NCCN Guidelines® Insights

Pancreatic Adenocarcinoma, Version 2.2014

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Pancreatic Adenocarcinoma discuss the diagnosis and management of adenocarcinomas of the exocrine pancreas and are intended to assist with clinical decision-making. These NCCN Guidelines Insights summarize major discussion points from the 2014 NCCN Pancreatic Adenocarcinoma Panel meeting. The panel discussion focused mainly on the management of borderline resectable and locally advanced disease. In particular, the panel discussed the definition of borderline resectable disease, role of neoadjuvant therapy in borderline disease, role of chemoradiation in locally advanced disease, and potential role of newer, more active chemotherapy regimens in both settings. (*J Natl Compr Canc Netw* 2014;12:1083–1093)

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Learning Objectives:

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

- Integrate into professional practice the updates to NCCN Guidelines for Pancreatic Adenocarcinoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Pancreatic Adenocarcinoma

Disclosure of Relevant Financial Relationships

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CRITERIA DEFINING RESECTABILITY STATUS

Tumors considered localized and clearly resectable should demonstrate the following:
- **No distant metastases**
- **No radiographic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion.**
- **Clear fat planes around the celiac axis, hepatic artery, and SMA.**

Tumors considered borderline resectable[1] include the following:
- **No distant metastases**
- **Venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement.**
- **Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.**
- **Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall.**

Adapted from: Callery MP, Chang KJ, Fishman EK, et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol 2009;16:1727-1733.

Tumors considered to be unresectable demonstrate the following:
- **HEAD**
  - **Distant metastases**
  - **Greater than 180 degrees SMA encasement, any celiac abutment**
  - **Unreconstructible SMV/portal occlusion**
  - **Aortic or inferior vena cava (IVC) invasion or encasement**
- **BODY**
  - **Distant metastases**
  - **SMA or celiac encasement greater than 180 degrees**
  - **Unreconstructible SMV/portal occlusion**
  - **Aortic invasion**
- **TAIL**
  - **Distant metastases**
  - **SMA or celiac encasement greater than 180 degrees**
- **Nodal status**
  - **Metastases to lymph nodes beyond the field of resection should be considered unresectable.**

[1]The panel endorses the use of a more restrictive definition of borderline resectable tumors in clinical trials. (Katz M, Marsh R, Herman J, et al. Borderline resectable pancreatic cancer: Need for standardization and methods for optimal clinical trial design. Ann Surg Oncol. 2013 Aug; 20(8):2787-95.)

PANC-B

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

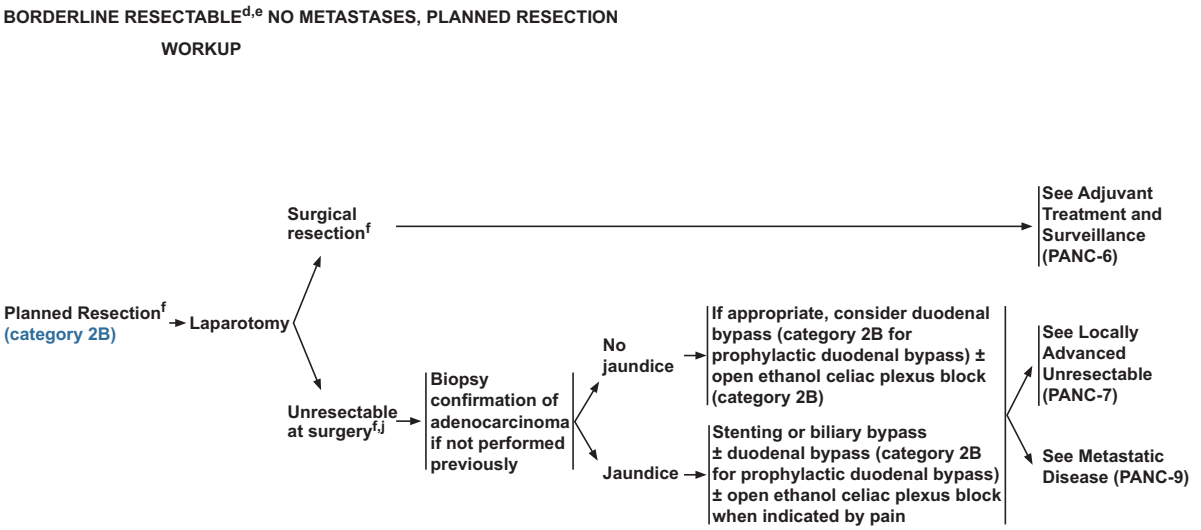
All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

