Cancer Care Program

CANCER CARE PROGRAM GUIDELINE

Clinical Practice Consensus Statement
Gastrointestinal

Adenocarcinoma of the Pancreas

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Revised: March 2020

BACKGROUND

The recommendations contained in this guideline are a consensus of the Nova Scotia Hepatobiliary Tumour Disease Site Group. They are based on currently accepted approaches to management, derived from a review of relevant scientific literature and previously published guidelines. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

On October 25, 2016, members of the medical, radiation, and surgical oncology as well as gastroenterology communities came together at the first Halifax Pancreatic Cancer Multidisciplinary Meeting to discuss the diagnosis, work-up and treatment of all stages of pancreatic cancer. These consensus statements are meant to assist the medical community in Halifax and Nova Scotia in the algorithmic work up of initial presentation of potential pancreatic cancer. Versions 2.0 and 3.0 were discussed at follow-up meetings on April 19, 2017 and November 23, 2017. In 2018, additional feedback was sought from oncologists in Sydney. Issues of timely and equitable access to ERCP and HPB surgery in Eastern Zone to meet the guideline statements were raised and resolved in 2019 and the final guideline submitted for the Cancer Portfolio Leadership Team in 2020.

The following guidelines are applicable to adenocarcinoma of the pancreas only.

The Basics

1. Participating in clinical trials is strongly encouraged when available.
2. Involvement of a multidisciplinary team is strongly recommended and all pancreatic cancer patients should be reviewed at the multidisciplinary rounds to assist in treatment decision-making.
3. Risks and benefits of treatments should be discussed with the patient.
4. These guidelines are not a substitute for consultation with an appropriate specialist.

Epidemiology:

- Pancreatic cancer is one of the most highly fatal cancers, with >95% of those affected dying of their disease.
- The 5-year overall survival (OS) rate remains 5-7% in Canada, with a median survival time of 3 to 6 months for metastatic disease.
- The high mortality rate is due primarily to the high incidence of metastatic disease at diagnosis.
- It is estimated that more than 200,000 patients die of pancreatic cancer each year worldwide.
- In Nova Scotia, it is estimated that there were 150 new cases in 2017.

Screening and Early Detection:

- There are no current screening programs recommended for the general population.
- However, some patients are at greater risk of developing pancreatic cancer compared to the general population though no evidence-based screening has been established. These include:
    - Lynch Syndrome
    - BRCA1 and BRCA2 mutations
    - p16 mutations
    - Peutz-Jeughers syndrome
    - Ataxia telangiectasia.
- Known risk factors include male gender, smoking, alcohol, chronic pancreatitis, diabetes mellitus type 2, germline mutations in *P16* and *BRCA2*, and a familial predisposition (such as MEN 1 and HNPCC).

DIAGNOSIS AND STAGING

Initial Presentation and Workup: (see Appendix A: Diagnostic Algorithm for Suspected Pancreatic Adenocarcinoma in NS)

The diagnosis of pancreatic cancer may be preceded by non-specific symptoms (such as weight loss, fatigue, dull epigastric pain), early satiety, steatorrhea, glucose intolerance, and jaundice (from extra-hepatic biliary obstruction).

Consensus Statement 1:
All patients who present with at least 2 symptoms suggesting pancreatic cancer (obstructive jaundice symptoms (including pruritis, acholic stool, choluria), weight loss, fatigue, epigastric pain, early satiety and glucose intolerance should be worked up for the cause including:

a. Full history, including performance status/Eastern Cooperative Oncology group (ECOG) status if possible.
b. Physical exam, including a lymph node exam and any palpable masses.
c. Biochemical workup including CBC+diff, INR, electrolytes, LFTs including Albumin, total and direct bilirubin, Cr and CA19-9.
d. Biphasic Pancreatic Protocol CT, preferably prior to any procedural intervention.
e. Diagnostic Workup, including referrals to hepatobiliary (HPB) surgery and endoscopic retrograde cholangiopancreatography (ERCP) if obstructive jaundice.

