Evolving Treatment Options for Locally Advanced Unresectable Pancreatic Ductal Adenocarcinoma

Pelin Cinar, MD, MS, and Andrew H. Ko, MD

Abstract

The best treatment strategy for patients with locally advanced unresectable pancreatic ductal adenocarcinoma (PDAC) remains the subject of considerable debate. This report presents a case of a 58-year-old woman with locally advanced unresectable PDAC who was treated with sequential FOLFIRINOX for 8 cycles followed by chemoradiation, and continues to show durable disease control 18 months later. The respective roles of systemic therapy and chemoradiation for locally advanced PDAC are discussed, including optimal sequencing of these modalities, recent improvements in chemotherapy, and the question of whether radiotherapy improves survival outcomes in this disease context. (*J Natl Compr Canc Netw* 2014;12:167–172)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the criteria used to determine if a PDAC is unresectable
- Summarize the treatment options for patients with locally advanced unresectable PDAC
- Explain the roles of systemic therapy and chemoradiation for locally advanced PDAC including optimal sequencing, recent improvements in chemotherapy, and whether radiotherapy improves survival outcomes in this disease context

From the Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, San Francisco, California.

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Correspondence: Andrew H. Ko, MD, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, 1600 Divisadero Street A729, Box 1770, San Francisco, CA 94143-1770. E-mail: andrewko@medicine.ucsf.edu

Case Report

A 58-year-old woman presented with intermittent dull epigastric pain for several months, gradually worsening over time with radiation to the mid-back. Initial diagnostic workup included an abdominal ultrasound that revealed a 1.7-cm pancreatic head mass. Abdominal CT scan confirmed a hypoattenuating mass localized at the junction of the superior pancreatic head and neck; these findings were thought to represent a possible pancreatic pseudocyst, and another CT scan using a dedicated pancreatic protocol was recommended to be performed 4 weeks later. This repeat imaging showed an enlarging pancreatic mass, now measuring 4.5 cm in maximal dimension, abutting both the superior mesenteric artery and celiac axis, with modestly enlarged periportal lymph nodes but no evidence of metastatic disease (Figure 1A). Subsequent endosonographic ultrasound (EUS) confirmed a hypoechoic irregular mass with poorly defined borders arising from the pancreatic head/neck and extending superiorly with encasement of the celiac trunk and abutment of the superior mesenteric artery (uT4NxMx). EUS-guided fine needle aspiration of the mass confirmed adenocarcinoma.

The patient's past medical history was significant only for paroxysmal atrial fibrillation, osteopenia, and a remote history 7 years earlier of a right calf melanoma, status post wide local excision, with no evidence of recurrence. She did have a family history of breast cancer in her mother and maternal grandmother (subsequent genetic testing did not reveal any *BRCA1/2* mutations). She had a remote history of tobacco use during her college years but none for the past 30 years, and drank alcohol socially. She appeared well on physical examination, with an ECOG performance status of 0 during her initial oncology consultation visit. Laboratory evaluation revealed an elevated serum CA19-9 level measuring 1182 U/mL (normal reference range, <37 U/mL).

Based on her diagnosis of locally advanced unresectable pancreatic ductal adenocarcinoma (PDAC), she was initiated on combination chemotherapy consisting of a biweekly FOLFIRINOX regimen (infusional 5-FU, leucovorin, irinotecan, and oxaliplatin). She received a total of 8 cycles of chemotherapy, with restaging CT scans after 4 and 8 cycles of treatment, showing the primary pancreatic head/neck mass to be stable to slightly smaller in size, but with persistent involvement/partial encasement of both the superior mesenteric artery and celiac trunk. Overall, she tolerated chemotherapy well, except for grade 2 thrombocytopenia and mild nausea and diarrhea, requiring a 20% dose reduction beginning with cycle 5.

