

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

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Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/guidelines/LAPC and www.asco.org/guidelines/MetPC and www.asco.org/guidelineswiki.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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ABSTRACT

Purpose

To provide evidence-based recommendations to oncologists and others for treatment of patients with locally advanced, unresectable pancreatic cancer.

Methods

American Society of Clinical Oncology convened an Expert Panel of medical oncology, radiation oncology, surgical oncology, gastroenterology, palliative care, and advocacy experts and conducted a systematic review of the literature from January 2002 to June 2015. Outcomes included overall survival, disease-free survival, progression-free survival, and adverse events.

Results

Twenty-six randomized controlled trials met the systematic review criteria.

Recommendations

A multiphase computed tomography scan of the chest, abdomen, and pelvis should be performed. Baseline performance status and comorbidity profile should be evaluated. The goals of care, patient preferences, psychological status, support systems, and symptoms should guide decisions for treatments. A palliative care referral should occur at first visit. Initial systemic chemotherapy (6 months) with a combination regimen is recommended for most patients (for some patients radiation therapy may be offered up front) with Eastern Cooperative Oncology Group performance status 0 or 1 and a favorable comorbidity profile. There is no clear evidence to support one regimen over another. The gemcitabine-based combinations and treatments recommended in the metastatic setting (eg, fluorouracil, leucovorin, irinotecan, and oxaliplatin and gemcitabine plus nanoparticle albumin-bound paclitaxel) have not been evaluated in randomized controlled trials involving locally advanced, unresectable pancreatic cancer. If there is local disease progression after induction chemotherapy, without metastasis, then radiation therapy or stereotactic body radiotherapy may be offered also with an Eastern Cooperative Oncology Group performance status ≤ 2 and an adequate comorbidity profile. If there is stable disease after 6 months of induction chemotherapy but unacceptable toxicities, radiation therapy may be offered as an alternative. Patients with disease progression should be offered treatment per the ASCO Metastatic Pancreatic Cancer Treatment Guideline. Follow-up visits every 3 to 4 months are recommended. Additional information is available at www.asco.org/guidelines/LAPC and www.asco.org/guidelines/MetPC and www.asco.org/guidelineswiki.

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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. There were an estimated 49,000 new diagnoses and 41,000 deaths from pancreatic cancer in the United States in 2015¹ and an estimated 338,000 deaths worldwide in 2012.² This disease is an unfortunate exception to

the general trend of improvement in cancer-related mortality. Indeed, one estimate suggests that pancreatic cancer will become the second leading cause of cancer-related death in the United States in the next decade.³ The 5-year overall survival (OS) rate remains $< 5\%$, for locally advanced, unresectable disease.

When patients present with pancreatic cancer, fewer than 10% have tumors that are potentially curable with resection, and approximately one third have metastatic disease. The rest (more than half of

THE BOTTOM LINE

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

What is the treatment of patients with locally advanced, unresectable pancreatic cancer (LAPC)?

Target Population

Patients diagnosed with LAPC.

Target Audience

Medical oncologists, radiation oncologists, surgeons, gastroenterologists, and other caregivers

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Key Recommendations

Recommendation 1.1: A multiphase computed tomography 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 LAPC should be carefully evaluated (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.3: The goals of care (including a discussion of an advance directive), patient preferences, and support systems should be discussed with every person diagnosed with LAPC and his or 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 LAPC 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).

Recommendation 2.1: Initial systemic therapy with combination regimens is recommended for most patients who meet the following criteria: Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, a favorable comorbidity profile, and 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 on the basis of extrapolation from data derived from studies in the metastatic setting. For some patients, chemoradiotherapy (CRT) or stereotactic body radiation therapy (SBRT) may be offered up front, on the basis of patient and physician preference (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.1: If there is local disease progression after induction chemotherapy, but without evidence of systemic spread, then CRT or SBRT may be offered to patients who meet the following criteria: First-line chemotherapy treatment is completed or terminated because of progression or toxicity; ECOG PS ≤ 2 ; a comorbidity profile that is adequate, including adequate hepatic and renal function and hematologic status; and patient preference (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.2: CRT or SBRT may be offered to patients who have responded to an initial 6 months of chemotherapy or have stable disease but 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, CRT or SBRT may be offered as an alternative to continuing chemotherapy alone for any patient with LAPC (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

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

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; summary table of recommendations in Data Supplement 7.) (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 5.2: Refer people with LAPC 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).

Recommendation 6.1: People with LAPC 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: intermediate; Strength of recommendation: strong).

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

Recommendation 7.2: A short course of palliative radiotherapy (five to 10 treatments) may be offered to for patients with LAPC who meet the following criteria: prominent local symptoms, such as abdominal pain and/or worsening jaundice and/or GI bleeding as a result of tumor invasion; local infiltration into the GI tract causing impending gastric outlet or duodenal obstruction; and patient preference (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 8.1: In the absence of randomized controlled trial evidence, the Panel recommends that people who have completed treatment and have stable disease or no disease progression schedule follow-up visits every 3 to 4 months that include a physical examination and liver and renal function laboratory testing for a 2-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 are not definitive, but the Panel recommends testing markers (cancer antigen 19-9) and imaging (computed tomography) should be performed at least every 3 to 4 months during the first 2 years. Imaging intervals can be increased to every 6 months once stability is comfortably established. The routine use of positron emission tomography imaging for the management of LAPC is not recommended. Tumor markers such as cancer antigen 19-9 should not replace imaging as an assessment (Type: Informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/guidelines/LAPC, www.asco.org/guidelines/MetPC, and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

all patients with pancreatic cancer) have disease that is considered locally advanced and unresectable pancreatic cancer (LAPC) because of local invasion of adjacent structures. This group of patients can be challenging to treat, because they generally have problems related to their local tumor burden before developing metastatic disease. The definition of LAPC 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.

