

When, What, and Why of Perioperative Treatment of Potentially Curable Pancreatic Adenocarcinoma

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The Oncology Grand Rounds series is designed to place original reports published in the Journal into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in Journal of Clinical Oncology, to patients seen in their own clinical practice.

A 64-year-old woman with a history of hypertension and type 2 diabetes had been in her usual state of health until she developed symptoms of diarrhea, abdominal bloating, and discomfort in the midepigastrium. Evaluation with a contrast-enhanced abdominopelvic computed tomography (CT) scan demonstrated a mass in the pancreatic body that was approximately 3.1 cm × 2 cm × 2.1 cm in size with abutment of the portal vein–superior mesenteric vein confluence for less than 180°. The confluence was narrowed but without thrombosis. No tumor–vessel interface was noted at the superior mesenteric artery, celiac artery, or common hepatic artery. Several peripancreatic lymph nodes were observed that measured up to 11 mm × 5 mm. No evidence for distant spread of disease was identified. An upper endoscopy with endoscopic ultrasound was performed and fine-needle aspirates of the pancreas mass were positive for malignant cells that were consistent with adenocarcinoma. Chest CT scan without intravenous contrast demonstrated no evidence of metastatic disease. The patient came to the clinic to discuss management of her newly diagnosed malignancy.

CHALLENGES IN DIAGNOSIS AND MANAGEMENT

Pancreatic cancer is the third leading cause of cancer-related death in the United States.¹ Surgical resection offers the only chance for cure, but less than 20% of patients present with early-stage disease amenable to surgery.² Pancreatectomy is a complex surgical procedure best performed at a high-volume surgical center, where perioperative mortality has steadily declined.³ Even with pancreatectomy, 75% of patients with localized disease develop tumor recurrence as a result of occult metastatic disease, poor tolerance and ineffectiveness of adjuvant therapy, and presence of residual tumor cells at surgical resection margins.^{4,5}

Marked regional variation is present in the management approach to localized pancreatic cancer. Use of neoadjuvant chemotherapy before surgical resection—an approach with growing utilization—is highlighted in the article by Mokdad and colleagues.^{6,7} Postoperative chemotherapy improves survival in patients with resected pancreatic cancer, but adjuvant treatment can be limited by postoperative complications, poor tolerance, and early disease recurrence. To improve compliance with systemic therapy, address occult micrometastatic disease earlier in the treatment course, and better select patients for surgical resection, an alternative approach of delivering therapy before resection has been advocated. Neoadjuvant

therapy also has the potential benefit of reducing positive margin rates, particularly when tumors involve surrounding vascular structures. Nevertheless, evidence in favor of neoadjuvant therapy remains limited for the management of localized pancreatic cancer.

SUMMARY OF RELEVANT LITERATURE

Randomized trials have demonstrated improved survival in patients with localized pancreatic cancer who have received adjuvant treatment. Initially, the European Study Group for Pancreatic Cancer (ESPAC)-1 study randomly assigned patients after resection to receive adjuvant fluorouracil (5-FU) chemotherapy, chemoradiotherapy, neither treatment, or both treatments. After a median follow-up time of 47 months, the 5-year survival rate was 21% among patients who received chemotherapy compared with 8% among those who did not, which suggested an overall survival (OS) benefit with use of 6 months of adjuvant 5-FU.⁸ The clinical benefit of gemcitabine in the adjuvant setting was demonstrated in the phase III CONKO-001 trial (Charite Onkologie 001). In CONKO-001, 368 patients who underwent resection for pancreatic cancer were randomly assigned to receive 6 months of gemcitabine 1,000 mg/m² on days 1, 8, and 15 of a 28-day cycle or observation. Patients who received gemcitabine achieved superior OS

(median OS, 22.8 months v 20.2 months; $P = .01$) and improved 5-year survival rates (20.7% v 10.4%) compared with surgery only.⁹

