

Diagnosis and management of pancreatic cancer

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About 1 in 79 Canadians will have pancreatic cancer in their lifetime, making it the 12th most common malignant disease and the 4th leading cause of death from cancer.^{1,2} A family physician can expect to encounter 1 to 2 patients with pancreatic cancer each year, with increases in case volumes anticipated as the Canadian population grows and ages.³ When considering all stages, the overall 5-year survival for pancreatic cancer is about 6% (Table 1),^{4,5} making it one of the most fatal diseases.¹

In the clinical setting, and for the purpose of this article, we use the term pancreatic cancer to refer to the ductal adenocarcinoma subtype, which accounts for 90% of cases.⁶ The aim of this article is to explore our current evidence-based understanding of pancreatic cancer (Box 1), focusing on diagnostic and treatment strategies relevant to the general clinician.

When should pancreatic cancer be suspected and how is it diagnosed?

Risk factors

Active smoking remains the most established environmental risk factor for pancreatic cancer (odds ratio [OR] 1.74, 95% confidence interval [CI] 1.61–1.87),⁷ and cessation is the only recommended disease-specific preventive measure. Other putative associations identified in epidemiologic case-control studies include body mass index (BMI) of more than 35 (OR 1.55, 95% CI 1.16–2.07), consumption of more than 6 alcoholic beverages per day (OR 1.46, 95% CI 1.16–1.83)⁷ and the presence of non-type O blood antigens (OR 1.42, 95% CI 1.21–1.66),⁸ which display aberrant expression on pancreatic ductal cells, thus affecting signal transduction and cellular adhesion. Allergies have recently been associated with a lower incidence of pancreatic cancer (OR 0.40, 95% CI 0.26–0.87); however, the mechanism for this association is unknown.⁹

A family history of pancreatic cancer is seen in 20% of patients (OR 2.41, 95% CI 1.04–4.74).⁷ Furthermore, 5%–10% of patients have a hereditary pancreatic cancer syndrome (Box 2^{7,10–13}), in which cancer is caused by one of several germline mutations.^{7,10}

Screening

A latency period of about 10 years between the start of pancreatic carcinogenesis and symptomatic disease has been shown.¹⁴ Thus, there is a theoretical benefit to screening; however, there is no consensus as to its optimal modality, interval or duration. Prospective observational studies of screening have included patients at high risk (Box 2) and have used a combination of endoscopic ultrasound, computed tomography (CT) imaging, magnetic resonance imaging (MRI) or endoscopic retrograde cholangiopancreatography.^{1,15} Relatives with a hereditary pancreatic cancer syndrome or unaffected adults in a familial pancreatic cancer kindred should be referred to a genetic counselor for further assessment and possible screening in a research setting.^{16,17} Most investigational protocols begin screening 10 years earlier than the age at which the youngest relative with pancreatic cancer received the diagnosis or at the age of 40–45 years, whichever occurs first.

Clinical presentation

The pancreas is located in the retroperitoneum, where initial growth of the cancer is silent; therefore, symptoms are usually a sign of advanced disease. Clinical presentation depends on the stage of disease and the location of the primary tumour: the pancreatic head, neck or uncinate process (70%); the body or tail (20%); or multifocal disease (10%).¹⁸ Because most tumours arise in the pancreatic head, signs and symptoms

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KEY POINTS

- Smoking cessation remains the only recommended measure for the prevention of pancreatic cancer.
- Triphasic abdominal contrast computed tomography scan is the imaging modality of choice for diagnosis.
- Surgery (pancreaticoduodenectomy, or distal or total pancreatectomy, depending on tumour location) remains the only therapy with curative potential.
- Adjuvant chemotherapy, with or without radiation therapy, should be administered to all patients following curative resection for pancreatic cancer.
- In advanced pancreatic cancer, gemcitabine alone, gemcitabine plus erlotinib and FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) have each shown a survival benefit over other chemotherapy options.

may include right–upper quadrant or epigastric pain (79%), jaundice (56%), nausea or vomiting secondary to obstruction of the gastric outlet (51%), diarrhea (43%) and steatorrhea due to pancreatic insufficiency (25%).¹⁹ New onset or worsening of previously stable diabetes, although not usually due to the cancer, should alert the physician to the possibility of pancreatic cancer (OR 7.9, 95% CI 4.7–12.5).²⁰ Furthermore, new or worsening back pain (49%) could signal cancer in the pancreatic body or tail. Finally, systemic manifestations may include profound and rapid weight loss (85%), anorexia (83%) or thromboembolic disease (3%).¹⁹