Unlike potentially curable (resectable) pancreatic cancer, where preoperative treatments can potentially improve margin-negative resectability, patients with LAPC rarely undergo resection with curative intent.⁴ Local control and quality of life (QOL) are the important issues in LAPC. Local symptoms are often difficult to manage and contribute to poor QOL. The advent of effective systemic therapy to control disease progression and the recognition that some patients (with certain molecular phenotypes, eg, SMAD-4 intact) are more likely to have local-dominant progression rather

than metastatic spread have heightened interest in developing modalities for more effective local control.⁵⁻⁸

Furthermore, people with LAPC are more likely to have significant symptom burdens referable to their primary malignancy, including pain, pancreatic insufficiency, biliary obstruction, and early satiety/gastric outlet obstruction. Although most people with unresectable LAPC are unlikely to be cured, the natural history and treatment approaches toward LAPC differ from those of metastatic disease because patients lack systemic dissemination.

Therefore, it is important to establish that the goals of treatment of patients with LAPC are controlling disease progression, symptoms, and the maintenance of QOL. In select cases, patients may be considered for surgical resection. However, this should be considered only at high-volume centers with experience with vessel reconstruction. It is unclear, however, if surgical resection improves survival in patients with LAPC. The oncologist should discuss the competing impact of disease progression and treatment toxicity on survival and QOL, including performance status (PS), and address the patient and caregiver's preferences of people being treated with LAPC. A frank discussion about the fact that approximately 30% to 50% of patients presenting with LAPC have evidence of metastatic disease within 3 months is important.^{9,10} Palliative care and/or a referral to a palliative care specialist should be involved, where feasible, at the very beginning of treatment. The focus of this clinical practice guideline is to help with clinical decision making, including determining the appropriate treatment of people with LAPC and how to help patients and their families to access and use palliative care services.

GUIDELINE QUESTIONS

This clinical practice guideline addresses eight overarching clinical questions: (1) After a histopathologic confirmation of pancreatic adenocarcinoma diagnosis, what initial assessment is recommended before initiating therapy for LAPC? (2) What is the appropriate initial treatment approach for people diagnosed with LAPC? (3) Which patients with LAPC may be offered radiation therapy (chemoradiotherapy [CRT]/stereotactic body radiation therapy [SBRT])? (4) Which people with LAPC may be initially offered radiation therapy? (5) Which people with LAPC whose disease has progressed (abdominal pain, worsening jaundice, increase in size of tumor and/or new metastatic lesions on imaging study; persistently increasing serum cancer antigen [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 LAPC, 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 LAPC?

METHODS

Guideline Development Process

The Expert Panel met via webinar and teleconference and corresponded through e-mail. On the basis of the consideration of the evidence, the authors contributed to the development of the guideline, provide critical review, and finalized the guideline recommendations. Members of the Expert

Panel are responsible for reviewing and approving the penultimate version of the guideline, which is then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee before publication (Appendix Table A1, online only).

The recommendations were developed by the multidisciplinary Expert Panel using a systematic review of articles (April 2002 to June 2015) of phase III randomized controlled trials (RCTs). Other peer-reviewed articles were used to inform the recommendations on palliative care and patient and clinical communication as well as the section on health disparities. Articles were selected for inclusion in the systematic review of the evidence on the basis of the following criteria: patients with LAPC, phase III RCTs of chemotherapy alone and/or with CRT and/or compared with a control arm, in English, and with human subjects.

Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; or published in a non-English language. The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.¹¹ In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided. In some selected cases where evidence is lacking, but there was a high level of agreement among the Panel members, informal consensus is used (noted with the Recommendations).

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement at www.asco.org/guidelines/LAPC, including an overview (eg, Panel composition, development process, and revisions), literature search terms and a data extraction quorum diagram, the recommendation development process (GLIDES and BRIDGE-Wiz), and information about quality assessment.

The ASCO Expert Panel Co-Chairs and guidelines staff will work to keep abreast of any newly published data that signal an update to this guideline. On the basis of formal review of the emerging literature, ASCO staff will determine the need to update and will post on the www.asco.org/guidelines when this guideline is being updated. The Methodology Supplement (available at www.asco.org/guidelines/LAPC) also provides information about the Signals update approach.

This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki to submit new evidence.

Guideline Disclaimer

The clinical practice guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Policy Implementation for Clinical Practice Guidelines (“Policy”; found at <http://www.asco.org/rwc>). All members of the Panel completed ASCO’s disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speakers’ bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

There were 26 RCTs that met eligibility criteria and form the evidentiary basis for some of the guideline recommendations.^{9,12-36} The trials were generally of high quality, but few compared similar interventions. Although some articles addressed treatment of LAPC, the majority studied patients with LAPC and patients with metastatic disease together. Some recommendations are based on informal consensus by the Panel, because there was no RCT evidence.

The primary outcome assessed for all included trials was therapeutic efficacy, including OS and/or adverse events. Data Supplement 1 Table 1 lists the patient and disease characteristics of the studies that were pertinent to the development of the recommendations. For most studies, the sample size was generally small (< 250 patients), but all were balanced for age and Eastern Cooperative Oncology Group performance status (ECOG PS). It is important to note that in all included trials, median age was younger (at least > 5 years younger and for most, 10 years younger) than the median age of patients who are diagnosed with pancreatic cancer in the general community. Previous treatments, if known, are also listed in the table. Of note, more men than women participated in trials for pancreatic cancer.