Two additional studies have demonstrated similar efficacy for 5-FU and gemcitabine in the adjuvant setting. The ESPAC-3 study evaluated 1,088 patients who underwent resection and compared treatment with gemcitabine with 5-FU for 6 months and found no statistically significant difference in disease-free survival or OS between the two arms.¹⁰ RTOG 97-04 randomly assigned patients to 5-FU versus gemcitabine chemotherapy for 4 months, sandwiched around 5-FU–based chemoradiation. No statistically significant differences were noted in OS, which emphasized the role for either 5-FU or gemcitabine in the adjuvant setting.¹¹ Given the efficacy of gemcitabine and 5-FU individually, the phase III ESPAC-4 trial compared gemcitabine and capecitabine (GEMCAP) with gemcitabine monotherapy in 732 patients with resected pancreatic cancer. ESPAC investigators reported at the 2016 ASCO Annual Meeting that median survival was 28 months for GEMCAP treatment compared with 25.5 months for gemcitabine monotherapy, with a similar adverse effect profile between the two treatment programs.¹² The 5-year survival rate was estimated as 28.8% with GEMCAP versus 16.3% for gemcitabine monotherapy, which identified GEMCAP as a new adjuvant treatment option for patients with surgically resected pancreatic cancer. Several recently completed or ongoing trials have evaluated or are evaluating other treatment programs in the adjuvant setting, including gemcitabine plus nab-paclitaxel and FOLFIRINOX (5-FU, folinic acid, irinotecan, and oxaliplatin).¹³⁻¹⁶

The role of radiation therapy remains uncertain in patients with resectable pancreas cancer. Results of two small studies that were led by the Gastrointestinal Tumor Study Group and European Organization for Research and Treatment of Cancer suggest a potential benefit to concurrent chemoradiotherapy with 5-FU compared with observation alone in patients with resected cancer in the head of the pancreas.^{17,18} Likewise, multiple retrospective analyses support a benefit for adjuvant chemoradiotherapy.¹⁹ Conversely, the ESPAC-1 trial discussed above did not confirm a benefit to adjuvant chemoradiation⁸; however, the usefulness of these randomized studies is limited as a result of issues with study design, sample size, treatment implementation, and antiquated radiation delivery, including use of split-course fractionation. To address these issues, the ongoing RTOG 0848 study was initiated and randomly assigns patients to adjuvant fluoropyrimidine-based radiotherapy or observation after 6 months of gemcitabine-based chemotherapy.²⁰ In addition, given the recent, promising results with respect to treatment response and tolerability of stereotactic body radiotherapy (SBRT), investigation of the role of SBRT in neoadjuvant treatment paradigms

is ongoing.^{21,22} SBRT offers several clinical advantages over standard long-course chemoradiation, including short treatment times—3 to 5 days compared with 28 days with long-course chemoradiation—and less acute toxicity. However, these advantages are balanced against the potential for greater rates of chronic toxicities.

Although adjuvant chemotherapy has demonstrated improved survival, benefits of a neoadjuvant treatment approach have been suggested, including earlier treatment of occult micrometastatic disease, better tolerance of systemic therapy preoperatively, improved selection of patients for surgical resection without rapidly progressive disease, and lower rates of positive surgical resection margins. Multiple phase II studies have evaluated neoadjuvant regimens that were composed of either chemotherapy alone or concurrent chemotherapy and radiation.^{7,23} These studies demonstrated the feasibility of administering neoadjuvant chemoradiation with 5-FU or gemcitabine as radiosensitizing agents.^{24,25} In a randomized phase II study of neoadjuvant treatment versus upfront surgical resection, Golcher and colleagues²⁶ demonstrated the feasibility of preoperative gemcitabine and cisplatin with concurrent radiation, but the study was underpowered to demonstrate this approach as being superior to upfront surgical resection. Most recently, a multi-institutional Alliance cooperative group study demonstrated the feasibility of FOLFIRINOX followed by chemoradiation as neoadjuvant therapy.²⁷ Prospective studies,²⁸⁻³⁰ including the NEOPA trial³¹ of preoperative gemcitabine and radiation therapy and SWOG 1505,³² which is comparing perioperative FOLFIRINOX with perioperative gemcitabine and nab-paclitaxel, are underway.