Consensus Statement 2:

All patients should be referred to the HPB surgical service (fax consult to HPB Surgery, 902-473-5297) to determine the resectability of the disease.

If there are questions about whether to refer a patient, HPB surgeons are available 24/7 (page 902 473-2222 and ask for the Liver Transplant Surgeon on call).

Only patients presenting with obstructive jaundice not stone related should be referred for ERCP. Suspected pancreas or ductal cancer or malignant obstruction should be immediately and directly referred to the QEII for Level 3 or 4 ERCP. ERCP Central Booking Halifax fax: 902-473-5548

Patients presenting with *de novo* metastatic disease should be referred concurrently to both HPB surgery and medical oncology, assuming an adenocarcinoma **pathological** diagnosis has been confirmed.

Consensus Statement 3:
At the time of ERCP, brushings will be attempted. If brushing pathology returns as suspicious or positive for adenocarcinoma, this will be sufficient for diagnosis. If brushing returns atypical cells, a biopsy is required to confirm diagnosis.

Atypical cells seen on ERCP brushings is insufficient for a diagnosis. Referral for biopsy should be made.

Consensus Statement 4:
These patients should be presented at the hepatobiliary rounds to assist in the direction of treatment.

Consensus Statement 5:
Endoscopic ultrasound (EUS) should be completed within 2 weeks after referral. Any delays in diagnosis must be conveyed to referring team and arrangements made elsewhere for pathological diagnosis.

Consensus Statement 6:
In the setting of no pathology is available, refer for appropriate biopsy (i.e. GI for an EUS for biopsy attempt on pancreatic lesion; interventional radiology for biopsy attempt in the metastatic setting). The referring physician will be the most responsible physician (MRP) for interventional radiology.

Consensus Statement 7:
Multidisciplinary collaboration should be the standard of care to formulate treatment plans and disease management for patients with pancreatic cancer.

Stage Information

Table 1: AJCC Cancer Staging System (8th edition) for Adenocarcinoma of the Pancreas.

Stage	Tumour Stage		Regional Lymph Node Involvement		Metastases	
Stage 0	Tis	Carcinoma *in situ*	N0	None	M0	Absent

Stage 1A	T1	Tumour ≤ 2 cm in size and confined to pancreas	N0	None	M0	Absent
Stage IB	T2	Tumour > 2 cm and less than 4 cm and confined to pancreas	N0	None	M0	Absent
Stage IIA	T3	Tumor is >4 cm in greatest dimension	N0	None	M0	Absent
Stage IIB	T1-3	As described above	N1	Involvement in 1 to 3 nodes	M0	Absent
Stage III	T4	Involvement of celiac axis or superior mesenteric artery	N_{any}	As above	M0	Absent
	T1-3	As described above	N2	Involvement in 4+ nodes		
Stage IV	T_{any}	As described above	N_{any}	As above	M1	Present

MANAGEMENT

Consensus Statement 8:
Neo-adjuvant treatment should be considered for patients with pancreatic cancer who meet any of the following criteria:

a. Radiographic findings suspicious of local-regional extrapancreatic disease but no distant metastatic disease.
b. Performance status not currently appropriate (but potentially reversible) for a major abdominal operation.
    a. If performance status is secondary to symptoms due to local-regional disease, neoadjuvant treatment may improve symptoms to make patient amendable for surgery.
c. Radiographic interface between primary tumor and mesenteric vasculature on cross-sectional imaging that does not meet criteria for primary resection.
d. CA 19-9 level (in absence of jaundice) >400 which suggests disseminated disease.

Consensus Statement 9:
A formal referral to palliative care should be made for:

a. All patients who are not a candidate for curative surgical resection (non-resectable local disease) and/or systemic therapy (poor performance status, patient preference).
b. At the initial diagnosis of metastatic disease.

See Appendix B: Neoadjuvant Treatment Algorithm for Pancreatic Adenocarcinoma

Consensus Statement 10:
If neoadjuvant systemic therapy has been completed, restaging evaluation is recommended before final surgical planning (CA19-9 level and full staging CT with pancreatic protocol) and representation at HPB rounds.