Diagnostic tests

Tumour markers have minimal diagnostic utility in pancreatic cancer (Figure 1).^{19–24} Biomarkers that have been evaluated include CA 19-9 (sensitivity 70%–90%, specificity 68%–91%), which has poor positive predictive value in both asymptomatic (0.9%) and symptomatic patients (72%), and carcinoembryonic antigen, which also has a low diagnostic yield (sensitivity 25%–54%, specificity 75%–91%).²⁵

Abdominal ultrasound is often used as an initial diagnostic test for patients with nonspecific abdominal pain. The sensitivity and specificity of ultrasound in diagnosing pancreatic tumours is 90% and 95%, respectively, but worsens for masses smaller than 3 cm.²¹ Ultrasound is limited by its operator dependency and inability to distinguish cancer from chronic or autoimmune pancreatitis; thus, ultrasound serves as a bridge to CT imaging. The putative diagnosis and stage of pancreatic cancer is usually made with tripha-

sic contrast-enhanced abdominal CT (sensitivity 89%–97%, specificity 95%), which provides orientation of the tumour with surrounding vessels and organs.²¹ Although MRI is considered equivalent to CT (sensitivity 81%–99%, specificity 70%–93%), its more limited availability has restricted its use to patients with contraindications to CT (e.g., pregnancy, nephropathy) or where resectability is unclear after CT.²²

The diagnostic accuracy of these imaging modalities obviates the need for preoperative tissue diagnosis in surgically resectable tumours. Endoscopic ultrasound (sensitivity 92%, specificity 96%) or CT-guided biopsy (sensitivity 80%–90%, specificity 98%–100%) is warranted in cases where malignancy is uncertain (autoimmune or chronic pancreatitis) and in unresectable disease before chemoradiation therapy.⁴ Routine preoperative biliary drainage with endoscopic retrograde cholangiopancreatography is unnecessary; however, brushings (sensitivity 40%–60%, specificity 91%–100%) may be helpful during therapeutic stenting for sepsis management in patients with cholangitis, an unknown pancreatic head mass or patients unable to undergo immediate surgery.^{23,24}

When and how can pancreatic cancer be surgically resected?

Pancreatic cancer is broadly classified into resectable, borderline resectable and advanced disease (Figure 2).^{26–39} Twenty percent of cases are candidates for surgery and have CT evidence of no distant metastases, with the primary tumour free from the hepatic portal and superior

Stage	Tumour grade	Node status	Distant metastases	5-yr survival, %*	Median survival, mo*	Characteristics
IA	T1	N0	M0	14	24	Tumour < 2 cm in pancreas only
IB	T2	N0	M0	12	21	Tumour > 2 cm in pancreas only
IIA	T3	N0	M0	7	15	Tumour extends beyond the pancreas, but with no involvement of the celiac or superior mesenteric artery
IIB	T1–3	N1	M0	5	13	Regional lymph node metastasis
III	T4	N0–1	M0	3	11	Tumour involves the celiac or superior mesenteric artery
IV	T1–4	N0–1	M1	1	5	Distant metastases

Note: Data adapted from Hidalgo and colleagues⁴ and the American Cancer Society.⁵
 *Statistics based on data from patients receiving stage-recommended treatment.

mesenteric veins and from the celiac, hepatic and superior mesenteric arteries.²⁶ The surgical procedure depends on the location of the tumour: pancreaticoduodenectomy (Whipple procedure) is used for lesions of the head, neck and uncinate process; distal pancreatectomy is used for lesions of the body or tail; and total pancreatectomy is used in multifocal disease.