Study Quality Assessment

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed and are shown in Data Supplement 1 Table 2. The study quality was high for this group of RCTs. Design aspects related to the individual study quality were assessed with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so on generally indicating a low potential risk of bias for most of the identified evidence. Follow-up times varied between studies, decreasing the comparability of the results. Refer to the Methodology Data Supplement for more extensive definitions of

ratings of evidence quality, strength of recommendations, and overall potential risk of bias.

Key Outcomes of Interest

Results for all outcomes of interest include response rate(s), OS, progression-free survival, disease-free survival, and adverse events. Outcomes are included in the Data Supplement. The studies compared outcomes chemotherapy versus observation, chemotherapy versus CRT, and combination chemotherapy with or without radiotherapy for people with LAPC.

Systematic Reviews and Meta-Analyses for LAPC

Fourteen systematic reviews or meta-analyses of various rigor and quality were obtained. As none were deemed suitable as the basis for recommendations, a formal assessment of quality was not performed. A summary table can be found in the Data Supplement.

The Data Supplement includes the literature review search terms, a quorum diagram of included and excluded articles, information on the WHO definition of palliative care, a pancreatic protocol computerized tomography (CT), and lists the summary of recommendations from the Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline.

RECOMMENDATIONS

Clinical Question 1: After a Histopathologic Confirmation of Pancreatic Adenocarcinoma Diagnosis, What Initial Assessment Is Recommended Before Initiating Therapy for LAPC?

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 PS, symptom burden, and comorbidity profile of a patient diagnosed with LAPC should be carefully evaluated (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

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 LAPC and his or 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 LAPC 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).

Literature review and analysis. Cross-sectional imaging with a CT scan of the abdomen and pelvis using a pancreatic protocol (Data Supplement 6) should be performed to evaluate the extent of disease of all patients with LAPC. In one center's retrospective experience, 56% of people with pancreatic cancer who were reimaged with a pancreatic protocol (Data Supplement 6) had a change in their treatment and stage.³⁷

Magnetic resonance imaging seems to be equivalently sensitive as a CT scan with respect to its ability to detect and stage pancreatic cancer, but CT is preferred because it is more easily interpreted and is less operator dependent. In one center's retrospective experience, 56% of people with pancreatic cancer who were reimaged with a pancreatic protocol (Data Supplement 6) had a change in their treatment and stage.³⁷

Similarly, acquisition and interpretation of endoscopic ultrasound images is operator dependent, and so the use of endoscopic ultrasound is most often used to facilitate acquisition of an additional biopsy specimen but not as a primary staging modality. A CT scan of the chest should be performed to assure that there are no intrathoracic metastases. Although the Panel has refrained from the use of anatomic stage designations for the purposes of these guidelines, an understanding of the radiographic interface between the primary tumor and the superior mesenteric vein/portal vein, common hepatic artery, celiac trunk, and superior mesenteric artery is important when establishing unresectability. A fuller definition and discussion of resectability can be found in the ASCO guideline "Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline" at www.asco.org/guidelines/pcpc.

Among patients with LAPC, baseline PS and comorbidity profile should be carefully evaluated, because these both have major implications with regard to a person's ability to tolerate therapy. PS has been consistently identified as a prognostic factor for people with pancreatic cancer. Measurement of constructs such as frailty, PS, and so on is important by a variety of means, and such measurements may be used to predict chemotherapy toxicity.³⁸ PS can determine the treatment approach (ie, single- or multiple-agent chemotherapy regimens or CRT). Patients with PS 0 to 1 (or equivalent) can be offered single or multiagent therapy, whereas most patients with PS 2 should be offered primarily single-agent chemotherapy. Similarly, the comorbidity profile can influence choice of chemotherapy agent; for example, avoid fluoropyrimidine-based regimens in patients with a known history of uncontrolled coronary artery disease. But, PS and comorbidities alone should not be used simply to rule in or out patients for treatment. For example, someone with controlled diabetes mellitus or low hemoglobin could still benefit from treatment.

Treatment decisions for patients with LAPC should be established within the context of a coordinated multidisciplinary group. Recent trials, with a variety of treatment techniques, emphasize that improved survival is conferred with multidisciplinary management of the cancer.³⁹ Care at high-volume pancreatic cancer treatment centers may lead to a change in therapeutic recommendations in approximately 25% of patients.⁴⁰

Furthermore, enrollment onto pancreatic cancer clinical trials should be encouraged, because current accrual to such trials is suboptimal. Improvement in enrollment to clinical trials will

accelerate progress toward improving survival. Particular attention should be paid to more closely matching supply of clinical trials to demand of patients with pancreatic cancer. Few patients age 75 years and older with PS that is less than fit and with comorbidities are included in trials for pancreatic cancer. Barriers to enrollment include clinical trial design (trial exclusions for those with comorbidities), need for travel, prohibitive illness, and lack of physician encouragement.

Clinical interpretation. The focus of the initial workup is to determine both the extent of disease and the ability of the patient to tolerate available therapies. The goals of therapy should be clearly evaluated and discussed with the patient and caregivers, particularly in the context of which treatment is likely to be best tolerated and QOL. There may be an immediate need for palliative treatment (eg, for pain). Risks and benefits must be clearly considered and discussed openly with a patient with LAPC and his or her caregivers.

Management decisions for patients with LAPC must be made in a multidisciplinary team environment. Improvement in enrollment to clinical trials will accelerate progress toward improving survival of people with LAPC in the population. The available therapies may then be understood on the basis of the perceived goals of care.

