This Evidence-based Series (EBS) was reviewed in 2015 and put in the Education and Information Section by the Gastrointestinal Cancer Disease Site Group (DSG) on January 5, 2016. (See Section 5: Document Summary and Review Tool for details)

The reviewed EBS report is available on the CCO web site and consists of the following sections:

- Section 1: Guideline Overview
- Section 2: Summary
- Section 3: Full Report
- Section 4: Document Assessment and Review Tool (2004 -2010)
- Section 5: Document Assessment and Review Tool (2010 -2015)

Report Date: January 5, 2016

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Phone: 905-527-4322 ext. 42822  Fax: 905-526-6775  E-mail: ccopgi@mcmaster.ca


# Table of Contents

## Section 1: Guideline Overview
Guideline Report History ................................................................. iii

## Section 2: Summary (February 2004)
Guideline Questions ........................................................................ iv
Target Population ........................................................................... iv
Recommendations ........................................................................... iv
Qualifying statements ......................................................................... iv
Update .......................................................................................... v
Methods ......................................................................................... v
Key Evidence ................................................................................... v
Related guideline ............................................................................. v
Contact Information .......................................................................... v
Preamble, Copyright, & Disclaimer .................................................... vii

## Section 3: Full Report (February 2004)
Questions .......................................................................................... 1
Choice of Topic and Rationale .......................................................... 1
Methods ........................................................................................... 1
Results ............................................................................................. 3
Interpretative Summary ...................................................................... 9
Ongoing trials .................................................................................. 10
DSG Consensus Process ................................................................. 12
External Review ................................................................................ 13
Practice guideline ............................................................................. 15
Journal Reference ............................................................................. 16
Acknowledgements ........................................................................... 16
References ......................................................................................... 17


The Treatment of Locally Advanced Pancreatic Cancer

Guideline Report History

<table>
<thead>
<tr>
<th>GUIDELINE VERSION</th>
<th>SYSTEMATIC REVIEW</th>
<th>PUBLICATIONS</th>
<th>NOTES AND KEY CHANGES</th>
</tr>
</thead>
</table>

¹: Web publication
The Treatment of Locally Advanced Pancreatic Cancer  
Practice Guideline Report #2-7  

C.C. Earle, O. Agboola, J. Maroun, L. Zuraw, and members of the Gastrointestinal Cancer Disease Site Group

Summary

Original Report Date: February 20, 2004

Guideline Question
What is the optimal treatment for patients with locally advanced (unresectable but non-metastatic) pancreatic cancer? The outcomes of interest were overall survival, disease-free survival, local control, adverse effects, and quality of life.

Target Population
These recommendations apply to adult patients with locally advanced (unresectable but non-metastatic) adenocarcinoma of the exocrine pancreas.

Recommendations
The intent of treatment of locally advanced pancreatic cancer is palliation in symptomatic patients and prolongation of life in medically suitable cases. The following options are appropriate:

- For medically suitable patients, current conventional practice is to offer combined chemotherapy and radiotherapy.
- Outside a clinical trial, 5-fluorouracil (5-FU) given as bolus or infusion is the preferred chemotherapeutic agent to combine with radiotherapy. The optimal mode and duration of 5-FU delivery is unclear, however infusional therapy appears to give better treatment outcome.

Qualifying Statements
- Specific anti-cancer treatments (such as resection, chemotherapy, and radiation) may be supplemented with supportive care (such as pain control, nutritional support, biliary stenting, and bowel decompression as needed) if appropriate.
- The evidence on which current conventional practice is based is relatively weak.
- Chemotherapy alone with gemcitabine is an acceptable alternative.
Update
- Supportive care alone is not recommended in patients who are medically suitable for chemotherapy and radiation treatment.

Methods
Entries to MEDLINE (1966 through February week 1, 2004), CANCERLIT (1983 through October 2001), EMBASE (1996 through 2004, week 6), and Cochrane Library (2003, Issue 3) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology to 2003 were systematically searched for evidence relevant to this practice guideline report. Due to a decision in April 2003 by the U.S. National Library of Medicine to no longer update the CANCERLIT database, as of May 2003, the CANCERLIT database will no longer be searched when updating. The most recent literature search was performed in February 2004.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative Gastrointestinal Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group, which comprises medical, and radiation oncologists, surgeons, a pathologist, and patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, the integration of this literature with the original guideline information.

Key Evidence
- There is evidence from two randomized trials that chemoradiotherapy with 5-FU provides a modest survival advantage over radiotherapy alone. One of two trials of chemoradiotherapy versus chemotherapy alone demonstrated a survival benefit for chemoradiotherapy.
- In three randomized trials, no chemotherapy regimen was shown to be superior to 5-FU in combination with radiation.
- Combination 5-FU and radiation is generally well tolerated, however, severe vomiting, mucositis, and leukopenia can occur in about 5% of patients. Although not superior to 5-FU in efficacy, other chemotherapeutic regimens appear to be more toxic.