Of importance, positive surgical resection margins are common after pancreatectomy and remain a strong negative prognostic factor for patient survival.^{8,10} Therefore, a subset of patients with resectable pancreatic cancer is classified by consensus guidelines as having borderline-resectable disease, which is characterized by local tumor anatomy thought to confer a high risk for microscopically positive surgical margins with upfront surgical resection (Table 1).^{27,33,34} Although single-institution experience is accumulating,³⁵ no studies have clearly demonstrated the benefit of neoadjuvant therapy, even in this subgroup of patients who are at high risk for recurrent disease as a result of local residual tumor cells and/or more aggressive disease biology. Thus, at the current time, data to guide a specific chemotherapy program with or without radiation for the optimal treatment of these patients are limited. Future clinical trial enrollment will be critical for identifying an optimal treatment approach, and a large, multi-institutional phase II trial has been initiated to examine two treatment programs in patients with borderline-resectable disease (Alliance protocol A021101).

Table 1. Proposed Diagnostic Criteria for Borderline Resectable Pancreatic Tumors

Vessel	AHPBA/SSAT/SSO ³³	NCCN 2.2016 ³⁴	Intergroup Trial ²⁷
PV-SMV	Abutment, encasement, or reconstructable occlusion	Abutment with vessel contour irregularity or encasement or reconstructable occlusion	Encasement or reconstructable occlusion
SMA	Abutment	Abutment	Abutment
Celiac trunk	No abutment	Abutment	Abutment
CHA	Abutment or reconstructable occlusion	Abutment or reconstructable occlusion	Abutment or reconstructable occlusion

NOTE. Abutment means tumor vessel interface < 180° of vessel circumference, and encasement means tumor vessel interface ≥ 180° of vessel circumference. Abbreviations: AHPBA, Americas Hepato-Pancreato-Biliary Association; CHA, common hepatic artery; NCCN, National Comprehensive Cancer Network; PV-SMV, portal vein–superior mesenteric vein; SMA, superior mesenteric artery; SSAT, Society for Surgery of the Alimentary Tract; SSO, Society of Surgical Oncology.

Analyzing patient data from the National Cancer Database between 2006 and 2012, Mokdad and colleagues asked whether patient survival differed between two groups of patients with stage I or stage II resected adenocarcinoma of the pancreatic head: those who received neoadjuvant treatment followed by resection and those who underwent upfront surgical resection with or without adjuvant therapy. The authors used propensity score matching to control for baseline differences in the two groups and demonstrated a modestly increased survival among patients who received neoadjuvant therapy.⁶ Although these findings are a valuable addition to the literature, inherent limitations of the nonrandomized retrospective design temper their immediate applicability to practice and, at the same time, further support the need for well-designed randomized studies that evaluate the neoadjuvant treatment approach.

SUGGESTED APPROACHES TO MANAGEMENT

In patients with nonmetastatic pancreatic cancer, the first consideration is whether radiographic evidence supports surgical resectability. This evaluation requires a staging work-up with a multiphasic pancreas-protocol abdomen and pelvis CT scan, together with measurement of serum cancer antigen 19-9 (CA 19-9) and consultation in a multidisciplinary pancreas clinic that is staffed by providers from gastroenterology, medical oncology, radiation oncology, radiology, and surgical oncology who have expertise in pancreatic cancer management.³⁶ Patients with likely resectable or borderline-resectable disease would be considered future surgical candidates, although whether patients with unresectable disease as a result of vascular involvement should also be considered for future resection is an ongoing area of research.³⁷ Patients with metastatic disease would not be considered surgical candidates, and chemotherapy remains the mainstay of current treatment programs for these patients.³⁸