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: ECOG PS 0 or 1, a favorable comorbidity profile, and 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 on the basis of extrapolation from data derived from studies in the metastatic setting. For some patients, CRT or SBRT may be offered up front, on the basis of patient and physician preference (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and analysis. Nearly half of patients with pancreatic cancer present with LAPC and have a poor prognosis. In the past, most chemotherapy regimens have failed to significantly improve OS. There are few compelling data on which is the best chemotherapy option, with or without radiation, for patients with LAPC. Therefore, enrollment in a well-designed clinical trial, whenever possible, is always warranted.

The Panel would like to highlight that the recommendations for treatment regimens for LAPC are based, in part, on evidence from RCT data in the metastatic setting as well as RCT data in the LAPC setting. It is recognized that treatment decisions are ultimately influenced by integral clinical elements, such as patient preferences, PS, and physician experience.

Recently reported chemotherapy regimens have produced improvements in OS for people with LAPC and metastatic pancreatic cancer.^{9,10,14,16,17,20,24} It should be noted that one meta-analysis that included multiple treatment regimens demonstrated that gemcitabine-based combination therapy in LAPC has provided a survival benefit over best supportive care and single-agent gemcitabine therapy.⁴¹ This particular meta-analysis included an examination of several gemcitabine-based combinations but

preceded the advent of the newer regimens that are most commonly used in the metastatic setting.^{28,34}

Newer regimens (eg, fluorouracil, leucovorin, irinotecan and oxaliplatin⁴² and gemcitabine plus nanoparticle albumin-bound paclitaxel¹⁶) have not been evaluated in RCTs involving LAPC, but these combination regimens are being used by many clinicians and so may be recommended for people with LAPC with good performance status (ECOG PS 0 and 1). This was considered by the Panel to be a reasonable approach, extrapolating from RCT outcomes for patients with metastatic pancreatic cancer and outcomes reported in single-arm case series.³⁴ For people with LAPC, regimens with gemcitabine only, or gemcitabine plus capecitabine (GEMCAP) alone or in combination,^{25,41} are perhaps better tolerated and might be considered a better option in patients with a borderline PS or on the basis of patient preference.

There are no RCT data to support duration of initial treatment. In practice, total duration of initial chemotherapy is variable and dependent on patient tolerability and tumor response. Duration may also be influenced as to whether consolidation CRT is planned. On the basis of consensus, the Panel recommends that patients considered for treatment with chemotherapy generally receive therapy for at least 6 months if tolerable, with repeat imaging conducted every 2 to 3 months. The decision regarding benefit from, and timing of, additional CRT is addressed in Clinical Question 3.

The Data Supplement provides details about RCT and treatment regimens and OS, progression-free survival, adverse events, and QOL for people with LAPC.

Clinical interpretation. There is a high likelihood of metastatic progression for patients with LAPC. Continuing chemotherapy, until progression, in responding patients who are tolerating a regimen is reasonable. Chemotherapy holidays can be used in practice to preserve QOL; however, this decision needs to be weighed against concerns regarding rapid disease progression after even a short break. There are no RCT studies that address this issue or help guide this decision.

Clinical Question 3: Which Patients With LAPC May Be Offered Radiation Therapy (CRT/SBRT)?

Recommendation 3.1. If there is local disease progression after induction chemotherapy, but without evidence of systemic spread, then CRT may be offered to patients who meet the following criteria: first-line chemotherapy treatment is completed or terminated; ECOG PS \leq 2; a comorbidity profile that is adequate, including adequate hepatic and renal function and hematologic status; and patient preference (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 3.2. CRT 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 PS 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, CRT may be offered as

an alternative to continuing chemotherapy alone for any patient with LAPC (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and analysis. Fluoropyrimidines and gemcitabine are the commonly agents used concurrently with radiotherapy. A range of gemcitabine doses has been used, but the dose of capecitabine has been more consistent. One meta-analysis (n = 229) included three RCTs and one retrospective study and reported superior outcome for gemcitabine over fluorouracil (12-month survival rate: relative risk, 1.54; $P = .03$), but at expense of higher hematologic toxicity.⁴¹ However, the meta-analysis involved studies where chemoradiation was used up front. The only RCT reporting toxicity and efficacy of gemcitabine (300 mg/m² once per week) versus capecitabine (830 mg/m² twice a day on days of radiotherapy) that was based on chemoradiation after induction chemotherapy demonstrated superior OS in the capecitabine arm (15.2 months ν 13.4 months, $P = .012$) with better QOL scores and less-frequent severe toxicity.⁹ However, this study only involved 114 people (74 of whom received CRT), and OS was not the primary outcome. A similar capecitabine-based regimen was used in the LAP07 study—133 people underwent CRT with a median OS of 15.2 months with low grade 3 or 4 toxicity rate (nausea 5.9%, vomiting 2.9%, diarrhea 4.9%). This OS may be misleading, because 49% of patients were censored after the first randomization; from protocol entry it was approximately 12 months. Two other RCTs involving gemcitabine-based CRT (one against fluorouracil-based CRT,⁴³ one against gemcitabine monotherapy¹⁶) used a higher dose of concomitant gemcitabine (600 mg/m² once per week). Both studies have shown superior survival outcomes for gemcitabine-CRT arms.¹⁶ However, toxicity was considerably higher in the E4201 trial comparing gemcitabine-CRT to single-agent gemcitabine (41% ν 9%). Taken together, these studies suggest that as a radiosensitizer, capecitabine is an extremely well-tolerated regimen with comparable or superior outcomes compared with low-dose gemcitabine.