Consensus Statement 11:
Combination systemic therapy with FOLFIRINOX or gemcitabine/abraxane may be considered for patients with locally advanced disease due to higher response rate than conventional single agent systemic therapy that may result in the conversion from unresectable to resectable disease for some patients.

Consensus Statement 12:
All patients with resected pancreatic cancer (R0 or R1 resections) who did not receive neoadjuvant treatment should be offered up to 6 months of evidence-based adjuvant systemic therapy in the absence of medical or surgical contraindications.

Consensus Statement 13:
Adjuvant treatment should be initiated within 8 -12 weeks of surgical resection, assuming complete recovery.

Consensus Statement 14:
A total of 6 months of adjuvant systemic therapy treatment (including the duration of the preoperative regiment) should be offered to patients.

Consensus Statement 15:
Adjuvant treatment should be offered with FOLFIRINOX in the absence of any contraindications. Gemcitabine monotherapy remains an option in those that dual systemic therapy is contraindicated.

Consensus Statement 16:
Routine adjuvant chemoradiation is not recommended but should be considered for patients who did not receive pre-operative treatment and present with positive margins or node-positive disease. Treatment plans should be discussed in a multidisciplinary committee.

Palliative Systemic Therapy for Metastatic Pancreatic Cancer

Consensus Statement 17:
All patients with metastatic pancreatic cancer should be considered for a clinical trial if available.

Consensus Statement 18:

For patients with metastatic disease, both FOLFIRINOX (combination 5fu/irinotecan/oxaliplatin) and nab-Pacliatxel (abraxane) plus gemcitabine can be considered first-line treatment options. Patients with performance status 2 or age >75 have only been studied with nab-Pacliatxel (abraxane) plus gemcitabine.

No data exists on the duration of palliative treatments. Ongoing discussion of goals of care, assessment of treatment response and tolerability should be used to guide treatment decisions.

Consensus Statement 19:
Patient with a strong family history of breast, ovarian and pancreatic cancer should have BRCA testing and if mutation positive, should be considered for a platinum based regimen such as cisplatin/gemcitabine.

FOLLOW-UP

Consensus Statement 20:
There is no evidence supporting routine follow-up impacting overall survival outcomes. For patients who have completed treatment for potentially curable pancreatic cancer and have no evidence of disease, follow-up should be

continued until recovery from treatment-related toxicities and subsequent radiographic monitoring for disease recurrence should be discussed on an individualized basis at 3- to 6-month intervals.

