjuvant chemotherapy with modified-FOLFIRINOX in resected pancreas cancer patients is superior to gemcitabine, although significantly more toxic and requires a central line. • Alternatively, six cycles of IV Gemcitabine with oral Capecitabine. ESPAC-4 randomized patients after R0 or R1 resection of pancreatic adenocarcinoma to 6 cycles of gemcitabine (1000 mg/m² on day 1, 8, and 15 every 4 weeks) alone or with 1660 mg/m² oral capecitabine administered for 21 days followed by 7 days' rest. The median overall survival was significant longer for patients in the gemcitabine plus capecitabine group [28·0 months compared with 25·5 months in the gemcitabine

	group], hazard ratio 0·82 [95% CI 0·68–0·98], p=0·032. (Evidence quality: high.) Regimens for patients not suitable for combination chemotherapy: • Six four-week cycles of Leucovorin 20 mg/m2 IV followed by 5-Fluorouracil 425 mg/m2 IV on each of five consecutive days has been shown to increase the median survival from 15.5 months to 20.1 months, the two-year survival from 30% to 40%, and the five-year survival from 8% to 21% when compared to no further treatment. Evidence quality: high. • Alternatively, six four-week cycles of Gemcitabine (1,000 mg/m2 IV over thirty minutes on days 1,8 and 15)5,7 may be offered. ESPAC-3[5] randomized patients with resected pancreatic cancer to gemcitabine or bolus 5-Fluorouracil and leucovorin. Median survival was 23.6 versus 23 months with gemcitabine and 5-Fluorouracil/leucovorin respectively [hazard ratio, 0.94 (95% CI, 0.81-1.08),p = 0.39]. Patients treated with 5-Fluorouracil/leucovorin had more grade 3 to 4 treatment related toxicity and treatment related hospitalizations. However, global quality of life scores were similar. In this trial, survival favored patients who completed the full 6 cycles of chemotherapy compared to those who did not (median survival 28 versus 15 months, HR 0.51 95% CI 0.44-0.60). Evidence quality: high. • Follow-up after resection: There is no evidence of survival improvement with close follow-up based on literature.[6-8] However, routine surveillance enables detection of asymptomatic recurrences. Consider CT scan after completion of adjuvant chemotherapy. Further bloodwork/imaging follow-up should be individualized to each patient. Systemic/palliative treatment has advanced over the last years but only patient with sufficient performance status is eligible; therefore, routine surveillance may improve the likelihood of detecting recurrence at a point when patients are well enough to receive chemotherapy. • There is no routine role for adjuvant radiotherapy at this time.

Goals and Recommendations for *Unresectable* Adenocarcinoma of the Pancreas

1. Maintain or improve the patient's quality of life (control or delay onset of tumour-related symptoms).
2. To prolong life, if possible.
3. Relieve biliary obstruction, if possible, by (Alberta guideline link):
    a. Endoscopic retrograde cholangiopancreatography with stent placement,
    b. Percutaneous transhepatic cholangiography with stent placement, or
    c. Palliative surgery.
4. Relieve pain with analgesics, celiac ganglion ablation (either percutaneous or endoscopic splanchnic-cectomy), or radiation.
5. Consider treatment on a clinical trial, if available.
6. To provide early access to palliative care services when appropriate.

Table 3. Management Recommendations for Unresectable Adenocarcinoma of the Pancreas.

Stage	Recommendations
Locally Advanced Stage III $T_4N_{any}M_0$ **Metastatic Disease** Stage IV $T_{any}N_{any}M_1$	**Locally Advanced:** Multidisciplinary collaboration to formulate care plans is important as a small proportion of patients may become resectable after chemotherapy. For that specific patient population, there is no randomized controlled data to guide the use of post-operative chemotherapy after administration of pre-operative chemotherapy. The Provincial Gastrointestinal Tumour Team recommends administration of a total of 6 months of chemotherapy (including the pre-operative regimen). Recommendation type: informal consensus, benefits outweigh harms; Evidence quality: low. **First line treatment** A discussion addressing goal of care, patient preferences concerning the balance of toxicity and efficacy should guide the decision for first line therapy for patients with good performance status.