There is a potential role for maintenance CRT in improving QOL. One recent article reports QOL for selected patients receiving selective chemoradiation for LAPC.¹⁰ After 12 weeks of induction GEMCAP chemotherapy, patients with stable and responding disease were randomized to a further cycle of GEMCAP followed by capecitabine or gemcitabine-based CRT¹⁰ and reported improved QOL, but there was no measurable improvement in OS.

In contrast to conventionally fractionated CRT, there is a growing interest in using induction chemotherapy to exercise systemic control and then using a short course of SBRT, which can be incorporated early during treatment, with minimum disruption to systemic therapy. This could be particularly beneficial to patients with predominant local symptoms. (See Clinical Question 4 and the *Literature review and analysis* section for more information.)

Of note, there is little hope that surgery can lead to R0 resection in people with LAPC (at initial diagnosis) with arterial encasement. But, surgery may be considered in patients with a dramatic response to systemic therapy and chemoradiation or SBRT and with an excellent PS. Resection after radiographic downstaging from T4 to T3 (ie, regression from an encased artery or for tumors abutting arterial structures after chemotherapy and/or chemoradiation) is rare. Although the likelihood of downstaging

these tumors to operability through CRT (with/without induction chemotherapy) is extremely small, CRT or SBRT does affect negative margins if patients undergo surgery, and complete pathologic responses have been reported in 3% to 5% of people.⁴ In borderline resectable disease and in select people with LAPC, a radiographic response from T4 to T3 disease may not be necessary for surgical consideration as long as patients had received maximal chemotherapy (6 months) and chemoradiation or SBRT. In these cases, the combination of chemotherapy and radiation therapy has resulted in a high proportion of patients having margin-negative resections despite having persistent tumor vessel involvement. In a single-institution study from Johns Hopkins, the authors reported on nine patients (21.6%) who underwent surgery; 79% were patients with LAPC and 84% had margin-negative resections. Although encouraging, additional prospective studies are needed to determine long-term outcomes of these patients.⁴⁴

CRT and SBRT can potentially maintain local control with a low incidence of grade 3 to 4 toxicity; therefore, its use in consolidation may allow a period of chemotherapy holiday. However, this remains a decision on the basis of clinician and patient preference, particularly relevant when using combination chemotherapy, which can be associated with significant, and often cumulative, toxicity.

Clinical Question 4: Which People With LAPC 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).

Literature review and analysis. Pancreatic adenocarcinoma is a relatively radioresistant tumor, and conventionally fractionated CRT results in 1-year local control rates of 40% to 60% only. Enthusiasm for delivering higher doses of radiation has been previously limited by concerns for damage to surrounding organs; however, advances in radiotherapy planning and delivery make it possible to deliver high-dose radiotherapy more precisely under image guidance. SBRT involves ablative doses of radiation delivered in one to five fractions over 1 to 2 weeks. In one recent survey of 28 international academic radiation oncologists from the United States, Europe, and Canada, 85.2% of the participants favored SBRT over conventional CRT for patients with pancreatic cancer.⁴⁵ Many phase I and II trials have reported 1-year local control of 75% to 100%.⁴⁶⁻⁵¹ Some of the initial studies using one- to three-fraction regimens reported high-incidence of grade 2 to 4 acute and late GI toxicities, mostly GI ulceration and perforation.^{47,52} More recently, five-fraction regimens (30 to 33 Gy in five fractions) have been shown to be associated with low incidence of GI toxicity, improvement in pancreatic pain, and 1-year local control of 78%.⁴⁹ The optimal sequencing of chemotherapy and SBRT remains unknown; SBRT has been used as up-front treatment^{46,50} or as a sandwich regimen during ongoing chemotherapy.^{47,48,51}

Clinical interpretation. SBRT is being increasingly used and may become much more relevant in the next few years as

randomized trials around SBRT are designed and implemented and more results are published. SBRT will be compared with chemotherapy alone in an upcoming Alliance cooperative group trial in people with borderline resectable disease. Emerging data suggest improved activity of SBRT over conventional CRT. So, while recognizing there are no phase III RCT data, the Panel believes there is enough published evidence for clinicians to consider fractionated SBRT (three to five treatments) as an alternative to CRT. However, given the risk of increased late toxicity, strict dose constraints should be used, and SBRT should be avoided when tumors directly invade the bowel and/or stomach on endoscopic evaluation. In addition, the use of fiducial markers and/or motion management through gating and/or active breathing control should be used to decrease the dose to adjacent organs at risk.

Clinical Question 5: Which People With LAPC Whose Disease Has Progressed (abdominal pain, worsening jaundice, increase in size of tumor and/or new metastatic lesions on imaging study; persistently increasing 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. See the ASCO Metastatic Pancreatic Cancer Clinical Practice Guideline (www.asco.org/guidelines/MetPC) and the summary table of recommendations for metastatic pancreatic cancer in the Data Supplement (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 5.2. Refer people with LAPC 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).

Literature review and analysis. Treatment of people with LAPC whose disease has progressed does not simply mirror that for metastatic disease. It depends on the pattern of progression (locoregional v disseminated) and whether the patient has received prior chemotherapy and/or radiation (with consideration for the sequence of therapy). For example, if a patient with locally advanced disease who has only received chemotherapy in the past develops locoregional progression at a later time, then radiation may be the appropriate modality.

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 LAPC 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).