During 2014, an estimated 46,420 people will be diagnosed with pancreatic cancer in the United States and approximately 39,590 will die of the disease.[1] It is the fourth most common cause of cancer-related death among men in the United States (after lung, prostate, and colorectal cancers) and women (after lung, breast, and colorectal cancers).[1] Furthermore, the incidence of pancreatic cancer in the United States has been increasing, possibly because of the increasing prevalence of obesity, an aging population, and other unknown factors.[2–4] Mortality rates have remained largely unchanged.[5,6]

As an overall guiding principle of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma, the panel believes that decisions about diagnostic management and resectability of pancreatic cancer should involve multidisciplinary consultation at high-volume centers with reference to appropriate imaging



[d]See Principles of Diagnosis and Staging (PANC-A).
[e]See Criteria Defining Resectability Status (PANC-B).
[f]See Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).
[j]See Principles of Palliation and Supportive Care (PANC-E).

PANC-5

studies to evaluate the extent of disease. In addition, the panel believes that increasing participation in clinical trials (currently only 4.6% of patients enroll on a pancreatic cancer trial[7]) is critical to making progress in this disease.

Management of Borderline Resectable Disease

Although it is clear that patients with visceral, peritoneal, or pleural metastases or with metastases to nodes beyond the field of resection derive no benefit from resection, institutions differ in their approaches to patients with locoregional disease involvement. Locoregional disease is divided into resectable, borderline resectable, and unresectable (locally advanced). The standard approach to therapy in patients with resectable disease has been postoperative treatment, with median survivals of 20.1 to 23.6 months under the most optimal clinical trial conditions.[8–11] However, it is becoming increasingly apparent that patients with borderline resectable disease, who are at higher risk for R1 resections, are potentially in need of a different management approach.

Definition of Borderline Resectable Disease

Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus group developed criteria in 2009 to define tumor resectability to improve patient selection for surgery and increase the likelihood of an R0 resection.[12] The NCCN Pancreatic Adenocarcinoma Panel has supported and adapted these criteria over the past several years. The absence of evidence of peritoneal or hepatic metastases after a thorough radiologic assessment is a criterion for both resectable and borderline resectable disease. The panel further defines patients with resectable disease as those who have clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA) and no radiologic evidence of superior mesenteric vein (SMV) or portal vein (PV) distortion. However, according to the 2013 NCCN criteria, radiologic findings

