Complete Summary

GUIDELINE TITLE

Chemotherapy or radiotherapy for resectable pancreatic adenocarcinoma: clinical practice guidelines.

BIBLIOGRAPHIC SOURCE(S)

Jonker D, Bouttell E, Kamra J, Spithoff K, Gastrointestinal Cancer Disease Site Group. Chemotherapy or radiotherapy for resectable pancreatic adenocarcinoma: clinical practice guidelines. Toronto (ON): Cancer Care Ontario (CCO); 2007 Nov 21. 22 p. (Evidence-based series; no. 2-23). [34 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Resectable pancreatic adenocarcinoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether patients with resectable adenocarcinoma of the exocrine pancreas should receive preoperative or postoperative chemotherapy and/or radiation

TARGET POPULATION

Adult patients with resectable pancreatic adenocarcinoma for whom a pancreatectomy is planned

INTERVENTIONS AND PRACTICES CONSIDERED

1. Preoperative chemotherapy and radiotherapy
2. Postoperative chemotherapy and/or radiotherapy versus surgery alone

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Quality of life
- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

Entries to MEDLINE (1976 to November week 1, 2007), CANCERLIT (1983 to October 2002), and the Cochrane Library (Issue 4, 2007) were searched. "Pancreatic neoplasms" (Medical subject heading [MeSH]) was combined with the

phrases "adjuvant" or "neoadjuvant" used as text words. Those terms were then combined with search terms for the following study designs or publication types: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials (RCTs) and clinical trials. A search of the 1999 through 2007 conference proceedings of the American Society of Clinical Oncology (ASCO) was also conducted. Reference lists of retrieved papers were scanned for additional citations.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were:

1. Phase III RCTs of a preoperative or postoperative treatment arm using chemotherapy (CT) and/or radiotherapy (RT) compared with a control arm of surgery alone in patients with resectable pancreatic adenocarcinoma. Where no phase III RCTs were available, randomized phase II trials were considered. Endpoints of interest were overall survival, median overall survival, adverse effects, and quality of life.
2. Syntheses of evidence in the form of meta-analyses of RCTs and evidence-based practice guidelines.

Published abstracts or presentations of RCTs, including publicly available data from the American Society of Clinical Oncology Web site, were also considered.

Exclusion Criteria

The following were not included in this systematic review:

1. Letters and editorials.
2. Articles in a language other than English.

NUMBER OF SOURCE DOCUMENTS

Seven randomized controlled trials and one trial reported in abstract were identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Where possible, the data were pooled to estimate the overall effect on survival for the following comparisons: chemoradiotherapy (CRT) versus no CRT and chemotherapy (CT) versus no CT. Pooling of survival data was performed at two years because these data were reported in all randomized controlled trials (RCTs) and two-year survival is considered a clinically relevant endpoint for patients with resectable pancreatic cancer. When the actual number of events (deaths) was reported, the reported data were used in the pooled analyses. The study results were pooled using Review Manager 4.2.7 (RevMan Analyses 1.0.2; version date: November 2003; © 2003 the Cochrane Collaboration), which is freely available through the Cochrane Collaboration. Results are expressed as relative risk ratios (RR), where RR <1.0 favours the experimental treatment, RR >1.0 favours control, and RR=1 indicates no difference in risk between groups. The random effects model was used for meta-analysis as it provides the more conservative estimate of effect. Data on toxicity for the adjuvant treatment in the phase III trials were summarized but not pooled.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Clinical trials of postoperative therapy for patients with resectable pancreatic cancer to date have been constrained by methodological limitations that make decisive conclusions difficult to reach. The Gastrointestinal Tumour Study Group (GITSG) study included few patients, and the European Organization for Research and Treatment of Cancer (EORTC) study did not stratify patients by resection margin status and lacked sufficient statistical power to detect a survival difference between groups for patients with pancreatic cancer. The European Study Group for Pancreatic Cancer (ESPAC-1) trial introduced considerable selection bias by allowing clinicians to choose the randomization scheme to which patients were entered; however, the authors published the results of the ESPAC 2x2 factorial design separately, which were free of data contamination and represented a clean methodological design. Patients in the ESPAC-1-plus trials were allowed to receive background therapy outside of the randomly assigned regimen, according to patient or physician preference, thus confounding the results of the comparisons. The ESPAC-1 trial reported that a considerable number of patients did not receive treatment according to protocol and variations in radiotherapy quality control were allowed between study centres. Of the patients for whom treatment details were available, 21% who were randomized to receive chemoradiotherapy (CRT) were given more or less than 40 Grays (Gy), and 9% received no CRT, while 33% who were randomized to receive chemotherapy (CT) were given less than six cycles, and 17% received no CT. Similarly, a significant number of patients randomized to the treatment arm of the Norwegian postoperative CT trial were not treated (20%) or did not complete therapy (37%). The Japanese study by Takada et al did not use an intention-to-treat analysis. Those limitations make the interpretation of some study results problematic and underline the importance of sufficiently powered trials with clean methodological designs to better clarify the role of postoperative therapy in this patient group.