The National Comprehensive Cancer Network guidelines³⁴ recommend that patients with resectable pancreatic adenocarcinoma without high-risk features undergo upfront surgical resection and receive adjuvant gemcitabine or fluoropyrimidine chemotherapy with or without chemoradiation, with neoadjuvant therapy recommended only when delivered as part of a clinical trial. For patients with high-risk features, which are defined as highly elevated serum CA 19-9, a large primary tumor, large regional lymph nodes, excessive weight loss, or extreme pain, neoadjuvant therapy with FOLFIRINOX or gemcitabine and nab-paclitaxel with or without concurrent

radiation therapy may be considered. For borderline-resectable disease, the guidelines recommend neoadjuvant therapy with an approach that is similar to that for patients with resectable disease with high-risk features. As a result of a lack of evidence, specific guidance is not provided regarding duration and make-up of neoadjuvant therapy programs or whether further treatment should be administered postoperatively. In the recently published ASCO Clinical Practice Guideline for Potentially Curable Pancreatic Cancer, primary surgical resection is considered for patients with no metastases, appropriate performance status, and no radiographic interface between the primary tumor and mesenteric vasculature.² Adjuvant therapy is recommended for all patients, whereas chemoradiation can be considered after 4 to 6 months of chemotherapy for patients who did not receive such therapy preoperatively and for those with positive margins or lymph nodes. Preoperative therapy is recommended for patients whose pancreas tumor demonstrates a radiographic interface with mesenteric vasculature or when distant disease is suspected but not clearly documented. Furthermore, the authors note that preoperative therapy may be offered as an alternate strategy for those patients who are being considered for upfront resection.

At Dana-Farber/Brigham and Women’s Cancer Center, patients with nonmetastatic pancreatic cancer are seen in a multidisciplinary clinic for consultation with providers from medical oncology, radiation oncology, radiology, gastroenterology, nutrition, and surgical oncology. The care team assesses patient functional status, comorbidities, and goals of care, evaluates for biliary obstruction requiring intervention, measures serum CA 19-9, and ensures appropriate pancreas-dedicated imaging to evaluate tumor involvement of adjacent vascular structures. For patients with adequate functional status, perceived ability to tolerate pancreatectomy, low serum CA 19-9—that is, < 10 times the upper limit of normal without biliary obstruction—and no abutment of mesenteric venous or arterial structures, upfront surgical resection is generally advised (Table 2 and Fig 1). Within 3 to 12 weeks of surgery, patients begin adjuvant chemotherapy with weekly gemcitabine or, alternatively, 5-FU and leucovorin. On the basis of the recently reported data from ESPAC-4, patients with excellent functional status are considered for adjuvant treatment with gemcitabine and capecitabine. Patients with a positive or close (< 1 mm) surgical resection margin or an otherwise locally invasive tumor receive long-course radiation concurrent with continuous infusion 5-FU or oral capecitabine after completing 5 months of adjuvant chemotherapy.

Patients are treated neoadjuvantly if they have abutment of mesenteric vascular structures or worrisome features on

Table 2. Classification of Nonmetastatic Pancreatic Cancer Used at Dana-Farber/Brigham and Women’s Cancer Center

Vessel	Upfront Surgical Resection (likely resectable)	Neoadjuvant Therapy for Potential Cure* (borderline resectable)	Neoadjuvant Therapy With Unlikely Cure (locally advanced)
PV-SMV	No abutment or encasement	Abutment, encasement, or reconstructable occlusion	Unreconstructable occlusion
SMA	No abutment or encasement	Abutment	Encasement
Celiac trunk	No abutment or encasement	Abutment	Encasement
CHA	No abutment or encasement	Abutment or reconstructable occlusion	Encasement or unreconstructable occlusion

NOTE. Abutment means tumor vessel interface < 180° of vessel circumference, and encasement means tumor vessel interface ≥ 180° of vessel circumference. Abbreviations: CHA, common hepatic artery; PV-SMV, portal vein–superior mesenteric vein; SMA, superior mesenteric artery.

