Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

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Introduction

• Pancreatic ductal adenocarcinoma is a disease associated with poor prognosis and an increasing impact on cancer-related mortality in the United States and worldwide.

• When patients present with pancreatic cancer, fewer than 10% have tumors that are potentially curable with resection and about one-third have metastatic disease. The rest (over half of all patients with pancreatic cancer) have disease that is considered locally advanced and unresectable (LAPC) due to local invasion of adjacent structures.

• The definition of locally advanced, unresectable pancreatic cancer implies that there is no evidence of metastatic disease. Although the definition of unresectability may vary somewhat, it is generally accepted that unresectability is determined by the presence and extent of local vascular involvement.

• The focus of this clinical practice guideline is to help with clinical decision making, including determining the appropriate treatment for people with locally advanced, unresectable pancreatic cancer and how to help patients and their families to access and use palliative care services.

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ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

• a systematic literature review by ASCO guidelines staff
• an expert panel provides critical review and evidence interpretation to inform guideline recommendations
• final guideline approval by ASCO CPGC

The full ASCO Guideline methodology supplement can be found at:

www.asco.org/guidelines/LAPC
Clinical Questions

1. After a histopathologic confirmation of pancreatic adenocarcinoma diagnosis, what initial assessment is recommended before initiating therapy for locally advanced, unresectable pancreatic cancer?

2. What is the appropriate initial treatment approach for people diagnosed with LAPC?

3. Which patients with locally advanced, unresectable pancreatic cancer may be offered radiation therapy [chemoradiotherapy (CRT)/ stereotactic body radiation therapy (SBRT)]?

4. Which people with locally advanced, unresectable pancreatic cancer may be initially offered radiation therapy?

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Clinical Questions

5. Which people with locally advanced, unresectable pancreatic cancer whose disease has progressed (abdominal pain, worsening jaundice, increase in size of tumor and/or new metastatic lesions on imaging study; persistently rising serum CA 19-9) should be offered additional treatment per the ASCO Metastatic Pancreatic Cancer Guideline?

6. When should the concept of palliative care be introduced? When should a palliative care consult be initiated?

7. For people with locally advanced, unresectable pancreatic cancer, what are the recommended strategies for relief of pain and symptom burden?

8. What is the recommended frequency of follow up care/surveillance for people with locally advanced, unresectable pancreatic cancer?
Target Population
People diagnosed with locally advanced, unresectable pancreatic cancer.

Target Audience
Medical oncologists, radiation oncologists, surgeons, gastroenterologists, and other caregivers
Summary of Recommendations

CLINICAL QUESTION 1
After a histopathologic confirmation of pancreatic adenocarcinoma diagnosis, what initial assessment is recommended before initiating therapy for locally advanced, unresectable pancreatic cancer?

Recommendation 1.1
A multiphase CT scan of the chest, abdomen and pelvis should be performed to assess extent of disease. Other staging studies should be performed only as dictated by symptoms. (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

Recommendation 1.2
The baseline performance status, symptom burden, and comorbidity profile of a patient diagnosed with locally advanced, unresectable pancreatic cancer should be carefully evaluated. (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)
Summary of Recommendations

**Recommendation 1.3**
The goals of care (including a discussion of an advance directive), patient preferences, as well as support systems should be discussed with every person diagnosed with locally advanced, unresectable pancreatic cancer and his/her caregivers. (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

**Recommendation 1.4**
Multidisciplinary collaboration to formulate treatment and care plans and disease management for patients with locally advanced, unresectable pancreatic cancer should be the standard of care. (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

**Recommendation 1.5**
Every person with pancreatic cancer should be offered information about clinical trials - therapeutic trials in all lines of treatment, as well as palliative care, biorepository/biomarker, and observational studies. (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)
CLINICAL QUESTION 2
What is the appropriate initial treatment approach for people diagnosed with LAPC?