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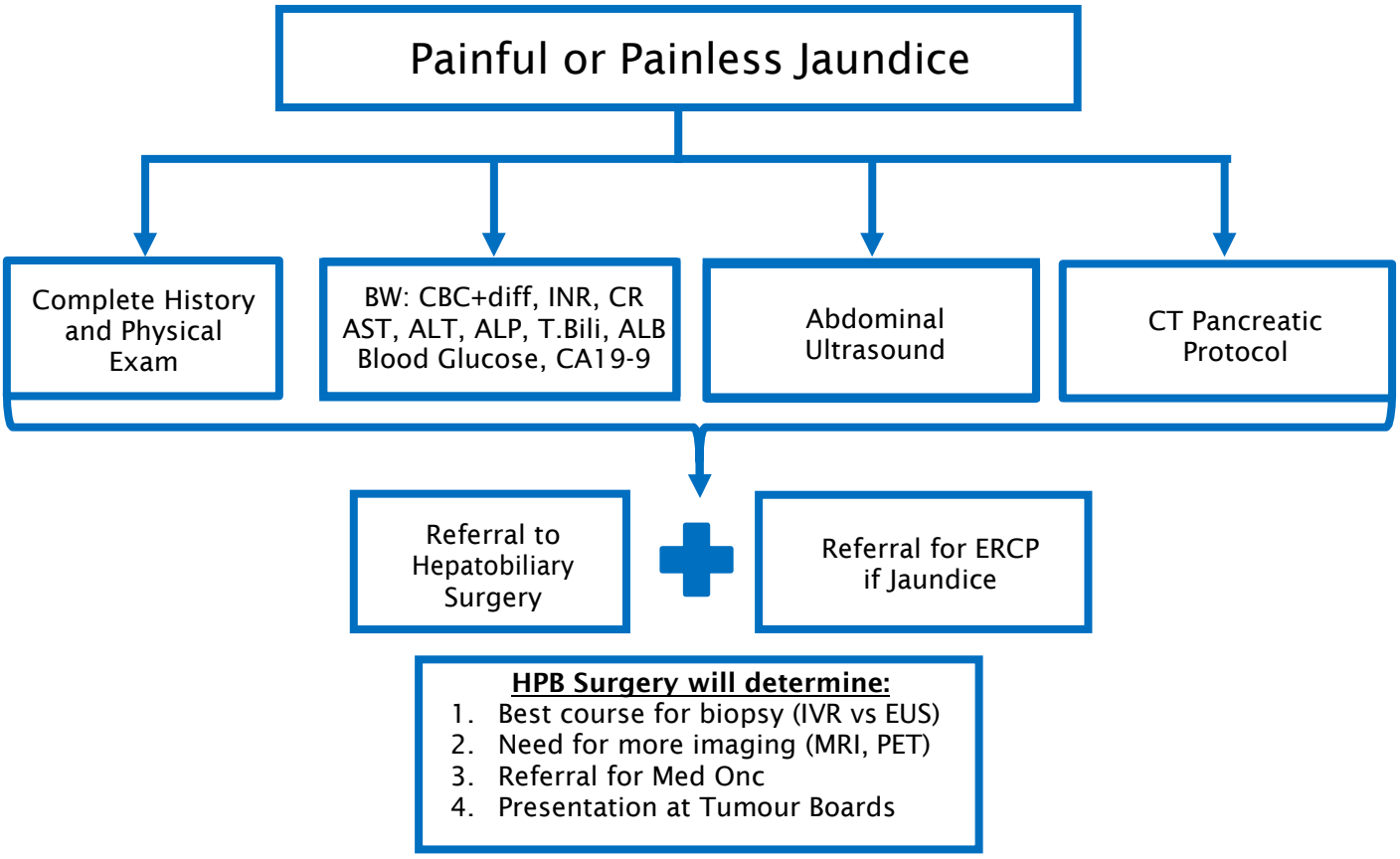
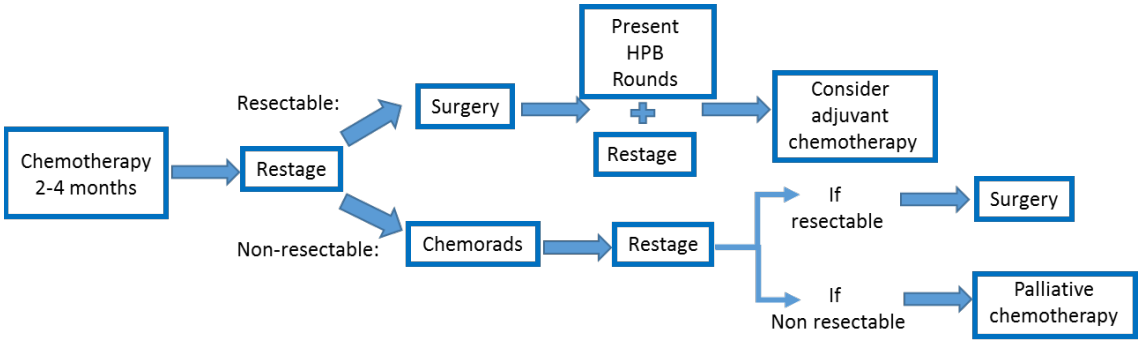
APPENDICES:

Appendix A: Diagnostic Algorithm for Suspected Pancreatic Adenocarcinoma in NS



Appendix B: Neoadjuvant Treatment Algorithm for Pancreatic Adenocarcinoma



Appendix C: Summary of Clinical Trial Results

Neoadjuvant Systemic Therapy

- The efficacy of neoadjuvant systemic therapy is controversial due to the inclusion of borderline resectable and resectable lesions in small retrospective studies.