Literature review and analysis. People with LAPC often tend to have a high symptom burden at the time of diagnosis, although

this varies with the extent of disease. It is recommended that providers conduct a full assessment of symptom burden, including psychological status. Social support should also be ascertained during the first visit. If available, a formal palliative care consult can introduce the patient to the full range of services available to assure that close attention will be paid to physical comfort, pain management, psychosocial concerns, and spiritual well-being throughout the full trajectory of the illness, whether the outcome is curative or palliative. If the patient with LAPC presents with extensive disease, is too ill to tolerate treatment, or has progressive disease for which there is no reasonable further anticancer treatment, then a hospice discussion and possible referral should take place.

Palliative care, in its broadest definition, is the supportive care of a person and family from diagnosis through treatment (either curative or noncurative) until death. Hospice care is a subset of palliative care focused on people near the end of life. Data Supplement 5 contains more information on the definition of palliative care.

Clinical Question 7: For People With LAPC, What Are the Recommended Strategies for Relief of Pain and Symptom Burden?

Recommendation 7.1. People with LAPC should be offered aggressive treatment of 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 to patients with LAPC who meet the following criteria: prominent local symptoms, such as abdominal pain and/or worsening jaundice and/or GI bleeding; local infiltration into the GI tract causing impending gastric outlet or duodenal obstruction; and patient preference (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. People with LAPC may experience additional distressing symptom burdens and concerns that require ongoing supportive care. A referral to a palliative care specialist should be offered at the first visit.

A short course of palliative radiotherapy of 20 to 30 Gy in five fractions or 30 Gy in 10 fractions is an option for control of local symptoms such as pain, bleeding, or jaundice, even in patients with good PS who are being treated with single-modality chemotherapy. (The Panel suggests that 3 to 4 weeks of recovery time should be allowed before restarting chemotherapy.) Radiation therapy can be an option, if indicated, for symptoms refractory to medical management (eg, pain and bleeding).⁵³ It is important to note that palliative radiotherapy may not necessarily prolong OS.

Pain. The mainstay of pain management is typically opiate medication, and physicians must address the level of pain and the degree of pain relief from analgesics at every clinic visit. Because of the proximity of the tumor to the celiac axis, the pain may be neuropathic in nature. This would warrant consideration of treatment of patients with LAPC with adjuvant medications such as gabapentin, pregabalin, nortriptyline, or duloxetine. Also, pain from pancreatic cancer may be amenable to treatment with a neurolytic celiac block to improve pain relief. In one study, 100 patients with unresectable pancreatic cancer experiencing pain were randomly

assigned to receive either neurolytic celiac plexus block or systemic analgesic therapy.⁵⁴ The group treated with the neurolytic block had a larger initial decrease in pain ($P = .005$), and the improvement effect lasted over time. Another RCT was conducted for 109 patients with inoperable abdominal or pelvic cancer, 38 of whom had pancreatic cancer.⁵⁵ The purpose of the trial was to look at the timing of neurolytic sympathectomy, performed either early after the diagnosis of the pain or later in the patient's course after failure to obtain pain relief with strong opioids. Early sympathectomy led to better pain control, less opioid consumption, and better QOL in these patients with cancer.

Anorexia, weight loss. People merit a consultation with a nutritionist and/or dietician if this service is available. Dietary intake can be assessed, along with the possible need for nutritional supplements. Some people experience exocrine pancreatic insufficiency and require pancreatic enzyme replacement. Pancrelipase replacement daily with meals can help improve digestion and absorption of nutrients. A placebo-controlled, double-blind trial of enteric-coated pancreatin microspheres was conducted in patients with unresectable cancer in the pancreatic head. Patients receiving pancreatic enzymes along with dietary counseling gained 1.2% (0.7 kg) body weight, whereas patients receiving placebo lost 3.7% body weight (2.2 kg).^{56,57} Appetite stimulant medications such as megestrol acetate or dronabinol may be considered in severe cases.

Depression and anxiety. The diagnosis of cancer is unsettling to any patient, and the knowledge of the aggressive nature of LAPC may lead to depression or anxiety even early in the course of the disease. All people can benefit from a discussion of their psychosocial concerns and their available support system. Some may warrant treatment with antidepressants or anxiolytics, and others may need referral for ongoing formal support from a social worker or psychiatrist.

Biliary obstruction. A frequent complication of an LAPC tumor is blockage of the biliary tree, causing obstructive jaundice. The preferred treatment is endoscopic placement of a permanent self-expanding metal stent in the bile duct to re-establish drainage to achieve relief of jaundice and pruritus, normalization of bilirubin levels to allow palliative chemotherapy, and prevention of other adverse outcomes such as cholangitis and frequent hospitalizations.⁵⁸ The choice of stent depends on patient prognosis and the relative costs of metal stents and repeat endoscopic retrograde cholangiopancreatographies. In general, metal stents are preferred. Plastic stents can be considered for patients expected to be treated with SBRT or to survive < 3 months.⁵⁹

Gastric outlet obstruction. Gastric outlet/duodenal obstruction occurs in up to 10% of patients with pancreatic cancer. Symptoms include early satiety, nausea, postprandial vomiting, and weight loss. Endoscopic duodenal stenting can be successful in the great majority of these patients, and median duration of stent patency is 6 months.⁵⁹

Ascites. People with LAPC may experience abdominal discomfort, sometimes with ascites (ie, from portal vein thrombosis or if the tumor compresses the portal vein). These patients may benefit from intermittent paracentesis, or, if the ascites reaccumulates quickly, placement of a long-term drainage catheter is suitable.