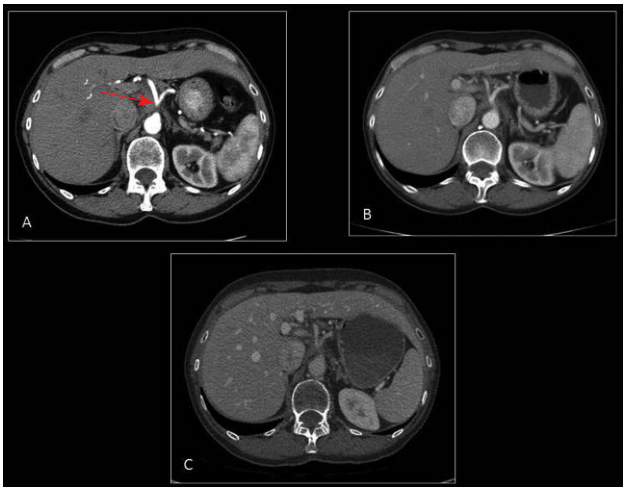

Figure 1 Axial contrast-enhanced CT of the abdomen showing infiltrative pancreatic tumor arising from the pancreatic head/neck and extending superiorly. The tumor encases the celiac axis (red arrow) in the CT scan obtained at diagnosis (A). Decreasing size of the infiltrative tumor with persistent encasement of the celiac axis is seen on the CT scan obtained 3 months (B) and 13 months (C) after completion of chemoradiation.

Secondary to the absence of metastatic disease after her eighth cycle of FOLFIRINOX, she went on to receive consolidative chemoradiation totaling 5040 cGy over 28 fractions, with capecitabine (at a dose of approximately 800 mg/m^2 twice daily) as a radiosensitizer. Her CA19-9 level declined to 17 U/mL at treatment completion. Absent any defined role for maintenance therapy, she has since been monitored at 3- to 6-month intervals, consisting of physical examination, CA19-9 levels, and CT scans of the abdomen, without any further therapeutic intervention. This included evaluation after completion of her combined modality therapy by a pancreatic cancer surgeon, who did not recommend surgical exploration because of persistent major arterial encasement. Eighteen months later, she has shown no evidence of either locoregional progression or metastatic disease (Figures 1B and 1C) and remains asymptomatic, with a CA19-9 measurement of 7 U/mL.

Discussion

This case report presents a patient with locally advanced PDAC who showed durable disease control 18 months after completion of sequential therapy with FOLFIRINOX-based chemotherapy followed by consolidative chemoradiation. Approximately one-third of patients diagnosed with PDAC present with locally advanced disease,[1] which is defined based on the primary pancreatic tumor's encroachment/encasement of nearby vessels to an extent that renders it unresectable despite the absence of evidence of metastatic disease. Consensus criteria for tumor unresectability, by NCCN and other expert groups, include greater than 180° encasement of the superior mesenteric artery (SMA) or celiac axis; abutment of the celiac axis; invasion or encasement of the aorta; or occlusion of the superior mesenteric vein (SMV) or portal vein (PV) without possibility of reconstruction, as assessed by multiphasic CT scanning.[2,3] Staging evaluation for locally advanced disease may also include diagnostic laparoscopy, because the finding of occult peritoneal metastases would inform decisions regarding the use of locoregional treatment modalities (ie, radiation and/or surgery). A separate, increasingly recognized category that may overlap substantially with locally advanced PDAC is borderline resectable disease, in which a lesser degree of SMA abutment or SMV/PV involvement may still allow for successful R0 resection, especially after a period of preoperative chemotherapy and/or radiation.[2–4]

Despite the frequency with which this stage of disease is encountered at diagnosis, there currently remains no uniformly accepted standard treatment. Although these patients have often been lumped together with those with metastatic disease in chemotherapy clinical trials, differences in biology and clinical outcomes between these subsets of patients suggest that the groups should be approached separately,[5] with consideration of a multimodality strategy that incorporates systemic and localized treatment specifically for patients with locally advanced disease. However, the respective roles and sequence of chemotherapy and radiation have yet to be clearly defined in this patient population.[6]