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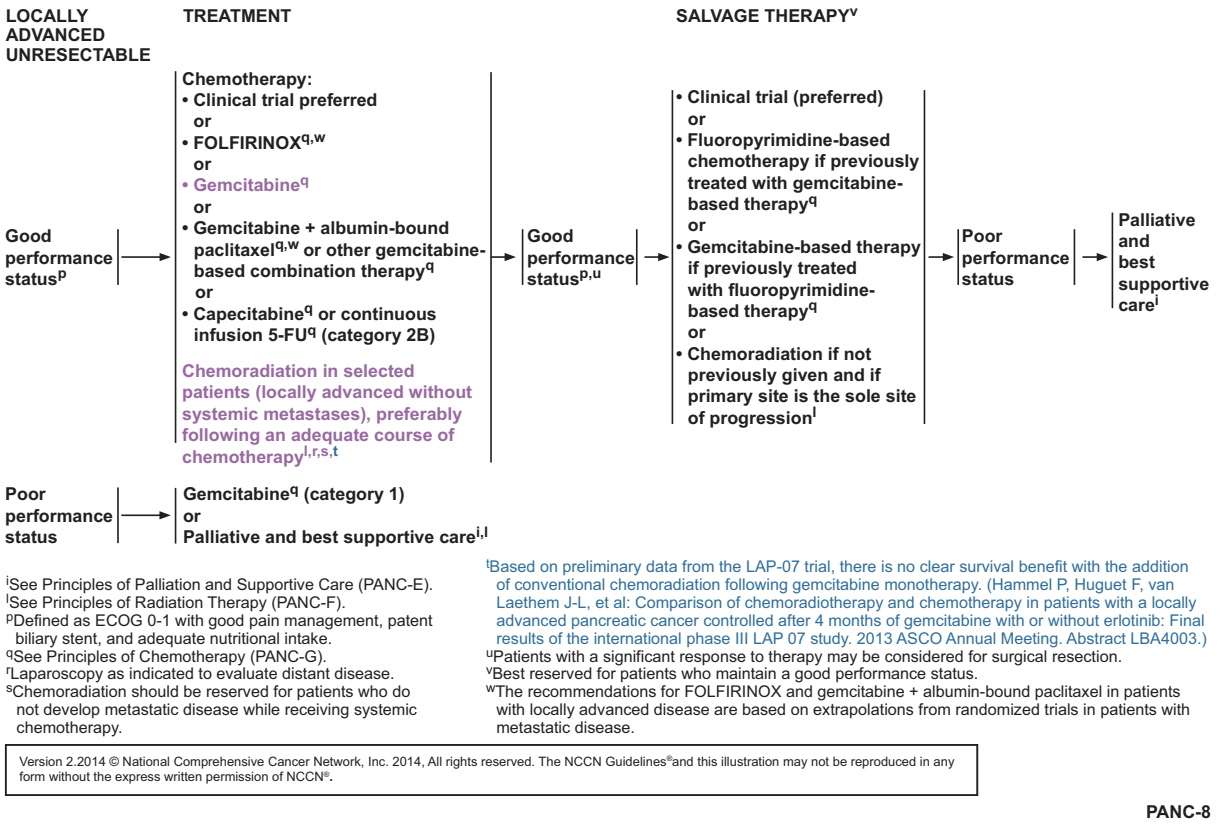

[i]See Principles of Palliation and Supportive Care (PANC-E).
[l]See Principles of Radiation Therapy (PANC-F).
[p]Defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.
[q]See Principles of Chemotherapy (PANC-G).
[r]Laparoscopy as indicated to evaluate distant disease.
[s]Chemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy.
[t]Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. (Hammel P, Huguet F, van Laethem J-L, et al: Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.)
[u]Patients with a significant response to therapy may be considered for surgical resection.
[v]Best reserved for patients who maintain a good performance status.
[w]The recommendations for FOLFIRINOX and gemcitabine + albumin-bound paclitaxel in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.

PANC-8

of venous involvement of the SMV or PV with distortion or narrowing of the vein, or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement, have characterized a tumor as borderline resectable. As for arterial involvement, radiologic findings of encasement of a short segment of the hepatic artery, without evidence of tumor extension to the celiac axis and/or tumor abutment of the SMA involving 180° or less of the artery circumference, classifies a tumor as borderline resectable according to the 2013 NCCN definition.

Other groups have also put forth definitions of resectability of pancreatic cancer,[13,14] and a more restrictive definition of borderline resectable pancreatic tumors was recently described by the Alliance for Clinical Trials in Oncology group.[15] Their definition uses degrees of contact (eg, interface between tumor and SMA measuring <180° of vessel wall circumference) rather than subjective terms such as *abutment*, *encasement*, and *distortion*.

During the 2014 NCCN Pancreatic Adenocarcinoma Panel meeting, an involved discussion took place regarding the definition of borderline resectable disease and its subsequent management. The panel discussed adopting the more restrictive criteria for borderline resectable disease put forth by the Alliance trial group.[15] More patients would be considered to have resectable disease based on the Alliance criteria versus the 2013 NCCN definition, and would thus not be offered neoadjuvant treatment (except select patients with poor prognostic features). The panel agreed that upfront resection would be inappropriate for patients with borderline resectable disease based on the Alliance definition, if adopted, because these patients are highly unlikely to have an R0 resection.