Venous thromboembolism. The occurrence of deep venous thrombosis, pulmonary embolism, and visceral vein thrombi (such as portal vein or superior mesenteric vein thrombus) is extremely prevalent in patients with pancreatic cancer. Indeed, in most

epidemiologic studies, pancreatic cancer ranks as one of the malignancies with the highest incidence of venous thromboembolism (VTE). This may be driven by the early expression of tissue factor on preneoplastic and neoplastic pancreas.⁶⁰ The development of VTE is highly consequential to people with cancer. It is associated with worsened short- and long-term mortality⁶¹ and is the second leading cause of death in malignancy, after cancer itself.⁶² Unfortunately, people with cancer remain woefully unaware of this complication of cancer and its treatments. As recommended by the ASCO guidelines on VTE, patients need to be educated on the warning signs and symptoms of this illness.⁶³ Primary prevention of VTE can be successfully achieved with the use of low-molecular-weight heparins (LMWHs). Two RCTs have addressed the utility of primary prophylaxis with LMWH in patients with advanced pancreatic cancer, and all have shown substantial reduction of VTE.^{64,65} Concordant with ASCO guidelines on VTE,⁶³ the Panel recommends consideration of primary prophylaxis in select high-risk patients on a case-by-case basis while undergoing systemic therapy. Treatment of pancreatic cancer–associated VTE is best achieved with extended LMWH monotherapy. The utility of treatment of incidentally identified visceral vein thrombi is unclear; decision to anticoagulate or not can be made on a case-by-case basis.

Clinical interpretation. Refer to other ASCO guidelines and other evidence-based guidelines (eg, VTE, peripheral neuropathy, fatigue, anxiety and depression, antiemetics, prophylaxis and management of fever and neutropenia, white blood cell growth factors) for more detailed information in the patient and survivor care and supportive care and treatment-related issues sections at www.asco.org/guidelines.

Clinical Question 8: What Is the Recommended Frequency of Follow-Up Care/Surveillance for People With LAPC?

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 to 3 months that include a physical examination and liver and renal function laboratory testing for a 2-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 are 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 2 years. Imaging intervals can be increased to every 6 months once stability is comfortably established. The routine use of positron emission tomography/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).

Literature review and analysis. There is no RCT literature that addresses the frequency or process of follow-up or surveillance in the setting of LAPC. It is the consensus of the Panel that the frequency of periodic assessment depends on the clinical comfort of the clinician and patient. However, clinical consensus suggests that the usual follow-up or surveillance should occur at a frequency of at least every 3 months for a 2-year duration. These intervals can be increased

once stability is established. Assessments should include a complete history and physical examination, laboratory testing of liver functions along with CA 19-9, and radiographic assessment (chest/abdominal/pelvic CT scans).

PATIENT AND CLINICIAN COMMUNICATION

This section is based on experience and selected literature but was not part of the systemic review of the literature. People with LAPC are faced with making difficult treatment decisions while being presented with complex medical information and a life-threatening diagnosis. Communication, within a context of realistic hope and action, between patients and their clinicians can improve patients' ability to make sound, informed decisions within their own personal value set.⁶⁶ Patients should fully understand goals of care before making decisions about treatment and care.

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.

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. Providers should ask patients about their personal goals and preferences. What do they hope for? What is important to them in their personal lives? What do they value more, extending life or maintaining the best possible QOL? Understanding a patient's specific goals should impact and shape conversations about goals of care and treatment recommendations.

Clinicians should clearly explain all potential treatment options, the potential outcomes of each, and possible adverse events/adverse 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. Patients should have the opportunity to participate in trials for their own treatment as well as being given the opportunity to contribute to research. 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 does not respond to treatment it will likely progress to metastatic disease.

Clinicians should also consider and proactively discuss QOL issues. In people with LAPC, dietary concerns, pain, and fatigue are major concerns. Dietary issues tend to be overlooked and yet are real problems, with significant impact on daily life. 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

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 is not

synonymous with a referral to hospice care. This discussion is important, because palliative care provides important support and can be part of an active cancer treatment paradigm.

It is important for patients to feel comfortable in the choices that they make, and knowing they have explored their options can bring comfort.⁶⁶ As such, clinicians should support a patient's desire to get a second opinion. Clinicians should address the costs of care and offer resources to specialists within the health care 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, although the prognosis may be short, is important. Patients deserve to know that their medical team is working to help them reach their goals. Even if cure is not possible, hope for an extension of life, or good QOL, is incredibly powerful.

Providing patients with resources to help them communicate better with their health care team is also advisable. Offer patients decision-making tools; urge patients to write down questions in between and in advance of appointments. Refer patients to resources that will extend the support and information you are able to provide. For pancreatic cancer, two such resources are the American Society of Clinical Oncology's patient-facing website, cancer.net and the Pancreatic Cancer Action Network at www.pancan.org.

LAPC

- Explain why patient is unlikely to be eligible for surgery.
- Describe the difference between locally advanced and metastatic disease.
- Discuss that locally advanced disease often progresses to metastatic disease.
- Explain all potential treatment options and possible adverse events/effects, including clinical trials, so patient can understand benefits and drawbacks of each and make an informed decision.
- Consider referral to a gastroenterologist.
- Discuss that a referral for a consult and palliative care services does not mean hospice—in conjunction with active treatment
- Urge people to write down questions to ask the clinician on first follow-up visit after diagnosis, before surgery and/or treatment begins.
- Consider offering people and their families a tool to discuss options—a decision aid to be used in conjunction with clinicians. A decision aid may not be appropriate or well received by people with LAPC.
- Support a second opinion; urge people to consider high-volume centers for chemotherapy and radiotherapy for LAPC.
- List resources and support (ie, www.pancan.org, cancer.net, and so forth).