Surgery

- Surgery remains the only potentially curative treatment option for patients with a diagnosis of pancreatic cancer.
- Approximately 20% to 25% of all pancreatic cancers appear resectable at the time of diagnosis.
- Curative-intent surgery is recommended for appropriate patients with early stage disease (Stage I and some Stage II).
- For early stage pancreatic cancers involving pancreatic head masses, pancreaticoduodenectomy or Whipple's surgery is the mainstay of treatment. For tumours of the pancreatic body and tail the most common surgery is a distal pancreatectomy which also routinely includes splenectomy.
- Even with surgery, up to 75% of patients with local disease will develop recurrence of the disease.
- The median survival of patients with potentially curable pancreatic cancer who undergo primary pancreatectomy alone is less than 20 months.

Neoadjuvant Chemoradiotherapy

- Neoadjuvant chemoradiotherapy can be safely delivered to patients with localized pancreatic cancer.
- However no study clearly demonstrates improved resectability or survival using neoadjuvant chemoradiotherapy.
- LAP07 Study
    - Randomized phase 3 study, patients treated with 4 months of neoadjuvant systemic therapy (Gemcitabine 1000mg/m2 weekly +/- erlotinib 100mg/d) and randomized to chemoradiotherapy versus 2 months of the same systemic therapy before.
    - Median OS from the date of the first randomization was 16.5 months for systemic therapy alone (95%CI, 14.5-18.5 months) versus chemoradiotherapy at 15.2 months (95%CI, 13.9-17.3 months; HR: 1.03; 95%CI, 0.79-1.34; P = .83).
    - Chemoradiotherapy was associated with decreased local progression (32%vs 46%, P = .03) and no increase in grade 3 to 4 toxicity, except for nausea.

Adjuvant Systemic Therapy

- CONKO001 Study
    - Randomized patients with either R0 or R1 resection to 6 months of gemcitabine (once a week for 3 weeks of every 4 weeks) versus observation alone.
    - 5-year OS rate of 22.5% vs 11.5% gemcitabine vs surveillance group, and a median DFS 13.4 vs 6.9 months.
- ESPAC-3

    - Randomized patients with either R0 or R1 resection either observation, 5FU (425mg/m2 bolus days 1-5 q28days) or gemcitabine (1000 mg/m2 once a week for 3 of every 4 weeks) for 6 months.
    - Median survival in observation group was 35.3 months versus 43.1 months in the 2 systemic therapy group.
    - Median DFS was 19.5 months (95% CI, 14.2-30.3 months) in the observation group, 23.0 months with 5FU (95% CI, 17.0-51.9 months) and 29.1 months with gemcitabine (95% CI, 19.5-45.4 months).
    - No statistical improvement in survival was seen with gemcitabine over 5FU, leaving both an option for treatment.
    - Treatment-related adverse events were higher with flourouracil plus leucovorin versus gemcitabine alone (> grade 3 events: 14% v 7.5%, respectively).
- ESPAC-4
    - A randomized phase 3 clinical trial looking at R0/R1 resected pancreatic cancer treated with either Gemcitabine (1000 mg/m2 once a week for 3 of every 4 weeks) or Gemcitabine + capecitabine (1660 mg/m2 daily for 3 of every 4 weeks) for 6 months.
    - Median OS was 25.5 months for gemcitabine (95% CI: 22.7-27.9) and 28.0 months for gemcitabine +cape (95% CI: 23.5-31.5) with 5 year estimated OS was 16% vs 29%.