*Also includes patients with a tumor that had no vascular abutment or encasement, but with provider concern regarding patient’s tolerance of surgery, high serum cancer antigen 19-9, or radiologic findings equivocal for metastatic disease.

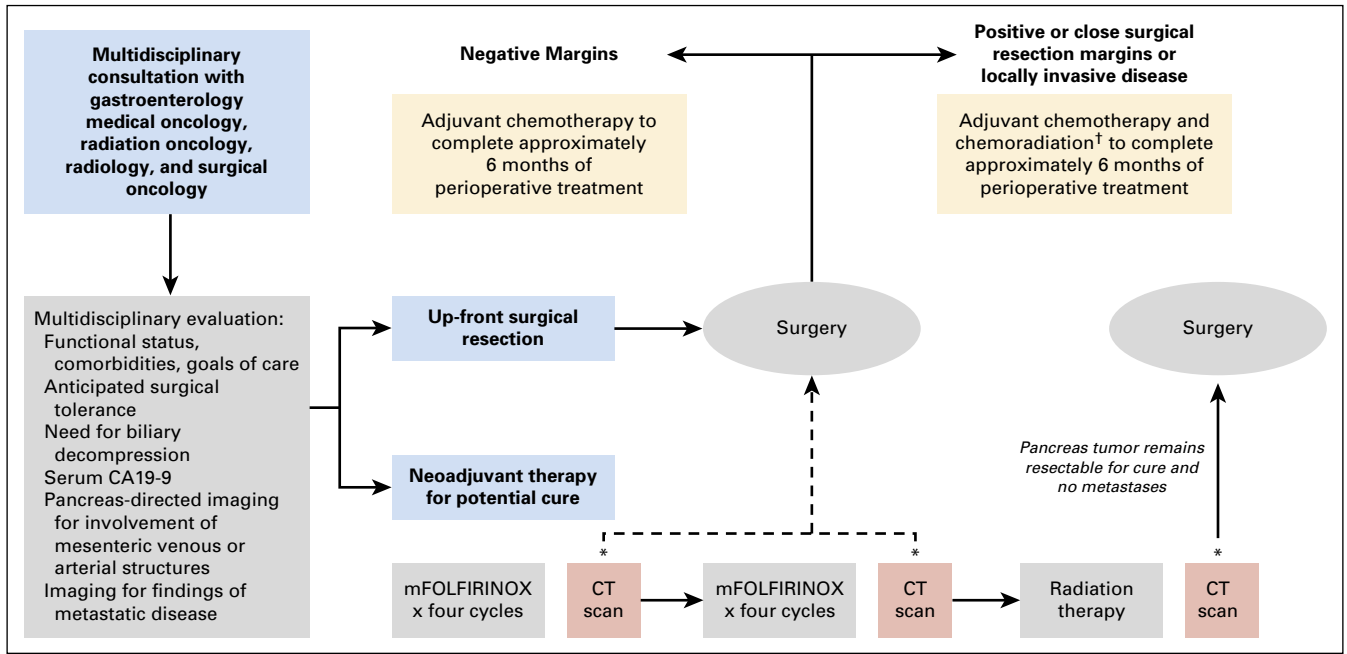


Fig 1. General treatment algorithm for patients recommended for upfront surgical resection or neoadjuvant treatment followed by surgical resection at Dana-Farber/Brigham and Women’s Cancer Center. *Multidisciplinary consultation after each computed tomography (CT) scan to determine management plan regarding a continuation of the treatment algorithm versus a change in treatment approach, including potential surgical resection. †Adjuvant chemoradiation is pursued only for patients who did not receive radiation preoperatively. Close surgical resection margin is classified as ≤ 1 mm. mFOLFIRINOX, modified fluorouracil, folinic acid, irinotecan, and oxaliplatin.