Owing to the technical complexity of these surgeries, minimally invasive approaches are not widely used, although laparoscopic distal pancreatectomy may provide similar oncologic results with the usual benefits of minimally invasive surgery.⁴⁰

Common postsurgical complications include delayed gastric emptying (5%–45%) and pancreatic anastomotic leaks (0%–13%).^{41,42} Delayed gastric emptying manifests as failure of dietary progression after 7 days, prolonged use of nasogastric decompression or emesis upon removal requiring reinsertion.⁴³ Management includes continued nasogastric decompression, use of promotility agents (metaclopramide, erythromycin) and ongoing nutritional support (jejunal or parenteral),⁴¹ with resolution usually within 2–6 weeks.

Pancreatic leaks (70%–90%) containing amylase-rich fluid occur within the first 1–2 weeks after surgery and present with abdominal pain and fever (temperature > 38.5°C). These symptoms are managed with antibiotics and percutaneous drainage, usually by interventional radiologists.^{41,44} Leaks with severe sepsis, peritonitis or hemorrhage require surgical irrigation and drainage, with rare cases requiring complete pancreatectomy.⁴⁴ In-hospital mortality from pancreatic leaks is as high as 5% with nonsignificantly shortened survival compared with patients without leaks (16.5 mo v. 27.5 mo, $p = 0.4$).⁴⁵ Diabetes and pancreatic insufficiency requiring lifelong treatment develop in patients undergoing total pancreatectomy.

Overall 5-year survival after pancreatic resection is 14.6%, but higher in well-differentiated disease (30%–40%) and disease that has not metastasized to the lymph nodes (25%–30%).⁴⁶ Postoperatively, blood glucose monitoring every 3–6 months should be considered because diabetes develops in more than 50% of patients with partial pancreatectomy.⁴⁷ Liberal use of enzyme replacements is recommended because of exocrine pancreatic insufficiency, occurring in 80% of patients and presenting as bloating, diarrhea and steatorrhea. Rising CA 19-9 levels may signal early recurrence; however, the appropriate surveillance interval and duration is unknown, and intensive follow-up may not be necessary outside of a clinical trial.⁴⁸

Is there a role for adjuvant or neoadjuvant therapy?

Adjuvant chemotherapy is recommended for all patients based on results from multiple randomized trials (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121368/-/DC1) and meta-analyses. Either gemcitabine or 5-fluorouracil (5-FU) prolongs median survival by 3 months (95% CI 0.3–5.7),^{28–31,49} but gemcitabine has been recommended as the first-line adjuvant agent owing to its lower toxicity profile versus 5-FU in the European Study Group for Pancreatic Cancer (ESPAC) 3 trial.⁵⁰ Common adverse effects with gemcitabine include myelosuppression (32%–73%, grade 3/4 2%–22%), hepatotoxicity (50%–80%, grade 4 2%–16%), nausea and vomit-

Box 1: Summary of the literature review

We searched Medline and PubMed databases (from 1947 onward) using the following medical subject headings (MeSH): "pancreas cancer," "pancreatic cancer," "PDAC," "cancer statistics," "pancreas cancer genetics" and "PDAC diagnosis and management." We searched the Cochrane database for relevant systematic reviews. We searched Google Scholar for clinical practice guidelines using the same MeSH terms. In addition, we reviewed the reference lists of identified studies. We prioritized queried articles based on clinical and biological relevance, as well as on the basis of citations and journal impact.

Box 2: Hereditary pancreatic cancer syndromes^{7,10–13}

- Familial pancreatic cancer:** Two or more first-degree relatives with pancreatic cancer failing to satisfy the criteria of another hereditary pancreatic cancer syndrome (below). Familial pancreatic cancer is genetically heterogenous, with some cases caused by germline mutations in *BRCA2* (2.8%–17.2%) and *PALB2* (1%–3%), despite a paucity of breast, ovary or other cancers in these families.
 Association with pancreatic cancer: standardized incidence ratio 6.79, 95% confidence interval (CI) 4.54–9.75.
 Prevalence: Not well-defined, but possibly the most common inherited cause of pancreatic cancer.
- Lynch syndrome (hereditary nonpolyposis colon cancer):** Colon cancer predisposition syndrome associated with tumour microsatellite instability and mutations involving DNA mismatch repair (*hMSH2*, *hMLH1*, *hPMS2*, *hMSH6*).
 Association with pancreatic cancer: odds ratio (OR) 3.68, 95% CI 1.45–5.88.
 Prevalence: 1/500 to 1/1000.
- Hereditary breast/ovarian cancer:** Families with early-onset breast cancer (age < 50 yr) or multiple breast or ovarian cancers with underlying *BRCA1/2* mutations.
 Prevalence: 1/400 to 1/500.
- Familial atypical mole melanoma:** Two or more blood relatives with melanoma and an underlying *CDKN2A/p16* mutation.
 Association with pancreatic cancer: OR 47.8, 95% CI 28.4–74.7.
 Prevalence: >1/1000.
- Hereditary pancreatitis:** Two or more first-degree relatives across 2 generations with recurrent pancreatitis and an underlying *PRSS1* mutation.
 Association with pancreatic cancer: OR 53 (95% CI 50–60).
 Prevalence: 0.3/100 000.
- Peutz-Jeghers syndrome:** A hamartomatous polyposis syndrome of the gastrointestinal tract associated with a *STK11* mutation.
 Prevalence: 1/25 000–1/300 000.