The panel agreed that this more standardized definition of borderline resectable disease would allow the collection of uniform data across institutions. However, some panelists argued against adoption of the more restrictive Alliance definition. Pan-

elists feared that many patients would now be defined as resectable by these criteria and, especially in the community setting, be found to be unresectable at surgery or have margin-positive resections. One panelist gave the example of fairly severe unilateral vein impingement of a little less than 180°, which would be classified as resectable by Alliance definition but would be unlikely to give an R0 resection even at a high-volume center.

The panel agreed that no perfect definition of borderline resectable disease is currently possible because of insufficient data. For now, the overall panel consensus was to keep a more liberal definition of borderline resectable disease for general practice (see PANC-B, purple text; page 1085), leaving the option of upfront resection for these patients in cases where the multidisciplinary team thinks an R0 resection can likely be achieved (category 2B; also see "Role of Neoadjuvant Therapy in Borderline Resectable Disease," next section). However, the panel realizes the need for uniformity in the definition of borderline resectable disease, particularly in the context of clinical trials. Therefore, the panel added a footnote stating that they endorse the use of a more restrictive definition of borderline resectable tumors in clinical trials (see PANC-B, blue text; page 1085).

Role of Neoadjuvant Therapy in Borderline Resectable Disease

The use of neoadjuvant therapy in the setting of borderline resectable disease has been a highly debated topic. Although no high-level evidence supports its use, many NCCN Member Institutions have been using an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease. In fact, for the 2013 version of the guidelines, the panel upgraded their recommendation for the use of neoadjuvant therapy in patients with borderline resectable disease from a category 2B to a category 2A, meaning that the majority of the panel believed that the neoadjuvant approach was acceptable in this population. Thus in 2013, both approaches had category 2A designations. The panel discussed the use of upfront resection versus a neoadjuvant approach again for the 2014 guideline update.

Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well tolerated.[16–21] In a phase I/II trial of neoadjuvant therapy in borderline resectable disease, 4 of 26 patients (15%) were able to undergo resection.[20] A randomized phase II trial comparing 2 different neoadjuvant regimens in borderline resectable disease was terminated early because of poor accrual, but 5 of 21 patients (24%) underwent resection.[19] A recent multi-institutional phase II trial found that full-dose gemcitabine, oxaliplatin, and radiation given preoperatively to patients with resectable (n=23), borderline resectable (n=39), or unresectable disease (n=6) found the approach to be feasible, with an overall R0 resection rate of 53%.[18] In this study, 63% of all evaluable patients underwent resection, with an R0 resection achieved in 84% of those patients.

In 2 retrospective reviews, 31% to 35% of patients with borderline resectable disease who completed neoadjuvant therapy had R0 resections.[22,23] A systematic review and meta-analysis of 19 cohort studies found that patients with unresectable disease (including both borderline and unresectable cases) undergoing neoadjuvant chemoradiation therapy had similar 1-year survival outcomes as those whose disease was initially deemed resectable.[24] In this study, 40% of treated patients ultimately underwent resection.

Overall, the panel believes that patients with pancreatic cancer should be selected for upfront surgery based on the likelihood of obtaining negative resection margins. Patients at high risk for positive surgical margins are not considered to be good candidates for an upfront resection because of the lack of clinical benefit of margin-positive resection. One panelist argued that upfront surgery in borderline resectable disease results in a high incidence of positive margins, which are clearly associated with poor outcomes, and that upfront resection therefore cannot be recommended for these patients. The use of neoadjuvant therapy in this population could potentially increase the chance for R0 resections.

