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ASCO SPECIAL ARTICLE

Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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Clinical Practice Guideline Committee approved: October 31, 2016

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, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gastrointestinal-cancer-guidelines and www.asco.org/guidelineswiki.

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ABSTRACT

Purpose

To update the Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline published on May 31, 2016. The October 2016 update focuses solely on new evidence that pertains to clinical question 4 of the guideline: What is the appropriate adjuvant regimen for patients with pancreatic cancer who have undergone an R0 or R1 resection of their primary tumor?

Methods

The recently published results of a randomized phase III study prompted an update of this guideline. The high quality of the reported evidence and the potential for its clinical impact prompted the Expert Panel to revise one of the guideline recommendations.

Results

The ESPAC-4 study, a multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy compared gemcitabine and capecitabine with gemcitabine monotherapy in 730 evaluable patients with resected pancreatic ductal adenocarcinoma. Median overall survival was improved in the doublet arm to 28.0 months (95% CI, 23.5 to 31.5 months) versus 25.5 months (95% CI, 22.7 to 27.9 months) for gemcitabine alone (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; $P = .032$). Grade 3 and 4 adverse events were similar in both arms, although higher rates of hand-foot syndrome and diarrhea occurred in patients randomly assigned to the doublet arm.

Recommendations

All patients with resected pancreatic cancer who did not receive preoperative therapy should be offered 6 months of adjuvant chemotherapy in the absence of medical or surgical contraindications. The doublet regimen of gemcitabine and capecitabine is preferred in the absence of concerns for toxicity or tolerance; alternatively, monotherapy with gemcitabine or fluorouracil plus folinic acid can be offered. Adjuvant treatment should be initiated within 8 weeks of surgical resection, assuming complete recovery. The remaining recommendations from the original 2016 ASCO guideline are unchanged.

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INTRODUCTION

ASCO first published evidence-based clinical practice guidelines on potentially curable pancreatic cancer in May 2016.[1] The goal of this February 2017 update is to provide oncologists and other clinicians with current evidence. The complete list of the original and updated recommendations is available in the Bottom Line Box and at www.asco.org/gastrointestinal-cancer-guidelines.

METHODS

Guideline Update Process

ASCO uses a signals[2] approach to facilitate guideline updating. This approach is intended to identify new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on routine literature searching and the expertise of ASCO guideline panel members to identify signals. The methodology supplement available at www.asco.org/gastrointestinal-cancer-guidelines provides additional information about the signals approach.

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Guideline Question

What is the treatment of patients with potentially curable pancreatic cancer?

Target Population

Patients diagnosed with potentially curable pancreatic cancer.

Target Audience

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

Methods

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

Updated Recommendation

Recommendation 4.1: All patients with resected pancreatic cancer who did not receive preoperative therapy should be offered 6 months of adjuvant chemotherapy in the absence of medical or surgical contraindications. The doublet regimen of gemcitabine and capecitabine is preferred in the absence of concerns for toxicity or tolerance; alternatively, monotherapy with gemcitabine or fluorouracil plus folinic acid can be offered. Adjuvant treatment should be initiated within 8 weeks of surgical resection, assuming complete recovery (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