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent experts' 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. Racial and ethnic disparities in health care contribute significantly to this problem in

the United States. People with LAPC 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.⁶⁷ One study evaluated the use and effectiveness of cancer-directed therapy in elderly patients with LAPC.⁶⁸ The SEER database was used to perform a retrospective cohort study in 1,696 patients diagnosed with LAPC. Cancer-directed treatment use rates identified patient and health system factors that were associated with receipt of treatment. In the cohort, 44% of patients received some form of cancer-directed therapy (24% radiation with concurrent chemotherapy, 13% radiation alone, and 7% chemotherapy alone). Older age, lower socioeconomic status, presence of comorbid illness, no care in a teaching hospital, and residence in the western United States were associated with a lower likelihood of receiving treatment ($P \leq .05$). Among those treated, younger age and certain geographic locations were the only predictors of receiving combined-modality therapy. The adjusted hazard ratio for death associated with any treatment in the Cox model was 0.53 ($P < .001$). This supports the effectiveness of cancer-directed treatment in elderly patients with LAPC, but use is low. Receipt of treatment is strongly correlated with non-disease-related factors, especially sociodemographic characteristics, indicating possible disparities in access to care. Other analyses in the SEER data again demonstrated patients with LAPC were less likely to receive treatment of pancreatic cancer if they were older, a member of a racial or ethnic minority, or unmarried.⁶⁹

Many other people lack access to care because of their geographic location and distance from appropriate treatment facilities.⁶⁷ 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. Thus, a significant proportion of patients with LAPC remain undertreated, possibly as a result of nonclinical factors, including insurance status and access to care.

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. Even in clinical trials, which enroll highly selected people, tolerance of and completion of therapy is challenging because of adverse events and toxicities.

In LAPC, obese patients have a worse prognosis than their counterparts with normal body mass index.⁷⁰ Additionally, Medicare patients older than 75 years had statistically significant shorter median survival times than clinical trial patients with advanced pancreatic cancer treated with gemcitabine.⁷¹ In one study, patients with a greater number of comorbid conditions accessed treatment at lower rates.⁶⁸ Comorbidity effects were assessed in a small study using the Charlson Comorbidity Index and Cumulative Illness Rating Scale; only treatment modality, and not Charlson Comorbidity Index score, had a significant impact on survival, suggesting treatments should be based on the possible impact of adverse effects of chemotherapy for this subset of patients.⁷²

People with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude such people to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

Because many people for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlight the importance of shared decision making regarding guideline use and implementation. Therefore, 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.

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for people with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

There are limited cost-effectiveness analyses regarding the various treatment modalities used in the multidisciplinary management of LAPC. However, the available data seem to support the recommendations outlined in this guideline.

One study (LAPC and metastatic pancreatic cancer) found in elderly patients that radiation plus fluorouracil had a cost-effectiveness ratio of \$68,724/quality-adjusted life year (QALY) relative to no treatment and suggested that radiation plus gemcitabine would be cost effective as well.⁷³ Another study (LAPC and metastatic pancreatic cancer) focused on the high cost of radiotherapy with the limited survival of pancreatic cancer. Compared with gemcitabine alone, gemcitabine plus SBRT had an incremental cost-effectiveness ratio (ICER) of \$69,500/QALY, whereas gemcitabine plus conventional radiotherapy versus gemcitabine alone had an ICER of \$126,800/QALY, and gemcitabine plus intensity-modulated radiation therapy versus gemcitabine plus conventional radiotherapy had an ICER of \$1,584,100/QALY. The authors concluded that these results indicated gemcitabine plus IMRT exceeded society's cost-effectiveness standards, and gemcitabine plus SBRT provided a clinical benefit potentially acceptable by cost-effectiveness standards.⁷⁴ Further studies are needed to understand the cost effectiveness of all treatment options for those patients diagnosed with LAPC.

EXTERNAL REVIEW

The draft was submitted to two external reviewers with content expertise. It was rated as high quality, and it was agreed it would be

useful in practice. Review comments were reviewed by the Expert Panel and integrated into the final manuscript before approval by the CPGC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

LIMITATION OF THE RESEARCH AND FUTURE DIRECTIONS

There are many research initiatives aimed at improving the diagnosis and treatment of 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.

Current clinical trials, such as RTOG 1201 (DPC-4–directed therapy) are investigating the role of biomarkers SMAD-4, SPARC, and hENT-1 in pancreas cancer. If these are found to be good predictive markers of tumor progression, there will be a need for sequencing at the time of diagnosis. Presently, it is difficult to obtain accurate molecular profiling with single-pass fine-needle aspirate (FNA) specimens obtained at the time of diagnosis, although immunohistochemistry is possible in some cases. However, cell blocks obtained from multiple-pass FNA and/or core biopsies are the likely resolution to that issue. In one study, cell blocks from multiple-pass FNA specimens from persons with LAPC were successfully sequenced and were able to identify commonly known pancreas cancer driver mutations.⁷⁵ 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. It will be officially tested in a cooperative group setting where persons with borderline resectable pancreatic cancer will be randomly assigned to neoadjuvant chemotherapy alone or chemotherapy alone with SBRT followed by surgery.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all people should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, and slide sets, as well as other clinical tools and resources, are available at www.asco.org/guidelines/LAPC. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Administrative support: Pamela B. Mangu

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Final approval of manuscript: All authors

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Locally Advanced, Unresectable Pancreatic Cancer

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline**

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Appendix

Table A1. Locally Advanced, Unresectable Pancreatic Cancer Guideline Expert Panel Membership

Name (and designation)	Affiliation/Institution
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