It was clear during panel discussion that the decision between the 2 approaches depends heavily on the definition of borderline resectable disease (see "Definition of Borderline Resectable Disease," page 1086). With the Alliance definition, surgery for borderline resectable disease would be highly unlikely to result in negative margins, and the panel agreed that upfront resection would be inappropriate if that definition had been adopted. Based on the more liberal NCCN definition, some panelists believe that upfront resection can be considered when the multidisciplinary team believes an R0 resection might be

achieved with vascular resection and reconstruction. Most panelists, however, believe that a neoadjuvant approach in these patients is the better option. The results of a panel vote thus downgraded the recommendation for upfront resection in borderline cases from a category 2A to a category 2B in the 2014 version of these guidelines (see PANC-5, blue text; page 1086). Clearly, the use of neoadjuvant therapy in borderline resectable disease represents an area in flux.

It is important to note that no randomized phase III trials have compared the approach of neoadjuvant therapy in borderline resectable disease versus surgery without initial therapy, and that the best regimens in the borderline neoadjuvant setting are unknown. Several phase II clinical trials are currently underway to determine the R0 resection rate after neoadjuvant chemotherapy in patients with borderline resectable or unresectable locally advanced disease (eg, ClinicalTrials.gov identifier: NCT00557492). In addition, the Alliance A021101 trial (ClinicalTrials.gov identifier: NCT01821612) is a single-arm pilot study evaluating the safety and efficacy of FOLFIRINOX before capecitabine-based chemoradiation and surgery in this population.[15] Initial results in patient series suggest that neoadjuvant regimens including FOLFIRINOX are a promising approach in patients with borderline resectable disease (see "Role of Highly Active Chemotherapy in Borderline Resectable and Locally Advanced Disease Settings," page 1090).[25,26] Additional randomized trials are needed.

Role of Chemoradiation in Locally Advanced Disease

Chemoradiation is a conventional option for the management of unresectable locoregional pancreatic cancer, although the utility of chemoradiation in this population is controversial.[27] It has mainly been used in selected patients who do not develop metastatic disease during initial chemotherapy, and occasionally before chemotherapy. The panel discussed the recently presented preliminary data from the LAP 07 trial[28] and the implications of those results on the recommendation for chemoradiation following chemotherapy in patients with locally advanced disease.

Chemoradiation Following Chemotherapy in Locally Advanced Disease

Starting with 2 to 6 cycles of systemic chemotherapy followed by chemoradiation therapy has been a recommended option for select patients with unresectable disease and good performance status who have not developed metastatic disease.[29–31] This sequence has been especially recommended when (1) it is highly unlikely that the patient will become resectable (ie, complete encasement of superior mesenteric/celiac arteries); (2) suspicious metastases are present; or (3) the patient may not be able to tolerate chemoradiation. Using an initial course of chemotherapy may facilitate systemic disease control while simultaneously helping to determine whether the disease is rapidly progressive. For example, a retrospective analysis of outcomes from the GERCOR studies indicated that first-line treatment with chemotherapy may be a useful strategy for selecting patients with locally advanced disease who are more likely to benefit from subsequent chemoradiation therapy.[29]

However, preliminary data from the international phase III LAP 07 trial showed no clear survival benefit (the primary outcome measure) with the addition of conventional chemoradiation following gemcitabine monotherapy.[28] In this study, 269 patients with disease control after induction chemotherapy were randomized to additional chemotherapy or to chemoradiation with capecitabine. Median overall survival was 16.5 months in the chemotherapy arm versus 15.3 months in the chemoradiation arm (hazard ratio [HR], 1.03; 95% CI, 0.79–1.34; P=.83)

Panelists pointed out that patients in LAP 07 received gemcitabine as induction therapy and that more active chemotherapy regimens preceding chemoradiation may allow for more benefit from chemoradiation. In addition, the panel noted that this sequence of therapy may have other benefits besides survival (eg, improved quality of life, decreased pain, decreased local progression). The panel thus decided to maintain their recommendation regarding the use of chemoradiation in patients with locally advanced pancreatic cancer following a course of more active chemotherapy if no metastatic disease develops during initial treatment. In addition, they added a footnote explaining that the LAP 07 trial did not show a survival benefit (see PANC-8, blue text; page 1087). Additional studies are clearly needed.

Upfront Chemoradiation in Locally Advanced Disease

Results from LAP 07 called into question the utility of chemoradiation following induction chemotherapy (see previous section on "Chemoradiation Following Chemotherapy in Locally Advanced Dis-

ease").[28] The panel thus reevaluated the data on up-front chemoradiation in this setting.