The initial positive result of the small GITSG study that led to a conventional recommendation for postoperative CRT has been refuted by the larger ESPAC-1 trial. It now appears more probable that the GITSG study was positive not because of the CRT but rather the subsequent two years of postoperative CT. Postoperative CRT with split-course radiotherapy (RT) can no longer be routinely recommended for patients after resection of pancreatic cancer. However, it is possible that CRT could still be beneficial if given with superior modern treatment planning techniques, with the elimination of split-course RT regimens and when given in combination with newer CT agents such as infusional 5-fluorouracil (5FU) or gemcitabine. Additionally, the role of postoperative CRT in margin-positive patients requires clarification, as only a small minority of patients in those studies were margin positive. The individual patient data (IPD) meta-analysis suggested improved outcomes with CRT in margin-positive patients compared to margin-negative patients; however, there was insufficient statistical power to make comparisons between those subgroups. These are topics of relevance for future trials.

Because of the complicated design of the ESPAC-1 study, and the differences in the results depending on randomization group, the ESPAC-1 investigators felt that a larger, more specific confirmatory trial would be appropriate (ESPAC-3). As that study, at interim analysis, has dropped the observation arm due to inferiority, there is now a clear role for postoperative CT for patients with resected pancreatic cancer. That trial continues to investigate the role of gemcitabine as postoperative therapy compared to 5FU/leucovorin (LV).

At present, there is more evidence available for the overall survival advantages seen with postoperative 5FU/LV than for gemcitabine in the postoperative setting. Most CT regimens used in the reported trials were 5FU-based for a period of at least four months. Given the extensive experience with the Mayo regimen in the colorectal cancer postoperative setting, and the use of this regimen in the largest trial (ESPAC-1), that would seem a reasonable choice for postoperative therapy. Although in the metastatic setting gemcitabine has been compared to 5FU/LV and found to be associated with better quality of life, studies comparing those two regimens in the postoperative setting are ongoing. The Radiation Therapy Oncology Group (RTOG) 9704 study evaluated the addition of gemcitabine to postoperative adjuvant 5FU CRT. All patients received 5FU CRT and either 5FU or gemcitabine before and after CRT. In this study, 42% of patients randomized to the 5FU CRT plus 5FU crossed over to receive gemcitabine. The addition of gemcitabine to 5FU CRT improved survival in patients with pancreatic head cancer but not in the analysis of all eligible patients. Emerging data from the ESPAC-3 trial will determine if six months of postoperative gemcitabine is equivalent or superior to 5FU/LV. The higher drug acquisition cost of gemcitabine and longer administration time should be considered prior to the widespread adoption of gemcitabine as standard postoperative therapy over the more studied 5FU/LV regimen. There are currently insufficient data to support the routine use of preoperative therapy for patients with potentially resectable pancreatic cancer.