multidisciplinary review, such as concern for poor surgical tolerance, high serum CA 19-9, or potential distant disease (Table 2 and Fig 1). If functional status permits, patients receive eight cycles of FOLFIRINOX administered every 2 weeks followed by radiation therapy, then surgical resection. For some patients, tolerability concerns lead to substitution of gemcitabine plus nab-paclitaxel for FOLFIRINOX. Radiation therapy is administered as long-course treatment with continuous infusion 5-FU (or oral capecitabine) or SBRT without concurrent chemotherapy. The goal for the total treatment course—neoadjuvant plus adjuvant—is for patients to receive 4 months of chemotherapy plus radiotherapy or 6 months of chemotherapy alone, primarily on the basis of the length of treatment programs evaluated in the adjuvant setting. When adjuvant chemotherapy is administered, it is generally a derivative of the neoadjuvant treatment program, depending on prior tolerance, recovery from surgery, and treatment response identified in the surgical resection specimen.

CLINICAL DISCUSSION

After her diagnosis, our patient was evaluated in the Dana-Farber/Brigham and Women’s Cancer Center pancreaticobiliary multidisciplinary clinic. Given the portal vein–superior mesenteric vein abutment identified on imaging (Fig 2), we recommended systemic therapy with modified FOLFIRINOX on an every-2-week cycle. After four, eight, and 12 cycles of therapy, restaging CT scans showed continued reduction in the size of the pancreatic mass. With this ongoing response, neoadjuvant radiation was deferred and the patient underwent a distal pancreatectomy that was notable for residual microscopic foci of adenocarcinoma staged as ypT3N1 with one of eight positive lymph nodes and negative resection margins. No additional therapy was administered after surgery. A surveillance program was initiated with interval clinic visits, serum CA 19-9 measurement, and imaging. The patient is now 3 years from initiation of neoadjuvant chemotherapy without evidence of disease recurrence.

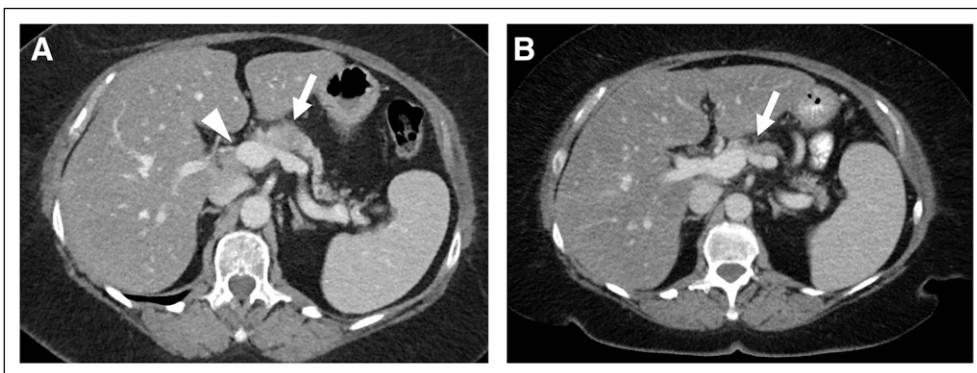


Fig 2. (A and B) Axial computed tomography (CT) images of the abdomen (A) before and (B) after neoadjuvant chemotherapy. (A) An initial diagnostic abdominopelvic CT scan demonstrated a hypodense mass in the proximal pancreatic body (arrow), with abutment of the portal vein–superior mesenteric vein confluence (arrowhead). (B) A follow-up abdominopelvic CT scan after 12 cycles of modified FOLFIRINOX (fluorouracil, folinic acid, irinotecan, and oxaliplatin) demonstrated a decrease in the size of the pancreatic body mass (arrow).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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