Related Guideline

For further information about this practice guideline report, please contact Dr. Jean Maroun, Chair, Gastrointestinal Cancer Disease Site Group, Ottawa Regional Cancer Centre, General Division, 503 Smyth Road, Ottawa, Ontario, K1H 1C4; TEL (613) 737-7700, ext. 6708; FAX (613) 247-3511.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.
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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle. The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

For the most current versions of the guideline reports and information about the PEBC, please visit the CCO website at: http://www.cancercare.on.ca
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The Treatment of Locally Advanced Pancreatic Cancer
Practice Guideline Report #2-7

C.C. Earle, O. Agboola, J. Maroun, L. Zuraw, and members of the Gastrointestinal Cancer Disease Site Group

Full Report

Original Report Date: February 20, 2004

I. QUESTION
What is the optimal treatment for patients with locally advanced (unresectable but non-metastatic) pancreatic cancer? The outcomes of interest were overall survival, disease-free survival, local control, adverse effects, and quality of life.

II. CHOICE OF TOPIC AND RATIONALE
Adenocarcinoma of the exocrine pancreas is the fifth most common cause of cancer death in both men and women (1,2). Smoking and a history of chronic pancreatitis are established risk factors, and there are data emerging to support occasional inherited susceptibilities as well as increased risk from a high-fat diet (3). It is a highly lethal disease, with only 5% of patients alive at five years. About half of patients present with metastatic disease and have a median survival time of less than six months, with a one-year survival rate of less than 20% (2). A minority (20%) presents with localized resectable disease, and up to a quarter of these patients can be cured with surgery (3). Adjuvant chemoradiotherapy may increase the cure rate (4). The remaining 30% of patients are diagnosed with incurable, locally advanced, unresectable but non-metastatic pancreatic cancer.

Locally advanced pancreatic cancer is usually not resectable because of invasion of the portal or superior mesenteric vessels, splenic vein thrombosis, or metastases to second level lymph nodes. Patients have a median survival time of six to ten months and a one-year survival rate of 20% to 40% (5-14). Several clinical trials have explored the value of chemotherapy (CT) and/or radiotherapy (RT, CT/RT) in this group of patients. A systematic review of this literature and a practice guideline on the topic are therefore warranted.
III. METHODS
Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of the Cancer Care Ontario Program in Evidence-based Care, using methods of the Practice Guidelines Development Cycle (16). Evidence was selected and reviewed by two members of the PGI Gastrointestinal Cancer Disease Site Group (DSG) and methodologists. Members of the Gastrointestinal Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the treatment of locally advanced pancreatic cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial (RCT) data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE (1966 to March week 3 2002), CANCERLIT (1983 to October 2001), and the Cochrane Library (2002, Issue 1) were searched with no language restrictions. “Pancreatic neoplasms” (Medical subject heading [MeSH]) was combined with “chemotherapy, adjuvant” (MeSH), “radiotherapy” (MeSH), “immunotherapy” (MeSH), and each of the following phrases used as text words: “chemotherapy”, “radiotherapy”, “radiation”, “immunotherapy”. These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, and randomized controlled trials. The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/cancerinfo/pdq/) and the proceedings of the 1996-2001 annual meetings of the American Society of Clinical Oncology (ASCO) and the 1999-2001 annual meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by each reviewer independently, and the reference lists from these sources were searched for additional trials.

Update

The original literature search was updated in February 2004 using the MEDLINE (March 2002 to February week 1 2004), EMBASE (1996 through 2004, week 6), and Cochrane Library databases (to Issue 3, 2003), along with abstracts from the 2003 proceedings of the annual meetings of ASCO and ASTRO. The PDQ database was also searched for relevant ongoing trials. Due to a decision in April 2003 by the U.S. National Library of Medicine to no longer update the CANCERLIT database, as of May 2003, the CANCERLIT database will no longer be searched when updating.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized trials and meta-analyses comparing combinations of chemotherapy, radiotherapy, and/or immunotherapy to each
other or supportive care alone in patients with locally advanced pancreatic cancer. Data on overall survival for patients with locally advanced pancreatic cancer had to be reported. Other outcomes of interest were disease-free survival, local control, adverse effects, and quality of life. If patients with metastatic disease were included in the study, results had to be reported separately for patients with locally advanced disease.

**Exclusion Criteria**
1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized trials.
2. Letters and editorials were not considered.