Recommendation 2.1
Initial systemic therapy with combination regimens is recommended for most patients who meet the following criteria:

1) ECOG PS 0-1
2) A favorable comorbidity profile
3) Patient preference and a support system for aggressive medical therapy

There is no clear evidence to support one regimen over another and physicians may offer therapy based on extrapolation from data derived from studies in the metastatic setting. For some patients, CRT or SBRT may be offered upfront, based on patient and physician preference. (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)
Summary of Recommendations

CLINICAL QUESTION 3
Which patients with locally advanced, unresectable pancreatic cancer may be offered radiation therapy (CRT/SBRT)?

Recommendation 3.1
If there is local disease progression following induction chemotherapy, but without evidence of systemic spread, then chemoradiotherapy may be offered to patients who meet the following criteria:

1) First line chemotherapy treatment is completed or terminated
2) Performance status of ECOG≤2
3) A comorbidity profile that is adequate, including adequate hepatic and renal function and hematological status
4) Patient preference

(Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)
Recommendation 3.2
Chemoradiotherapy may be offered to patients who have responded to an initial 6 months of chemotherapy or have stable disease, or have developed unacceptable chemotherapy-related toxicities or show a decline in performance status, as a consequence of chemotherapy toxicity. (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

Recommendation 3.3
If there is response or stable disease after 6 months of induction chemotherapy, chemoradiotherapy may be offered as an alternative to continuing chemotherapy alone for any patient with locally advanced, unresectable pancreatic cancer. (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)
Summary of Recommendations

CLINICAL QUESTION 4
Which people with locally advanced, unresectable pancreatic cancer may be initially offered SBRT?

Recommendation 4.1
Clinicians may offer SBRT for treatment of patients with LAPC, although the evidence quality is intermediate so additional prospective and/or randomized trials are required to definitively compare results of SBRT with chemotherapy alone and SBRT. (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

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Summary of Recommendations

CLINICAL QUESTION 5
Which people with locally advanced, unresectable pancreatic cancer whose disease has progressed (abdominal pain, worsening jaundice, increase in size of tumor and/or new metastatic lesions on imaging study; persistently rising serum CA 19-9) should be offered additional treatment per the ASCO Metastatic Pancreatic Cancer Guideline?

Recommendation 5.1
All people who have not benefited from first line treatment and have disease progression should be offered treatment per the ASCO Metastatic Pancreatic Cancer Treatment Guideline (www.asco.org/guidelines/MetPC) (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 5.2
Refer people with locally advanced, unresectable pancreatic cancer who have not benefited from treatment and have disease progression for a clinical trial. (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)
Summary of Recommendations

CLINICAL QUESTION 6
When should the concept of palliative care be introduced? When should a palliative care consult be initiated?

Recommendation 6.1
People with locally advanced, unresectable pancreatic cancer should have a full assessment of symptom burden, psychological status, and social supports, as early as possible - preferably at the first visit. In most cases, this will indicate a need for a formal palliative care consult and services. (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong)
Summary of Recommendations

CLINICAL QUESTION 7
For people with locally advanced, unresectable pancreatic cancer, what are the recommended strategies for relief of pain and symptom burden?

Recommendation 7.1
People with LAPC should be offered aggressive treatment for the pain and other symptoms of the cancer and/or cancer-directed therapy. (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong)

Recommendation 7.2
A short course of palliative radiotherapy (conventional RT or SBRT) may be offered for patient with locally advanced, unresectable pancreatic cancer who meet the following criteria:
1) Prominent local symptoms such as abdominal pain, and/or worsening jaundice, and/or gastrointestinal bleeding
2) Local infiltration into the gastro-intestinal tract causing impending gastric outlet or duodenal obstruction
3) Patient preference
(Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)
CLINICAL QUESTION 8
What is the recommended frequency of follow up care/surveillance for people with locally advanced, unresectable pancreatic cancer?