The Norwegian study by Bakkevold et al demonstrated superior outcomes with combination chemotherapy using 5FU, doxorubicin, and mitomycin-C (MMC) compared to observation alone. Although that study provides further evidence for the role of chemotherapy as postoperative treatment, it is not possible to determine the independent effect of the doxorubicin or the mitomycin from the

trial, and there is an absence of supporting data for those agents. In addition, significant toxicity was observed in patients who received the combined chemotherapy regimen. Therefore, the routine use of doxorubicin or MMC in the postoperative setting cannot be recommended.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Development and Internal Review

This evidence-based series was developed by the Gastrointestinal Cancer Disease Site Group (DSG) of Cancer Care Ontario's (CCO's) Program in Evidence-Based Care (PEBC).

Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of the original guideline document and the review and approval of the report by the PEBC Report Approval Panel, the Gastrointestinal Cancer DSG circulated the clinical Practice Guideline and Systematic Review to clinicians in Ontario for review and feedback.

Methods

Feedback was obtained through a mailed survey of 59 practitioners in Ontario (medical oncologists, radiation oncologists, and hepatobiliary surgeons). The survey consisted of items evaluating the methods, results, and discussion used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on May 24, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal DSG reviewed the results of the survey.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Postoperative chemotherapy is recommended for patients with resectable pancreatic adenocarcinoma. Patients should be referred to a medical oncologist to discuss chemotherapy after gross complete excision of a pancreatic adenocarcinoma. Acceptable regimens include six months of 5-fluorouracil (5FU) plus folinic acid or single-agent gemcitabine.
- The role of postoperative radiotherapy is not clear and warrants further study. Postoperative radiotherapy is not recommended when used in a split-course schedule for patients with negative margins. In margin-positive patients, there may be a role for postoperative radiotherapy.
- There is insufficient evidence to support the use of preoperative chemotherapy or radiotherapy or the use of intraoperative radiotherapy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Preoperative Therapy

One abstract report of a randomized trial of 38 patients reported no significant survival benefit for preoperative gemcitabine and accelerated hyperfractionated radiotherapy compared to no preoperative therapy.

Postoperative Therapy

- Seven phase III randomized controlled trials (RCTs) have examined postoperative combinations of chemotherapy and/or radiotherapy in comparison to a surgery-alone control arm. A published individual-patient-data meta-analysis of five of the seven reported trials demonstrated no advantage to postoperative combination chemoradiotherapy but supported an advantage of postoperative chemotherapy alone, with the mature evidence available being for 5-fluorouracil (5FU)-based chemotherapy.
- The Gastrointestinal Tumour Study Group (GITSG) trial of 43 patients reported an improvement in survival with four weeks of combined radiotherapy and 5FU followed by two years of weekly 5FU (median survival 21.0 months versus [vs.] 10.9 months; one-sided log rank p=0.035).

- The European Organization for Research and Treatment of Cancer (EORTC) trial including 114 patients with pancreatic head cancer demonstrated no advantage to split-course radiotherapy administered concurrently with infusional 5FU without a subsequent two years of postoperative chemotherapy (median survival 17.1 months vs. 12.6 months; two-sided log rank p=0.099) (4).
- The European Study Group for Pancreatic Cancer (ESPAC-1) trial demonstrated no advantage for combination radiotherapy and 5FU (median survival 15.9 months vs. 17.9 months, favouring no chemoradiotherapy [CRT]) but a significant survival benefit with six months of 5FU and leucovorin, using the Mayo regimen (median survival 20.1 months vs. 15.5 months).
- A Norwegian trial including patients with carcinoma of the ampulla of Vater indicated a survival benefit for postoperative chemotherapy with 5FU, doxorubicin, and mitomycin-C (MMC) up to two years post-surgery (median survival 23 months vs. 11 months) but no significant long-term survival.
- A Japanese study reported no survival benefit for adjuvant perioperative plus postoperative chemotherapy with 5FU plus MMC and oral 5FU until progression.
- The German Charité Onkologie (CONKO)-001 trial demonstrated a significant increase in disease-free survival for gemcitabine compared to observation alone; however, in the intention-to-treat population, no significant difference in overall survival was reported.
- A second Japanese trial reported no significant survival benefit for postoperative 5FU plus cisplatin over observation alone.
- An ongoing trial (ESPAC-3) comparing postoperative 5FU with gemcitabine has closed the observation arm at interim analysis due to the inferiority of that arm compared to the postoperative chemotherapy arms.