FOLFIRINOX

- The phase III Unicancer GI PRODIGE 24/CCTG PA.6 trial randomized n=493 patients aged 18-79, with histologically proven pancreatic ductal adenocarcinomas, 21-84 days after R0 or R1 resection, WHO PS ≤1, with adequate hematologic and renal function, and no cardiac ischemia to receive modified FOLFIRINOX (oxaliplatin 85mg/m^2, irinotecan 180 mg/m^2 reduced to 150 mg/m^2 after a protocol-specific safety analysis, leucovorin 400 mg/m^2, and fluorouracil 2400 mg/m^2) or gemcitabine (1000 mg/m^2 on day 1, 8, and 15 every 4 weeks, for 24 weeks). After a median follow-up of 33.6 m, disease-free survival (primary endpoint) was 21.6 m in the modified-FOLFIRINOX group and 12.8 m in the gemcitabine group (stratified HR for cancer-related event, second cancer, or death = 0.58, 95%CI: 0.46-0.73; p<0.001). The median overall survival (secondary endpoint) was 54.4 m in the modified-FOLFIRINOX group and 35.0 m in the gemcitabine group (HR = 0.64, 95%CI: 0.48-0.86; p=0.003). At 3 years, the overall survival rate was 63.4% in the modified-FOLFIRINOX group vs 48.6% in the gemcitabine group. Grade 3/4 adverse events occurred in 75.9% of patients in the modified-FOLFIRINOX group vs 48.6% of patients in the gemcitabine group.[4]
- Adjuvant chemotherapy with modified-FOLFIRINOX in resected pancreas cancer patients is superior to gemcitabine, although significantly more toxic.
- For **carefully selected** patients with metastatic disease, performance status (**ECOG 0 or 1**), age ≤ 75 years, and a normal or nearly normal bilirubin, FOLFIRINOX prolongs overall survival (11.1 months *versus* 6.8 months, HR 0.57, 95% CI 0.45-0.73, *p* = 0.0001) and delays the deterioration in quality of life when compared to Gemcitabine alone.[9, 10] The rate of grade 3/4 toxicities emphasizes the need for education, monitoring, and active management (see Table 4 and 5 below) (Evidence quality: High).
- The Provincial Gastrointestinal Tumour Team agree that FOLFIRINOX may also be considered for patients with locally advanced disease given that a high response rate may result in the conversion of some patients to resectable disease. At present, no randomized studies have explored the use of FOLFIRINOX in locally advanced pancreatic cancer patients (see Appendix A for a list of current clinical trials using this regimen). Several retrospective reviews have demonstrated the efficacy and tolerability of FOLFIRINOX in this patient group, despite the use of dose modifications and adverse events.[11-13]

nab-Paclitaxel plus Gemcitabine

- Patients may also be considered for treatment with nab-Paclitaxel plus Gemcitabine. An international, phase III trial of 861 metastatic pancreatic cancer patients compared the efficacy and safety of nab-Paclitaxel plus Gemcitabine versus Gemcitabine alone.[14] Median overall survival was 8.5 months in the intervention arm compared to 6.7 months in the control arm (HR 0.72, 95% CI 0.62–0.83, p<0.001). Median progression-free survival was 5.5 months versus 3.7 months in the nab-Paclitaxel plus Gemcitabine versus Gemcitabine alone group, respectively (HR 0.69, 95% CI 0.58–0.82, p<0.001). According to independent review, the response rate was 23% versus 7% in the nab-Paclitaxel plus Gemcitabine group versus the control group, respectively (p<0.001) (Evidence quality: high). The Provincial Gastrointestinal Tumour Team adapts the eligibility criteria based on the above mentioned phase III study.[14] The Provincial Gastrointestinal Tumour Team agree that nab-Paclitaxel plus Gemcitabine may also be considered for patients with locally advanced disease.
- Patients eligible for nab-Paclitaxel plus Gemcitabine should meet the following criteria:
    - ≥18 years of age
    - *Karnofsky performance status score ≥70*
    - Have not previously received chemotherapy for metastatic disease (patient could have received treatment with Fluorouracil or Gemcitabine as a radiation sensitizer in the adjuvant setting if the treatment had been received at least 6 months ago)
    - Have histologically or cytologically confirmed metastatic or locally advanced adenocarcinoma of the pancreas
    - Have adequate hematologic, hepatic, and renal function, including:
        - Absolute neutrophil count of ≥1.5x10^9 per litre
        - Hemoglobin level of ≥9 g per deciliter
        - Bilirubin level at or below the upper limit of the normal range

Gemcitabine

- For patients not suitable for combination chemotherapy (due to patient preference or comorbidities) with a performance status of ECOG ≤2, Gemcitabine (1,000 mg/m^2 IV over thirty minutes once weekly for seven of eight weeks and subsequently weekly for three of four weeks) has been shown to offer a “clinical benefit response” (improvement in pain, performance status, and weight) in 23.8%.[15, 16] In addition, it may prolong median survival (to 5.65 months) and improve twelve-month survival (to 18%). Treatment should be continued until progression or until significant clinical deterioration secondary to tumour-related symptoms.

	Second line treatment for patients who wish to pursue cancer directed therapy**:**
	
	• After progression on Gemcitabine based treatment, for patients with an ECOG of 0-1, suitable for combination chemotherapy:
	  • "OFF" regimen: Leucovorin (200 mg/m^2 IV over thirty minutes) followed by a continuous intravenous infusion of 5-Fluorouracil (2,000 mg/m^2 over twenty-four hours) on days 1, 8, 15, and 22 with Oxaliplatin (85 mg/m^2 IV over two hours) on days 8 and 22 of every six week cycle ("OFF" regimen) has been shown to increase median overall survival compared to Leucovorin and 5-Fluorouracil alone; from 3.3 months to 5.9 months (p =0.010) in patients with a good performance status.[17] Note that FOLFOX is not interchangeable with "OFF" as it has been shown to be inferior to Leucovorin and 5-Fluorouracil in terms of OS in the second line.[18]
	
	  • Nanoliposomal irinotecan (80 mg/m², equivalent to 70 mg/m² of irinotecan base) with 5-Fluorouracil and Leucovorin is the preferred second line treatment option as the addition of nanoliposomal irinotecan increased median overall survival to 6.1m (95%CI 4.8-8.9) compared to 4.2m (95%CI 3.3-5.3m) in the fluorouracil and folinic acid alone group (HR 0.67, 95% CI 0.49-0.92; p=0.012).[10] Nanoliposomal irinotecan is not currently funded. Fluorouracil plus irinotecan could be considered if nanoliposomal irinotecan is unavailable.
	