Recommendation 8.1
In the absence of RCT evidence, the Panel consensus is that patients with LAPC who have completed treatment and have stable disease or no disease progression, schedule follow-up visits every 2-3 months that include a physical exam and liver and renal function laboratory testing for a two year duration. The intervals can then be increased to every 6 months. (Type: Informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong)

Recommendation 8.2
Data is not definitive, but the Panel recommends testing markers (CA 19-9) and imaging (CT) should be performed at least every 3 months during the first two years. Imaging intervals can be increased to every 6 months once stability is comfortably established. The routine use of PET/CT imaging for the management of LAPC is not recommended. Tumor markers such as CA 19-9 should not replace imaging as an assessment. (Type: Informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong)
Patient and Clinician Communication

- People with LAPC are faced with making difficult treatment decisions while being presented with complex medical information and a life-threatening diagnosis.

- Clear communication with people with LAPC and their caregivers about the diagnosis, treatment options and goals of care is key for patient understanding. The clinician is also responsible for offering ancillary support services, including considering referral to a palliative care consult and services.

- In order for patients to make informed decisions, providers should describe the potential impact of the diagnosis of pancreatic cancer on the people diagnosed with the disease and their families. It is important to provide realistic hope within honest, yet supportive discussions.

- Clinicians should clearly explain all potential treatment options, the potential outcomes of each, and possible adverse events/side effects so patients can understand benefits and drawbacks of each and make an informed decision. Treatment discussions should include relevant clinical trials at every stage of treatment.

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Patient and Clinician Communication

• In particular in patients with LAPC, people with pancreatic cancer need to understand the reasons they are not eligible for surgery.

• It is also helpful to ensure patients at this stage know that their disease is not metastatic, but that if it doesn’t respond to treatment it will likely progress to metastatic disease.

• Clinicians should also consider and proactively discuss quality of life issues. In people with LAPC, dietary concerns, pain and fatigue are major concerns.

• Referral to a registered dietitian and/or gastroenterologist with early intervention can be of great benefit. Clinicians should also consider use of and discuss the possible need for pancreatic enzyme replacement therapy.

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Patient and Clinician Communication

• Referral to palliative care services can facilitate addressing many of the non-treatment-related issues patients face and should be considered for all people with pancreatic cancer, regardless of stage of disease or expected prognosis.

• Patients should understand that referral to consult and palliative care services are not synonymous with a referral to hospice care.

• Clinicians should address the costs of care and offer resources to specialists within the healthcare system who can discuss in detail what a patient should expect and for resources and information about managing the costs related to cancer care.

• Providing realistic hope to people diagnosed with LAPC, while the prognosis may be very short, is very important. Even if cure isn’t possible, hope for an extension of life, or good quality of life, is incredibly powerful.

• Providing patients with resources to help them communicate better with their healthcare team is also advisable.
Health Disparities

- Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many people have limited access to medical care.

- People with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.

- Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.
Multiple Chronic Conditions

• Creating evidence-based recommendations to inform treatment of people with additional chronic conditions, a situation in which the patient may have two or more such conditions—often referred to as multiple chronic conditions (MCCs)—is challenging.

• In LAPC, obese patients have a worse prognosis than their normal-BMI counterparts. Additionally, Medicare patients over 75 years of age had statistically significant shorter median survival times than clinical trial patients with advanced pancreatic cancer treated with gemcitabine.

• In consideration of recommended care for patients with LAPC, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

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Cost Implications

• There are limited cost-effectiveness analyses regarding the various treatment modalities employed in the multidisciplinary management of LAPC.

• However, the available data appear to support the recommendations outlined in this guideline.
Limitation of the Research & Future Directions

• There are many research initiatives aimed at improving the diagnosis and treatment for pancreatic cancer. Groups are collaborating to find treatments, improve screening and diagnosis with biomarkers of pancreatic cancer (which could help physicians diagnose the disease earlier) and provide better treatments to people with pancreatic cancer.

• Overall, the future of precision medicine for LAPC relies on the outcomes of clinical trials. Determining the most valuable predictive markers will ultimately result in targeted treatments soon after diagnosis instead of relying on disease progression to dictate therapies.

• SBRT is an emerging modality that many centers are using in borderline resectable PCA and LAPC. Additional prospective studies are needed to determine the true efficacy of this modality.
Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/guidelines/LAPC

Patient information is available at www.cancer.net and www.pancan.org
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