Results of 2 early randomized trials comparing up-front chemoradiation to chemotherapy in locally advanced disease provided contradictory results.[32,33] Three phase II trials also assessed the up-front chemoradiation approach in locally advanced pancreatic adenocarcinoma, with median survival rates ranging from 8.2 to 9.0 months.[34–37] Results from small, single-arm trials of up-front chemotherapy followed by chemoradiation in locally advanced disease have been discussed.[38]

The more recent phase III randomized ECOG-4201 trial, which assessed gemcitabine compared with gemcitabine plus radiotherapy followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer, was closed early because of poor accrual. However, an intention-to-treat analysis of data for the 74 patients enrolled in this study showed that median overall survival was significantly longer in the chemoradiation arm (11.1 vs 9.2 months; P=.017).[39] However, the poor accrual rate decreased the statistical power of the findings, no difference was seen in progression-free survival, and the confidence intervals for overall survival overlapped between the groups of patients, leading some to state that the results do not rise to the level of evidence required to determine standard of care.[40]

The benefit of chemotherapy versus up-front chemoradiation was also addressed in the phase III FFCD-SFRO study from France, in which patients with locally advanced pancreatic cancer were randomly assigned to receive either gemcitabine alone or an intensive induction regimen of chemoradiation with 5-FU plus cisplatin followed by gemcitabine maintenance treatment.[41] In this study, gemcitabine alone was associated with a significantly increased overall survival rate at 1 year compared with chemoradiation (53% vs 32%; HR, 0.54; 95% CI, 0.31–0.96; P=.006). This study was stopped before the planned accrual, because an interim analysis revealed that patients in the chemoradiation arm had a lower survival rate. Also, patients in the chemoradiation arm experienced severe toxicity and were more likely to receive a shorter course of maintenance therapy with gemcitabine, suggesting that the observed differences in survival were most likely attributable to the extreme toxicity of this particular chemoradiation regimen.

Thus, the panel agreed that the role of up-front chemoradiation in the setting of locally advanced pancreatic cancer is still undefined, and they do not currently recommend it for standard treatment. The panel pointed out that if patients present with poorly controlled pain, bleeding, or local obstructive symptoms, it may be preferable to start with up-front chemoradiation therapy.[34,42]

Role of Highly Active Chemotherapy in Borderline Resectable and Locally Advanced Settings

Historically, most studies in the locally advanced setting used gemcitabine monotherapy. However, the field is placing an increasing emphasis on understanding the role of modern, more active regimens, such as FOLFIRINOX and gemcitabine/albumin-bound paclitaxel, in locoregional unresectable disease. The potential role of more active chemotherapy in this setting is to improve local and distant disease control. Rarely, locally advanced disease may become resectable, but the long-term outlook for these patients is uncertain. A potential role also exists for more active chemotherapy in the borderline resectable setting, with the goal of increasing R0 resection rates and preventing systemic disease.

Some studies and case reports have addressed the use of chemotherapy with or without chemoradiation to convert selected patients with locally unresectable disease to a resectable status or increase R0 resection rates in borderline cases.[25,26,43–51] Patients with a significant response to chemotherapy and/or chemoradiation may be considered for surgical resection. After resection, these patients have similar survival rates as those whose disease was initially determined to be resectable.[52] Importantly, results from 2 retrospective studies suggest that radiographic response does not correlate with pathologic response.[53,54] Therefore, if no apparent tumor shrinkage is observed after neoadjuvant treatment and no extrapancreatic progressive disease is evident, surgery should still be attempted.

Some groups have reported results from patient series that suggest that neoadjuvant regimens, including FOLFIRINOX, are a promising approach to treating patients with borderline resectable pancreatic cancer.[25,26] In one series, 12 of 18 patients (67%) who had FOLFIRINOX followed by gemcitabine- or

capecitabine-based chemoradiation underwent pancreatectomy.[25] All 12 had margin-negative resections and 7 (58%) were alive at a median time from diagnosis of 22 months (range, 18–35 months), including 5 with no evidence of disease.