POTENTIAL HARMS

- Adverse effects reported in the phase III trials differed between treatment groups. In the Gastrointestinal Tumour Study Group (GITSG) trial, there were four adverse reactions in the treatment group. Three patients developed leukopenia with a white blood cell (WBC) count of 1.5 to 1.9 $x10^6$/L, and one patient developed a rash. No life-threatening toxic reactions or deaths due to therapy were reported.
- In the European Organization for Research and Treatment of Cancer (EORTC) study, 35 (44%), patients received only three days of 5-fluorouracil (5FU) chemotherapy (CT) during the second course of radiotherapy (RT), because of grade one or two toxicity. No leukopenia or thrombocytopenia worse than World Health Organization (WHO) grade one occurred. A further seven patients developed minor toxicity, especially nausea and vomiting. In one patient, full treatment was not completed due to the development of duodenal ulceration, which precluded administration of the second course of RT.
- The European Study Group for Pancreatic Cancer (ESPAC) study only collected toxicity data in a substudy involving centres with "resources to complete and return requested information," in what appears to be a poorly controlled fashion. In those 246 patients, grade 3-4 toxicities were seen in 1 out of 74 patients on chemoradiotherapy (CRT), 28 of 118 on CT, and 25 of 54 on CRT and CT. The most common side effects were stomatitis (32%),

neutropenia (25%), and diarrhea (10%). Dose reductions of 5FU occurred in 22% of patients.

- In the Norwegian study, only 24 of the 30 patients randomized to postoperative treatment with 5FU, doxorubicin, and mitomycin-C (MMC) received any CT. Toxicity was generally excessive in treated patients. Of 22 patients evaluable for toxicity, 16 (73%) were hospitalised due to toxicity during the first course of CT. Only 13 patients were able to complete all six scheduled courses, and six of those patients were hospitalised during their last treatment course. Gastrointestinal toxicity, mainly grade one, was the most common adverse reaction. Hematological toxicity was noted as moderate. Cardiotoxicity and nephrotoxicity were each observed in two patients. Five patients developed sepsis during treatment, with one toxic death.
- The German Association of Medical Oncology of the German Cancer Society (AIO) study of postoperative gemcitabine versus observation reported that gemcitabine was well-tolerated and severe (grade 3 or 4) toxicity was rare. In the gemcitabine group, 26 out of 186 patients experienced serious adverse events, only five of which were considered treatment-related.
- The Japanese study by Kosuge et al comparing postoperative cisplatin and 5FU to surgery alone reported that minor toxicity (grade 1 or 2) was common, especially nausea and vomiting, and a few patients experienced toxicity of grade 3 or higher. All toxicities were resolved with conservative treatment.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Trials comparing 5-fluorouracil (5FU) to gemcitabine in the postoperative setting are ongoing. The evidence for a survival benefit is more convincing for 5FU-based regimens.
- Evidence of a possible role for radiotherapy in patients with margin-positive resections is limited to a subgroup analysis in which the effect of therapy was dependent on margin status. Recommendations that there may be a role for postoperative radiotherapy in suitable patients are based on the expert opinion of the panel since this is the best available evidence.
- The studies available used a split-course radiotherapy regimen, and conventional radiotherapy has not been studied in a randomized trial. There is currently no evidence to support or refute the use of postoperative radiotherapy when used with more modern treatment-planning techniques.
- As there are insufficient data available on preoperative therapy for resectable pancreatic adenocarcinoma, such therapy should only be considered in the setting of a clinical trial.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Jonker D, Bouttell E, Kamra J, Spithoff K, Gastrointestinal Cancer Disease Site Group. Chemotherapy or radiotherapy for resectable pancreatic adenocarcinoma: clinical practice guidelines. Toronto (ON): Cancer Care Ontario (CCO); 2007 Nov 21. 22 p. (Evidence-based series; no. 2-23). [34 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Nov

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Gastrointestinal Cancer Disease Site Group (DSG) was polled for conflicts of interest. D. Jonker is a co-investigator in adjuvant trials for pancreatic cancer. No other conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on March 28, 2008.

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