ing (26%–55%, grade 3/4 2%–3%) and diarrhea (38%, grade 3/4 2%). Toxicities with 5-FU include stomatitis (65%, grade 3/4 10%), nausea or vomiting (30%–60%, grade 3/4 3%–4%) and myelosuppression (10%–55%, grade 3/4 0%–22%).³¹

The benefit of adjuvant radiation therapy is unclear based on the results of the ESPAC-1 trial.²⁸ Median survival with chemoradiation (13.9 mo, 95% CI 12.2–17.3) was similar to that seen with observation alone (16.9 mo, 95% CI 12.3–24.8), but was longer when chemoradiation was followed by chemotherapy (19.9 mo, 95% CI 14.2–22.5) and longest with adjuvant chemotherapy alone (21.6 mo, 95% CI 13.5–27.3). Criticism of the ESPAC-1 study design has prevented total abandonment of adjuvant radiation therapy, and it is still administered at some institutions. Common adverse effects of radiotherapy include dermatitis, nausea and vomiting, diarrhea and myelosuppression.

The evidence for benefit of neoadjuvant therapy (i.e., administered before surgery) at the cost of delaying surgery is controversial. Theoretical benefits include preoperative eradication of

micrometastatic disease, reduction in tumour volume facilitating resection, ensuring that patients receive this type of treatment (some never receive adjuvant therapy owing to prolonged recovery from surgery) and improved perfusion of peritumoral tissues before surgical disruption of the vasculature and lymphatics. A meta-analysis mainly consisting of heterogeneous phase I and II studies found a median overall survival of 23.3 (range 12–54) months, with perioperative mortality of 5.3% (95% CI 4.1%–6.8%).⁵¹ These figures are comparable with those for upfront resection with adjuvant therapy. Because no phase III trials comparing outcomes between neoadjuvant and adjuvant therapy exist, most centres currently refrain from using neoadjuvant therapy outside of research protocols.

What is the management of borderline resectable disease?

Pancreatic cancer with partial abutment or encasement of the hepatic portal or superior