Adjuvant Chemoradiotherapy

- The risk of local failure after surgery alone is >50% and with adjuvant systemic therapy, can be up to 25%.
- RTOG9704
    - Following resection, patients randomized to chemorads with either 5FU (continuous at 250 mg/m2/day) or gemcitabine (1000mg/m2 weekly) both given for 3 weeks pre-CRT and 12 week post CRT. CRT consisted of 50.4Gy over 28 fractions with continuous infusion 5FU 250mg/m2/day.
    - Median survival and 5-year OS of 20.5 months and 22% with Gemcitabine vs. 17.1 months and 18% with 5-FU.
- EORTC-40013-22012/GERCOR study
    - In this phase 2 study in the adjuvant setting, patients randomized to 4 cycles of gemcitabine vs 2 cycles of gemcitabine followed by weekly gemcitabine with concurrent radiation (50.4Gy).
    - Rates of local failure after gemcitabine alone versus after radiation plus gemcitabine were 24% and 11% respectively.
    - Median DFS was 12 months in the CRT arm and 11 months in the control arm and median OS was 24 months in both arms.

First-line Therapy

- ACCORD 11 trial
    - Median survival 11.1 months vs 6.8 months (HR 0.57, 95% CI 0.45-0.73) when compared to gemcitabine alone.
    - Delays the deterioration in quality of life when compared to Gemcitabine alone.
    - FOLFIRINOX has much higher rates of Grade 3/4 AEs compared to gemcitabine alone:
        - Neutropenia 45.7% vs 21%

        - Thrombocytopenia 9.1% vs 3.6%
        - Fatigue 23.6% vs 17.8%
        - Emesis 14.5% vs 8.3%
        - Neuropathy 9% vs 0%
        - Diarrhea 12.8% vs 1.8%
        - Febrile Neutropenia 5.4% vs 1.2%
- MPACT study
    - A randomized phase III trial comparing nab-Paclitaxel (125mg/m2 once a week for 3 of every 4 weeks) plus Gemcitabine (1000 mg/m2 once a week for 3 of every 4 weeks) versus Gemcitabine alone (1000 mg/m2 once a week for 3 of every 4 weeks).
    - Median OS 8.5 months in the intervention arm compared to 6.7 months in the control arm; Median PFS 5.5 months versus 3.7 months.
- Gemcitabine monotherapy has been shown to offer clinical benefit in 23.8% or patients (improved performance status, weight and improvement in pain).
    - Compared to bolus 5-FU, median survival improved from 4.4 months to 5.65 months and improve twelve-month survival from 2% to 18%.

BRCA Testing

- Emerging evidence suggests BRCA-mutated or familial pancreatic cancer may be sensitive to cisplatin-based regimens.
- On a retrospective analysis, patients who had BRCA1 or 2 mutation has superior OS observed when treated with platinum vs those treated with non-platinum chemotherapies (22 vs 9 months).

Nanoknife Ablation

- Nanoknife Ablation of irreversible electroporation (IRE) is a tissue ablation technique using short, repetitive non-thermal high energy pulses of electricity to theoretically kill cancer cells.
- It is being increasing utilized in Europe and the United States.
- The procedure can be done percutaneously or laparoscopically, however most are done as open surgery, requiring hospitalization afterward.
- Little research has been done evaluating the effectiveness of this treatment modality.
- Martin et al., 2015 Annals of Surgery Vol 262, p.486-492
    - A multicenter, prospective study from July 2010 to October 2014 identified stage 3 locally advanced pancreatic cancer.
    - 150 patients underwent IRE alone, and 50 patients underwent pancreatic resection plus IRE.
    - All patients underwent an average of 6 months of “induction chemotherapy” and 52% underwent chemoradiation therapy.
    - Within 29 months of follow-up, 6 patients had local recurrence. Median survival was 24.9 months (and compared to historical controls).
    - Complication rates was 37%.
- PANFIRE Study
    - A Phase 1/2 study prospective study evaluating the role of IRE in locally advanced pancreatic cancer.

- 25 patients were enrolled with 13 receiving systemic chemotherapy before IRE and 9 patients receiving surgical bypass before IRE.
- Median event-free survival after IRE was 8 months, the median time to local progression after IRE was 12 months and the median OS was 11 months from IRE.
- 11 major complications (nine grade III, two grade IV) in 10 patients were identified.