	After progression on FOLFIRINOX: (Recommendation type: informal consensus, benefits outweigh harms; Evidence quality: low).
	  • Gemcitabine plus NAB-paclitaxel can be offered as second-line therapy to patients who meet all of the following criteria: an ECOG PS of 0 to 1, a relatively favorable comorbidity profile, and patient preference
	Gemcitabine or a fluoropyrimidine can be considered for patients who have ECOG PS $\leq$ 2 unsuitable for combination regimens due to patient preference or comorbidities (Recommendation type: informal consensus, benefits outweigh harms; Evidence quality: low). Patients should not have previously progressed on the selected agent.

FOLFIRINOX Regimen:[8]

		5-Fluorouracil 400 mg/m^2 IV bolus
Oxaliplatin 85 mg/m^2 IV over two hours	Leucovorin 400 mg/m^2 IV over two hours	5-Fluorouracil 2,400 mg/m^2 CIV over forty-six hours
	Irinotecan 180 mg/m^2 IV over ninety minutes	

Table 4. Reported Adverse Events with FOLFIRINOX or Gemcitabine

Adverse Events (Grade 3/4 Toxicities)	FOLFIRINOX	Gemcitabine	Statistics
Neutropenia Grade 3: Neutrophils 0.5-1.0 Grade 4: Neutrophils <0.5	45.7%	21.0%	p < 0.001
Febrile Neutropenia	5.4%	1.2%	p = 0.03
Thrombocytopenia Grade 3: Platelets 25-50 Grade 4: Platelets <25	9.1%	3.6%	p = 0.04
Fatigue Grade 3: Difficulty performing some ADLs Grade 4: Interfering with ADLs	23.6%	17.8%	*NS*
Emesis Grade 3: ≥ 6 episodes, ≥24h IV hydration Grade 4: Life-threatening consequences	14.5%	8.3%	*NS*
Diarrhea Grade 3: ≥7 stools/d, ≥24h IV fluids, hospitalization	12.7%	1.8%	p < 0.001

Grade 4: Life-threatening consequences			
Peripheral Neuropathy	9.0%	0.0%	$p < 0.001$

Table 5. FOLFIRINOX Dose Modification Recommendations.

Toxicity	Decision at Day 0		Occurrence	Irinotecan Dose	Oxaliplatin Dose	5-Fluorouracil Bolus Dose	5-Fluorouracil CIV Dose
	Proceed	Delay					
Neutrophils	≥ 1.5 × 10^9/L	< 1.5 × 10^9/L	First	150 mg/m^2	85 mg/m^2	Omit	2,400 mg/m^2
or mid-cycle febrile neutropenia*			Second	150 mg/m^2	60 mg/m^2	Omit	2,400 mg/m^2
Platelets	≥ 75 × 10^9/L	< 75 × 10^9/L	First	180 mg/m^2	60 mg/m^2	300 mg/m^2	1,800 mg/m^2
or mid-cycle platelet count < 50 × 10^9/L*			Second	150 mg/m^2	60 mg/m^2	300 mg/m^2	1,800 mg/m^2
Diarrhea		Grade 3/4	First	150 mg/m^2	85 mg/m^2	Omit	2,400 mg/m^2
		Grade 3/4	Second	150 mg/m^2	60 mg/m^2	Omit	1,800 mg/m^2
Mucositis		Grade 3/4	First	180 mg/m^2	85 mg/m^2	300 mg/m^2	1,800 mg/m^2
Hand-foot syndrome		Grade 3/4	First	180 mg/m^2	85 mg/m^2	300 mg/m^2	1,800 mg/m^2
* Discontinue treatment after third occurrence or if toxicity fails to resolve after two-week delay.							

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Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Gastrointestinal Tumour Team. Members of the Alberta Provincial Gastrointestinal Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, hepatologists, gastroenterologists, interventional radiologists, nurses, nurse practitioners, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gastrointestinal Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in January 2008. This guideline was revised in March 2009, August 2009, March 2010, June 2011, October 2013, March 2014, June 2015 and November 2017.

Maintenance

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2022. If critical new evidence is brought forward before that time, the guideline working group members will revise and update the document accordingly.

Abbreviations

Acronym, Description
ADL, activities of daily living; AJCC, American Joint Committee on Cancer; CI, confidence interval
CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; HR, hazard ratio
IV, intravenous; MRI, magnetic resonance imaging;
OFF, 5-fluorouracil + leucovorin + oxaliplatin; TNM, tumour-node-metastasis

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GI Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

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