**Synthesizing the Evidence**
Quantitative meta-analysis was not undertaken because the trials were too clinically heterogeneous to pool. The doses of radiotherapy varied widely, as did the chemotherapeutic agents and schedules.

**IV. RESULTS**

**Literature Search Results**
Eight randomized trials involving 733 evaluable patients met our inclusion criteria (6-15). Two randomized trials compared chemoradiotherapy with radiotherapy alone, two compared chemoradiotherapy with chemotherapy alone, three compared different chemotherapy regimens combined with radiation, and one compared different types of radiation (Table 1).

There were no papers describing a randomized comparison of chemotherapy and/or radiation to supportive care alone. There were many reports of trials of the treatment of metastatic pancreatic cancer, either with chemotherapy or immunotherapy that enrolled patients with locally advanced pancreatic cancer. However, none reported the results of treatment separately for patients with locally advanced disease and thus, were not included in this systematic review.

A trial by Burris et al (17) that compared gemcitabine to 5-fluorouracil (5-FU) in the treatment of advanced pancreatic cancer did not meet the eligibility criteria for inclusion in this systematic review because the results for patients with locally advanced disease were not reported separately. However, it is included in the discussion in the Disease Site Group Consensus Process section.

**Update**
Updating procedures obtained 11 new reports (1u-11u). These consist of nine RCTs (1u-9u), one abstract report of a meta-analysis (10u), and a preliminary report of an ongoing clinical trial (11u). Four of the RCT reports were fully published (1u,2u,5u,8u), and five were available as abstracts only (3u,4u,6u,7u,9u). Of the nine RCTs obtained, six provided data on quality of life (1u,3u,5u,8u,9u).

<table>
<thead>
<tr>
<th>Author, Year (Reference)</th>
<th>Radiation (Gy)</th>
<th>Chemotherapy</th>
<th>Number of Patients Randomized (Evaluable)</th>
<th>Median Survival (Months)</th>
<th>% 1-year Survival (Estimator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moertel et al, 1969 (5)</td>
<td>35-40 35-40</td>
<td>5-FU Placebo</td>
<td>NR (32) NR (32)</td>
<td>10.4* 6.3 mean</td>
<td>NR (25*) 66 (mean)</td>
</tr>
<tr>
<td>GITSG 9273, 1981 (6-8)</td>
<td>60 40</td>
<td>5-FU 5-FU</td>
<td>111 (86) 117 (83)</td>
<td>11.4 8.4</td>
<td>44* 39*</td>
</tr>
</tbody>
</table>