Most previous studies in locally advanced pancreatic cancer have evaluated whether any benefit is derived from delivery of upfront chemoradiation. Two cooperative group studies published in the 1980s produced discordant results, with one trial suggesting a survival benefit with initial chemoradiation (Gastrointestinal Tumor Study Group) and the other (ECOG) indicating no such benefit, compared with chemotherapy alone.[7,8] Results from 2 additional contemporary studies in the gemcitabine era have added further uncertainty to the role of upfront chemoradiation. One study conducted by a French cooperative group (FFCD-SFRO) actually indicated a detrimental effect of sequential chemoradiation followed by chemotherapy, compared with gemcitabine-based chemotherapy alone (8.6 vs 13.0 months; stratified log-rank P=.031).[9] However, it is important to note that this study used a chemoradiation approach (cisplatin and 5-FU concurrent with radiotherapy) that may have been too toxic for many patients, preventing or delaying them from being able to receive further gemcitabine-based chemotherapy after completion of chemoradiation. A separate trial conducted by ECOG (E4201) did find a significant survival advantage using a similar strategy of initial chemoradiation (this one with low-dose weekly gemcitabine as a radiosensitizer) followed by continued gemcitabine, compared with gemcitabine alone (11.0 vs 9.2 months in favor of the combined modality approach; stratified log-rank P=.034).[10]

Currently, there is increasing interest in the delivery of chemoradiation later, rather than initially, in the treatment course of a patient with locally advanced PDAC, as discussed in the present case study. The University of California San Francisco favors a strategy of delivering chemotherapy initially for a defined period upfront, generally 3 to 6 months, because it provides optimal and timely systemic therapy to control or eradicate occult micrometastatic disease, while limiting the later use of radiation to that subgroup of patients whose tumors are well-controlled during this initial period of systemic therapy. In so doing, a subset of individuals (13%–39% in selected series[11–17]) are spared the toxicities associated with radiation if they are found to have metastatic dissemination during induction chemotherapy. A qualitative systematic review published in 2009 noted that, although the superiority of chemoradiation to chemotherapy alone remains unproven, this paradigm of induction chemotherapy followed by chemoradiation is a promising strategy.[18] One of the earlier studies to suggest a potential benefit of using delayed chemoradiation consisted of a

retrospective analysis conducted by the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR). In this analysis, study investigators showed that patients who received consolidative 5-FU–based chemoradiation after at least 3 months of initial gemcitabine-based chemotherapy had a median survival of 15.0 months, compared with 11.7 months for patients who were continued on chemotherapy alone (P=.0009).[11] Smaller single-arm phase II studies have also shown promising survival results with this sequential approach of upfront chemotherapy (primarily gemcitabine-based) followed by chemoradiation,[12–15] especially those who ultimately receive both modalities (Table 1). The SCALOP trial, reported in early 2013, was a randomized phase II study in which patients with locally advanced disease received induction chemotherapy with gemcitabine/capecitabine followed by chemoradiation with either capecitabine or gemcitabine as a radiosensitizer.[16] Median overall survival was significantly superior in the capecitabine-chemoradiation arm (15.2 months).

More recently, a phase III European study conducted by GERCOR (LAP-07) evaluated induction gemcitabine with or without erlotinib, followed by either consolidative chemoradiation or continuation of systemic therapy, for patients with locally advanced disease. Results of this 442-patient study were reported at the 2013 ASCO Annual Meeting.[18] Provocatively, patients with stable disease or better who were randomized to receive chemoradiation did not fare better than those randomized to continue with chemotherapy alone (median survival, 15.2 vs 16.4 months, respectively; P = not significant). This study raises an important question regarding whether radiation should routinely, if ever, be offered to patients with locally advanced PDAC, although data regarding quality of life and patterns of locoregional versus distant disease progression in each arm are yet not available.

The choice of systemic therapy in patients with locally advanced PDAC has generally been similar to that for metastatic PDAC, with the decision regarding which regimen to use based on several factors, including patient performance status, laboratory parameters, and preexisting comorbid medical conditions. It is important to recognize that certain newer chemotherapies, such as the FOLFIRINOX regimen (which the present patient received), have only been formally evaluated in prospective phase III clinical trials in the metastatic setting,[19] whereas the experience using these regimens for locally advanced disease is significantly more limited.[20,21] The NCCN Clinical Practice Guidelines in Oncology for Pancreatic Adenocarcinoma, however, do not make a distinction in choice of chemotherapy between patients with metastatic versus locally advanced disease (to view the most recent version of these guidelines, visit NCCN.org).[2] Similar selection principles apply in both settings; that is, FOLFIRINOX should be reserved solely for patients with good to excellent performance status (ECOG 0–1). Currently, given the magnitude of benefit observed with FOLFIRINOX compared with gemcitabine in terms of response rate and overall and progression-free survivals for patients with metastatic disease, it seems reasonable to extrapolate these data to the locally advanced setting, although further prospective validation is certainly required for this patient population, ideally in the context of randomized phase II/III studies.