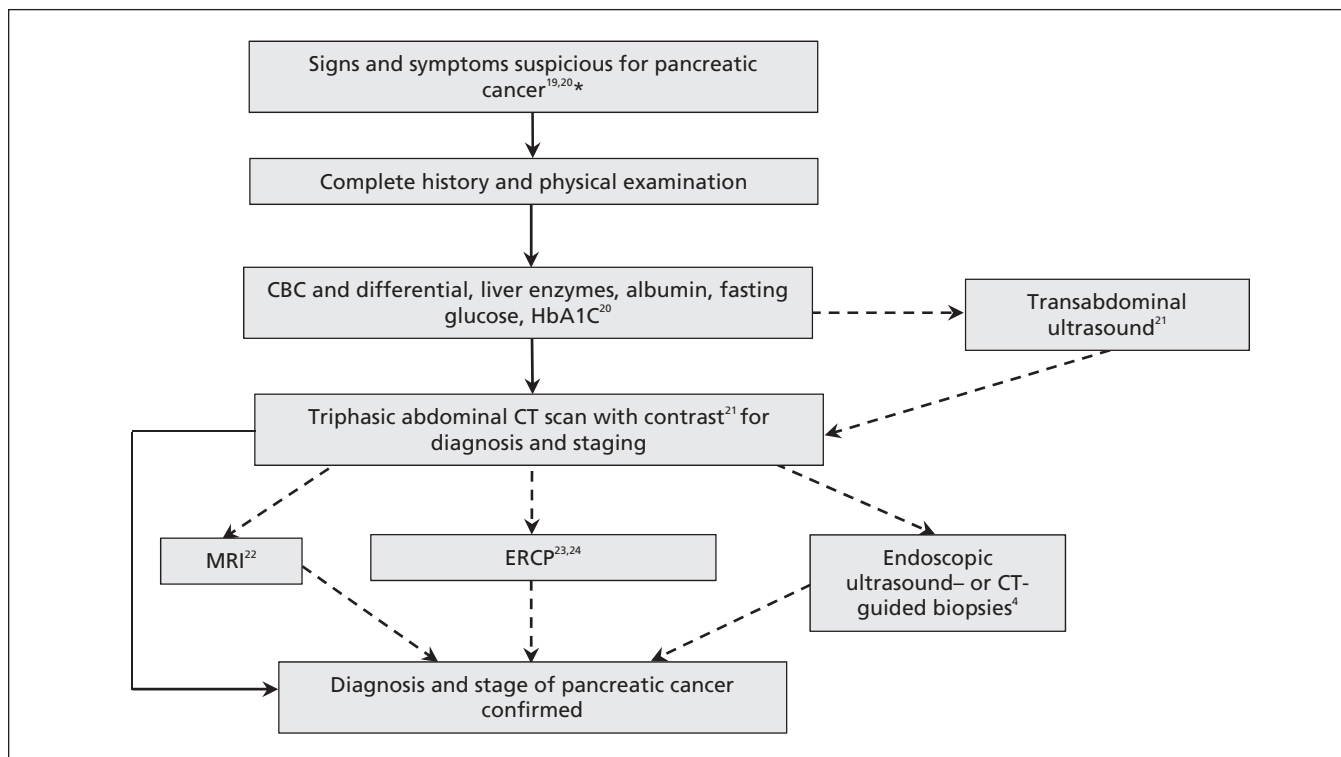


Figure 1: Diagnostic algorithm for pancreatic cancer. Laboratory investigations include a complete blood count (CBC), liver enzyme tests for biliary obstruction, and fasting glucose and glycated hemoglobin (HbA1C) tests to monitor for new onset or worsening diabetes. A transabdominal ultrasound can be performed for patients presenting with jaundice or nonspecific abdominal pain, followed by computed tomography (CT) if suspicious for pancreatic cancer. Patients with contraindications to CT, intolerance to contrast or in whom resectability is questioned can undergo magnetic resonance imaging (MRI). Endoscopic retrograde cholangiopancreatography (ERCP) is not routinely used, but cytologic brushings for diagnosis can be taken in those with cholangitis and an unknown pancreatic mass, or with jaundice who are unfit for immediate surgery. Endoscopic ultrasound- or CT-guided biopsies are used when diagnosis is unclear after imaging, in unresectable cases before palliative treatment or before neoadjuvant treatment. *Painless jaundice, pain in the right-upper quadrant or epigastric pain, indigestion, early satiety, steatorrhea, weight loss, abdominal mass. Dashed lines indicate imaging modalities that can be contained but are not routinely necessary.