The experience with FOLFIRINOX in 22 patients with locally advanced pancreatic cancer at the Massachusetts General Hospital Cancer Center through February 2012 was recently reported.[45] An overall response rate of 27% was observed, and the median progression-free survival was 11.7 months. Five patients (23%) were able to undergo R0 resections, although 3 of these patients experienced distant recurrence by 5 months. It was also reported that 32% of patients receiving FOLFIRINOX required 1 or more hospitalization or visit to the emergency department during treatment.

The panel thus discussed removing gemcitabine monotherapy as an option for patients with locally advanced disease and good performance status. Many panelists stated that they would not give gemcitabine monotherapy to these patients so that they would not miss the rare chance to have their disease converted to resectable status. However, other panelists pointed out that some patients may not be interested in or good candidates for more intensive regimens even if they had good performance status (ie, elderly, psychosocial considerations). In addition, some panelists believe that, when conversion to resectability is highly unlikely, giving gemcitabine up-front and leaving the option for more intensive therapy later is appropriate. Others countered that they are seeing some patients with surprisingly good responses that might not have been predicted in advance, and who are subsequently having R0 resections.

An important question that was raised during the discussion was whether borderline resectable disease and locally advanced disease are surrogates for more aggressive disease. The panel questioned whether the use of intensive regimens in these populations puts patients through increased toxicity for little gain. Overall, because of the lack of strong data on FOLFIRINOX and gemcitabine/albumin-bound paclitaxel in locally advanced disease, the panel agreed it is appropriate to leave gemcitabine monotherapy as an option in this setting (see PANC-8, purple text; page 1087). Studies are desperately needed in both the locally advanced setting and the neoadjuvant/borderline resectable setting to determine optimal treatment strategies.

Conclusions

The optimal management of borderline resectable and locally advanced pancreatic adenocarcinoma remains to be determined. The field is in great need of high-quality studies in these settings. In the meantime, the panel bases recommendations on available data and consensus of expert opinion. This year the panel discussed:

- The definition of borderline resectable disease, and decided not to adopt a more restrictive definition for fear that more patients, whose disease would then be classified as resectable, would be found to have unresectable disease at surgery or have margin-positive resections.
- The role of neoadjuvant therapy in borderline disease, and voted to downgrade the recommendation for up-front surgery in this population to category 2B. Most of the panel now believes that neoadjuvant therapy is the better approach in this population to potentially increase the rate of margin-negative resections.
- The role of chemoradiation in locally advanced disease, and decided to maintain their recommendation for the possible use of chemoradiation in patients with locally advanced pancreatic cancer following a course of chemotherapy if no disease progression occurs during initial treatment. The panel pointed out, however, that results from LAP 07 did not show a survival benefit for chemoradiation following gemcitabine monotherapy.
- The potential role of newer, more active chemotherapy regimens in both the locally advanced and borderline resectable settings, and decided against changing their recommendations of allowing gemcitabine monotherapy at this time. The panel is hopeful that more active regimens will increase margin-negative resection rates and prevent or delay metastatic disease in these populations, but strong data are still lacking. Thus, less intensive regimens are still listed as appropriate options in patients with locally advanced disease and good performance status.

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Posttest Questions

1. True or False: Most of the NCCN Pancreatic Adenocarcinoma Panel now believes that neoadjuvant therapy to potentially increase the rate of margin-negative resections is a better approach than up-front resection in patients with borderline resectable disease.
2. True or False: Results from the LAP 07 trial showed a survival benefit to chemoradiation following gemcitabine monotherapy in patients with locally advanced pancreatic cancer.
3. Which of the following are listed as appropriate treatment options for patients with locally advanced disease and good performance status in the NCCN Guidelines for Pancreatic Adenocarcinoma?
   a. FOLFIRINOX
   b. Gemcitabine/albumin-bound paclitaxel
   c. Gemcitabine monotherapy
   d. Chemotherapy followed by chemoradiation in patients who do not develop metastases
   e. All of the above