2016 Recommendations

Recommendation 1.1: A multiphase computed tomography scan of the abdomen and pelvis using a pancreatic protocol or magnetic resonance imaging should be performed for all patients to assess the anatomic relationships of the primary tumor and to assess for the presence of intra-abdominal metastases. Endoscopic ultrasonography and/or diagnostic laparoscopy may be used as supplemental studies, and to facilitate acquisition of a biopsy specimen. A chest x-ray may be performed to stage the thorax. Other staging studies should be performed only as dictated by symptom burden. A serum level of CA 19-9 and baseline standard laboratory studies should be assayed (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.2: The baseline performance status, symptom burden, and comorbidity profile of a patient diagnosed with potentially curable pancreatic cancer 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 advance directives), patient preferences, and support systems should be discussed with every patient diagnosed with potentially curable pancreatic cancer 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 potentially curable 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 should be offered information about clinical trials, including 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: Primary surgical resection of the primary tumor and regional lymph nodes is recommended for patients who meet all of the following criteria: no clinical evidence for metastatic disease, performance status and comorbidity profile appropriate for a major abdominal operation, no radiographic interface between primary tumor and mesenteric vasculature on high-definition cross-sectional imaging, and a CA 19-9 level (in absence of jaundice) suggestive of potentially curable disease (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Recommendation 3.1: Preoperative therapy is recommended for patients with pancreatic cancer who meet any of the following criteria: radiographic findings suspicious but not diagnostic for extrapancreatic disease, a performance status or comorbidity profile not currently appropriate (but potentially reversible) for a major abdominal operation, a radiographic interface between primary tumor and mesenteric vasculature on cross-sectional imaging that does not meet appropriate criteria for primary resection or a CA 19-9 level (in absence of jaundice) suggestive of disseminated disease (Type: evidence based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Recommendation 3.2: Preoperative therapy should be offered as an alternative treatment strategy for any patient who meets all criteria in Recommendation 2.1 (Type: evidence based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Recommendation 3.3: If preoperative therapy is administered, a complete restaging evaluation (see Clinical Question 1) is recommended after completion of treatment and before final surgical planning (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Updated Recommendation 4.1: All patients with resected pancreatic cancer who did not receive preoperative therapy should be offered 6 months of adjuvant chemotherapy in the absence of medical or surgical contraindications. The doublet regimen of gemcitabine and capecitabine is a new option; alternatively, monotherapy with gemcitabine alone or fluorouracil plus folinic acid can be offered if there are concerns about toxicity or tolerance. Adjuvant treatment should be initiated within 8 weeks of surgical resection, assuming complete recovery (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.2: Adjuvant chemoradiation may be offered to patients who did not receive preoperative therapy and present after resection with microscopically positive margins (R1) and/or node-positive disease after completion of 4 to 6 months of systemic adjuvant chemotherapy as outlined in Recommendation 4.1. There is clinical equipoise regarding the benefit of adjuvant radiation therapy in this setting pending results of an ongoing international randomized controlled trial (RCT) (Type: Informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.3: For patients with pancreatic cancer who received preoperative therapy, there are no RCT data to guide the administration of postoperative therapy. The panel recommends that a total of 6 months of adjuvant therapy (including preoperative regimen) be offered based on extrapolation from adjuvant therapy trials (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Recommendation 5.1: Patients with potentially curable 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 some instances, this may indicate a need for a formal palliative care consult and services (Type: informal consensus, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 5.2: Patients who have undergone pancreatectomy for potentially curable pancreatic cancer should receive ongoing supportive care for symptom burden that may result from the operation and (preoperative and/or adjuvant) chemotherapy (Type: informal consensus, benefits outweigh harm; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 6.1: In the absence of RCT evidence, the panel recommends that patients who have completed treatment of potentially curable pancreatic cancer and have no evidence of disease be monitored for recovery of treatment-related toxicities and recurrence. Visits may be offered at 3- to 6-month intervals; the role of serial cross-sectional imaging, the extent to which surveillance intervals should be prolonged over time, and the duration of recommended surveillance are all undefined (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

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/gastrointestinal-cancer-guidelines 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.

The Expert Panel used e-mail to consider the new evidence published in the October 2016 update (Appendix Table A1, online only). The revised guideline was circulated in draft form to the Expert Panel and approved. ASCO's Clinical Practice Guidelines Committee leadership reviewed and approved the final document.

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 patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

This is the most recent information as of the publication date. For the most recent information, and to submit new evidence, please visit www.asco.org/guidelines/pcpc and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

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 Expert 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; speaker's 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 Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

The February 2017 Update focuses solely on new evidence that pertain to clinical question 4 of the guideline: What is the appropriate adjuvant regimen for patients with pancreatic cancer who have undergone an R0 or R1 resection of their primary tumor?

Updated Recommendation 4.1

All patients with resected pancreatic cancer who did not receive preoperative therapy should be offered 6 months of adjuvant chemotherapy in the absence of medical or surgical contraindications. The doublet regimen of gemcitabine and capecitabine is preferred in the absence of concerns for toxicity or tolerance; alternatively, monotherapy with gemcitabine or fluorouracil plus folinic acid can be offered. Adjuvant treatment should be initiated within 8 weeks of surgical resection, assuming complete recovery (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Final results from ESPAC-4, a multicenter, international, open-label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine and capecitabine versus monotherapy of gemcitabine in 730 evaluable patients with resected pancreatic ductal adenocarcinoma were recently published.[3] Of note, this population had a high risk for recurrence: 39% of patients had poorly differentiated histology, 60% only had R1 resection (ie, margin positive), and 80% had involved nodes. Median survival was improved in the doublet arm to 28.0 months (95% CI, 23.5 to 31.5 months) versus 25.5 months (95% CI, 22.7 to 27.9) for gemcitabine alone (hazard ratio, 0.82; 95% CI, 0.68 to 0.980; $P = .032$). Grade 3 and 4 adverse events were similar in both arms, although higher rates of hand-foot syndrome and diarrhea occurred in patients randomly assigned to the doublet arm. On the basis of these data, the combination of gemcitabine and capecitabine is a new option for adjuvant therapy in this setting.

Clinical Interpretation

Substantial randomized trial evidence establishes the benefit of adjuvant systemic therapy in this setting. Therefore, the panel recommends that all patients with resected pancreatic cancer who did not receive preoperative therapy be offered 6 months of adjuvant chemotherapy. The doublet regimen of gemcitabine and capecitabine has shown improvement in survival, as demonstrated in a randomized trial with appropriate data and safety monitoring,[3] and is therefore preferred. Monotherapy with gemcitabine or fluorouracil plus folinic acid can be offered if concerns for toxicity or tolerance exist. For patients who receive monotherapy, gemcitabine is favored given evidence of less toxicity.

ADDITIONAL RESOURCES

More information, including Data and Methodology Supplements, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. 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 jco.org.

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Manuscript writing: All authors
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Appendix

Table A1. Resectable and Borderline Resectable Pancreatic Cancer Treatment Guideline Expert Panel Membership

Name (and designation)	Affiliation/Institution
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