Table 1 Prospective Studies In Locally Advanced Pancreatic Ductal Adenocarcinoma Evaluating Induction Chemotherapy Followed by Chemoradiation

	Sample Size (n)	Induction Chemotherapy Regimen	Median Survival (mo)
Ko et al[12]	25	Gemcitabine, cisplatin	13.5
Moureau-Zabotto et al[13]	59	Gemcitabine, oxaliplatin	12.2
Crane et al[14]	69	Gemcitabine, oxaliplatin, cetuximab	19.2
Kim et al[15]	37	Gemcitabine, cisplatin	16.8
Mukherjee et al (SCALOP)[16]	114	Gemcitabine, capecitabine	12.7
Hammel et al (LAP-07)[17]	442	Gemcitabine +/– erlotinib	15.2[a]

[a]Includes only patients with controlled disease after induction chemotherapy who were randomized to receive chemoradiation.

Recently reported data from the phase III MPACT trial,[22] in which the combination of gemcitabine and nab-paclitaxel also showed improvements in overall survival when compared with single-agent gemcitabine in patients with metastatic PDAC, likewise should prompt further investigation specific to the locally advanced setting. The question remains whether the availability of more-effective systemic regimens such as these mitigates or enhances the relative value of radiation in this patient population; notably, the lack of benefit of chemoradiation observed in the LAP-07 trial was in the context of less-effectual chemotherapy (gemcitabine +/– erlotinib). For example, whether the patient in the present case benefited specifically from the sequential application of both chemotherapy and radiation or would have achieved similar long-term disease control had she been treated with FOLFIRINOX alone is unclear.

Ongoing and planned multicenter studies will attempt to answer some of these questions regarding whether newer combination chemotherapy regimens and radiation techniques will result in better outcomes for patients with locally advanced PDAC. The RTOG 1201 trial, for example, will investigate induction chemotherapy using a more contemporary regimen, followed by intensity-modulated versus conventional radiotherapy versus continued chemotherapy alone, in this setting. This trial is also interesting because patients will be stratified according to intratumoral expression of SMAD4, a protein involved in transforming growth factor β signaling whose presence or absence may correlate with patterns of disease progression (ie, locoregional vs metastatic) in pancreatic cancer, serving as a potentially useful biomarker to assess which patients are the most suitable candidates for radiation therapy.[14,23] Multiple studies have also explored the role of stereotactic body radiotherapy with and without chemotherapy in locally advanced PDAC,[24,25] although this approach should ideally be evaluated in a prospective randomized study design compared with conventionally fractionated radiation. Although any and all of these approaches allow for the possibility of later surgical exploration with intent of R0 resection, a greater emphasis is being placed on developing separate trials of novel neoadjuvant therapies for patients with borderline resectable, as opposed to truly unresectable, tumors.

For now, the optimal treatment approach for patients with locally advanced PDAC must be considered on a case-by-case basis, ideally in the context of a multidisciplinary planning conference. Even though these patients, by definition, have inoperable disease, it is encouraging that some, like the patient in this case study, may have durable disease control after combined modality therapy, with an associated life expectancy measurable in multiple years.

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Posttest Questions

1. True or False: A patient without metastatic disease, but whose pancreatic tumor encases the celiac artery, would be defined as having locally advanced unresectable disease.
2. Based on reported studies evaluating induction chemotherapy followed by chemoradiation for locally advanced PDAC, approximately what proportion of patients are no longer suitable candidates for radiation after induction chemotherapy (due primarily to the development of metastatic disease)?
   a. 5%–10%
   b. 15%–40%
   c. 50%–55%
   d. 65%–70%
3. True or False: LAP-07, the largest randomized trial in locally advanced PDAC to evaluate systemic therapy with or without consolidative chemoradiation, showed that consolidative chemoradiation improves survival in this patient population.