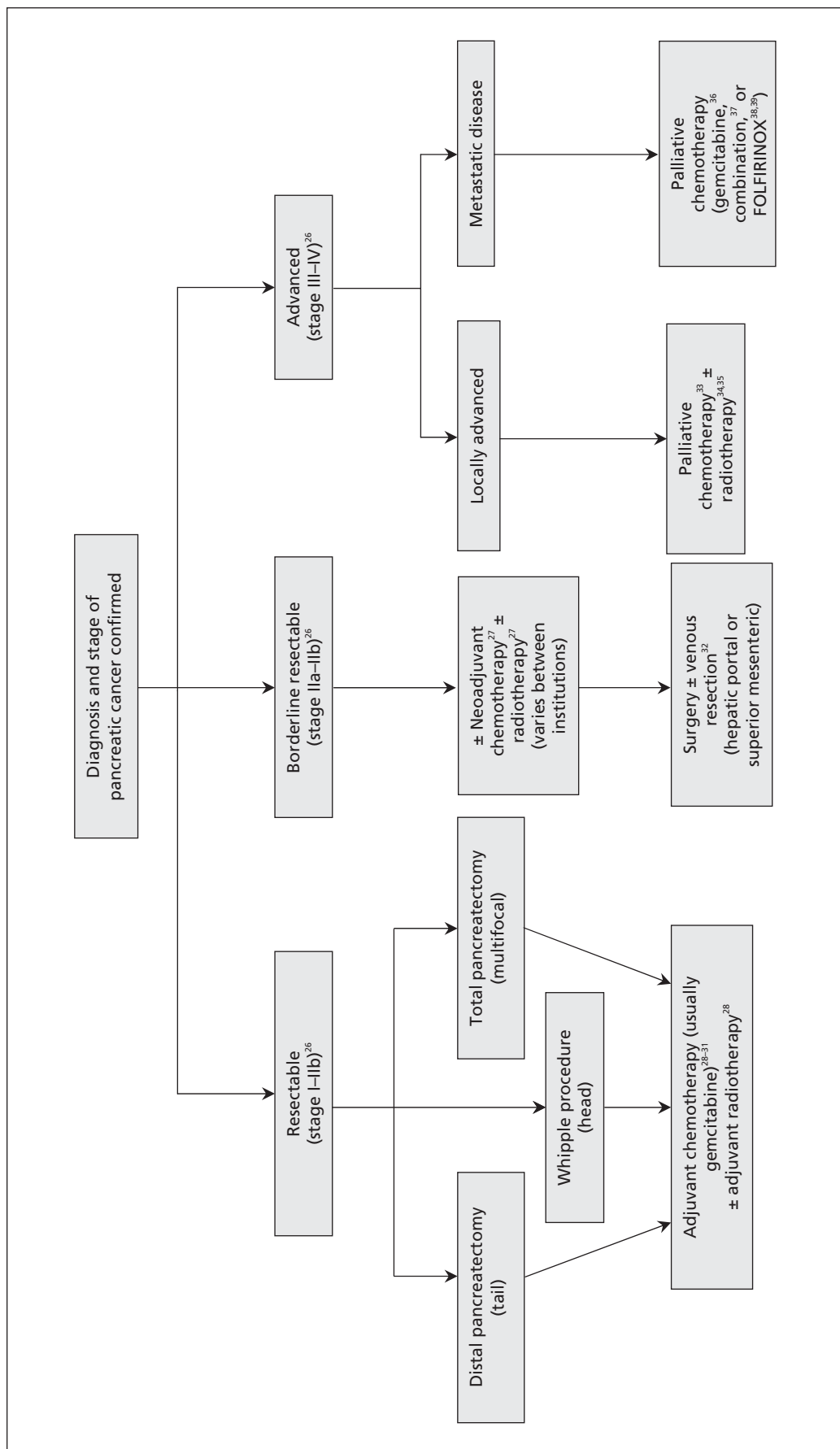


Figure 2: Treatment algorithm for pancreatic cancer.

mesenteric veins is considered borderline resectable, and surgery is attempted only if complete resection is possible.²⁶ A 6-year prospective study involving 110 patients with resection of the hepatic portal vein, superior mesenteric vein or both for suspected tumour infiltration showed median overall survival of 14.5 (range 7.3–24) months, with perioperative mortality of 3.7%.³² These results suggest that major venous resection and reconstruction is safe in experienced hands and results in oncologic results equivalent to those of complete resection.

A role and optimal regimen for neoadjuvant therapy in borderline resectable disease is unclear, based on inconclusive findings regarding median survival in a retrospective study of neoadjuvant treatment versus immediate surgery (35 mo v. 27 mo; $p = 0.7$).²⁷

What treatment options exist for advanced pancreatic cancer?

Patients with advanced pancreatic cancer include those with locally advanced or metastatic disease and have a median overall survival of 2–3 months without treatment.⁵² Locally advanced disease, representing 30% of cases, appears radiographically as extensive involvement of the hepatic portal vein, superior mesenteric vein and retroperitoneum, in addition to encasement of major arteries (celiac, hepatic, superior mesenteric) or infiltration of the aorta.^{4,26} A meta-analysis of palliative chemotherapy versus supportive care showed improved survival in locally advanced disease (hazard ratio [HR] 0.64, 95% CI 0.42–0.98), with equivalent results between gemcitabine and 5-FU (HR 0.75, 95% CI 0.42–1.31).³³ A survival benefit with chemotherapy followed by chemoradiation (Appendix 1) was seen in the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) phase II/III study³⁴ and furthered by the Eastern Cooperative Oncology Group-E4201 trial³⁵ comparing gemcitabine plus radiotherapy with gemcitabine alone. Combination chemoradiation therapy is now central to the management of locally advanced disease.

Distant organ involvement, typically that of the liver, peritoneum or lung, occurs in 50% of cases. For patients with such involvement, gemcitabine provides a slight improvement in overall survival over 5-FU (5.65 mo v. 4.41 mo, $p = 0.003$).³⁶ Individual clinical trials of combination gemcitabine with various cytotoxic agents^{53–56} have failed to show a survival benefit over gemcitabine alone (Appendix 1), but significantly improved overall survival was seen when these studies were pooled (HR 0.91, 95% CI 0.85–0.97).³⁷ Furthermore,

patients with a good performance status (Karnofsky performance score > 90%) survived longer with combination gemcitabine (HR 0.76, 95% CI 0.67–0.87), whereas patients with a poor performance status did not (HR 1.08, 95% CI 0.90–1.29). Combination therapy also showed higher grade 3/4 toxicity: neutropenia (risk difference [RD] 5%, 95% CI 1%–10%), thrombocytopenia (RD 5%, 95% CI 2%–8%) and nausea or vomiting (RD 3%, 95% CI 0%–5%).⁵⁷ Combination chemotherapy is reserved for patients with a good performance status.

Targeted therapy in pancreatic cancer has centred on the epidermal growth factor pathway. A phase III study of the epidermal growth factor receptor inhibitor erlotinib with gemcitabine versus gemcitabine alone showed marginally increased overall survival (6.24 v. 5.91 mo, $p = 0.04$)⁵⁸ and 1-year survival (23% [95% CI 18%–28%] v. 17% [95% CI 12%–21%], $p = 0.02$). However, toxicity was increased at all grades, including fatigue (32%; percent difference gemcitabine–erlotinib v. gemcitabine 0.85%), rash (25%; percent difference 15.2%), diarrhea (20%; percent difference 5.2%) and, rarely, interstitial lung disease (0.7%; percent difference 0.6%). Currently, combination gemcitabine/erlotinib is considered for patients with good performance status in the metastatic setting.

More recently, FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) has shown a substantial increase in median overall survival over gemcitabine alone in metastatic pancreatic cancer (11.1 mo [95% CI 9.0–13.1] v. 6.8 mo [95% CI 5.5–7.6 mo]; HR 0.57, 95% CI 0.45–0.73, $p < 0.001$).³⁸ However, a higher grade 3/4 toxicity was also seen: neutropenia (45.7% v. 21.0%, $p < 0.001$), thrombocytopenia (9.1% v. 3.6%, $p = 0.04$), diarrhea (12.7% v. 1.8%, $p < 0.001$) and sensory neuropathy (9.0% v. 0%, $p < 0.001$). A longitudinal follow-up study (median 26.6 mo, 95% CI 20.5–44.9) showed a longer time to symptomatic deterioration for patients in the FOLFIRINOX group.³⁹

Future directions

Accelerated progress in understanding pancreatic cancer relies on robust partnerships between clinicians and basic scientists, such as the current global effort to develop more integrated translational pancreatic cancer programs.⁵⁹ Next-generation sequencing has revolutionized the field of pancreatic cancer genetics, and notable findings include the recent discovery of germline mutations in the ataxia telangiectasia mutated gene (*ATM*) in a small proportion (2.4%–4.6%) of familial pancreatic cancer, and the involvement

of axon guidance pathways as an unexpected molecular change in some tumours.^{60,61} Further investigations are ongoing to determine what role these mutations and pathways play in pancreatic carcinogenesis. Other initiatives, such as the International Cancer Genome Consortium efforts to sequence the genomes of 750 pancreatic cancer specimens, will generate new data and catalyze genotype-specific “personalized” treatment strategies.⁶²

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