Table 1. Randomized trials in locally advanced pancreatic cancer.
<table>
<thead>
<tr>
<th>Author, Year (Reference)</th>
<th>Radiation (Gy)</th>
<th>Chemotherapy</th>
<th>Number of Patients Randomized (Evaluable)</th>
<th>Median Survival (Months)</th>
<th>% 1-year Survival (Estimate†)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>b) chemoradiotherapy versus chemotherapy alone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG, 1985 (9)</td>
<td>40 -</td>
<td>5-FU</td>
<td>NR (47)</td>
<td>8.3</td>
<td>NR (28)</td>
</tr>
<tr>
<td>GISG 9283, 1988 (10)</td>
<td>54 -</td>
<td>5-FU + SMF</td>
<td>24 (22)</td>
<td>9.7*</td>
<td>41*</td>
</tr>
<tr>
<td><strong>c) chemoradiotherapy with comparison of different chemotherapy regimens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG, 1980 (12)</td>
<td>60 -</td>
<td>mCCNU+5-FU</td>
<td>NR (33)</td>
<td>8.8</td>
<td>NR (40)</td>
</tr>
<tr>
<td>GISG 9277, 1985 (11)</td>
<td>60 40</td>
<td>5-FU doxorubicin</td>
<td>79 (73)</td>
<td>8.5</td>
<td>NR (33)</td>
</tr>
<tr>
<td>Earle et al, 1994 (13)</td>
<td>50-60 50-60</td>
<td>5-FU hycanthone</td>
<td>44 (44)</td>
<td>7.8</td>
<td>NR (34)</td>
</tr>
<tr>
<td><strong>d) comparison of different types of radiation beams</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG, 1989 (14)</td>
<td>photons -</td>
<td>Gemcitabine + Marimastat</td>
<td>239 randomized</td>
<td>5.5</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>mixed neutrons</td>
<td>Gemcitabine + placebo</td>
<td>239 randomized</td>
<td>5.5</td>
<td>17</td>
</tr>
<tr>
<td><strong>e) chemotherapy versus other chemotherapy regimens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bramhall et al 2002 (1u)</td>
<td>- -</td>
<td>Gemcitabine + Marimastat Gemcitabine + placebo</td>
<td>239 randomized</td>
<td>5.5</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>- -</td>
<td>Gemcitabine + placebo</td>
<td>239 randomized</td>
<td>5.5</td>
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<tr>
<td>Maisey et al 2002 (2u)</td>
<td>- -</td>
<td>5-FU 5-FU + MMC</td>
<td>107 102</td>
<td>5.1</td>
<td>NR (27)</td>
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<tr>
<td></td>
<td>- -</td>
<td>Gemcitabine + Zarnestra Gemcitabine + Placebo</td>
<td>688 randomized</td>
<td>6.4</td>
<td>NR (33)</td>
</tr>
<tr>
<td>Van Cutsem et al 2002 (3u)</td>
<td>- -</td>
<td>Gemcitabine + Cisplatin</td>
<td>42 randomized</td>
<td>9.1</td>
<td>NR (27)</td>
</tr>
<tr>
<td></td>
<td>- -</td>
<td>Gemcitabine + Cisplatin</td>
<td>42 randomized</td>
<td>9.1</td>
<td>NR (27)</td>
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<tr>
<td>Wang et al 2002 (4u)</td>
<td>- -</td>
<td>Gemcitabine + Cisplatin</td>
<td>42 randomized</td>
<td>9.1</td>
<td>NR (27)</td>
</tr>
<tr>
<td></td>
<td>- -</td>
<td>Gemcitabine + Cisplatin</td>
<td>42 randomized</td>
<td>9.1</td>
<td>NR (27)</td>
</tr>
<tr>
<td>Moore et al 2003 (5u)</td>
<td>- -</td>
<td>Gemcitabine BAY 12-9566</td>
<td>139 138</td>
<td>6.6</td>
<td>NR (27)</td>
</tr>
<tr>
<td></td>
<td>- -</td>
<td>Gemcitabine + Cisplatin</td>
<td>96 99</td>
<td>8.3</td>
<td>NR (27)</td>
</tr>
<tr>
<td>Heinemann et al 2003 (6u)</td>
<td>- -</td>
<td>Gemcitabine + Cisplatin</td>
<td>96 99</td>
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<td>NR (27)</td>
</tr>
<tr>
<td></td>
<td>- -</td>
<td>Gemcitabine + Cisplatin</td>
<td>96 99</td>
<td>8.3</td>
<td>NR (27)</td>
</tr>
<tr>
<td>Rocha Lima 2003 (7u)</td>
<td>- -</td>
<td>Gemcitabine + Irinotecan Gemcitabine</td>
<td>180 180</td>
<td>6.3</td>
<td>NR (27)</td>
</tr>
<tr>
<td></td>
<td>- -</td>
<td>Gemcitabine + Cisplatin</td>
<td>96 99</td>
<td>8.3</td>
<td>NR (27)</td>
</tr>
<tr>
<td><strong>f) Chemoradiotherapy versus observation alone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Shinchi et al 2002 (8u)</td>
<td>50.4 (28f)</td>
<td>5-FU</td>
<td>16 15</td>
<td>13.2</td>
<td>53.3</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>Gemcitabine</td>
<td>16 15</td>
<td>13.2</td>
<td>53.3</td>
</tr>
<tr>
<td><strong>g) chemoradiotherapy versus chemoradiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al 2003 (9u)</td>
<td>50.4-61.2</td>
<td>5-FU (bolus)</td>
<td>18 16</td>
<td>14.5</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>50.4-61.2</td>
<td>Gemcitabine</td>
<td>18 16</td>
<td>14.5</td>
<td>NR</td>
</tr>
</tbody>
</table>
Outcomes (Table 1, Sections a. to g.)

Chemoradiotherapy versus Radiotherapy Alone (Table 1a)

Two randomized trials evaluated combined-modality therapy compared with radiotherapy alone (6-9) (Table 1a). The first trial was published by Moertel et al in 1969 and included patients with locally advanced stomach, colon, and pancreatic cancer (5). Radiation was given as 6 fractions per week, with a weekly dose of 9-12 Gy, to a total dose of 35-40 Gy. Patients who were randomly assigned to chemotherapy received 5-FU 45 mg/kg daily for the first three days of radiation. Toxicity, in the form of nausea, vomiting, diarrhea, and marrow suppression, was more frequent with chemoradiotherapy than with radiotherapy alone, but it was described as tolerable. No deaths were ascribed to therapy. The addition of chemotherapy to radiation significantly increased survival for patients with all three tumor types. For patients with locally advanced pancreatic cancer, the mean survival time was significantly increased from 6.3 to 10.4 months when 5-FU was added to radiotherapy (p<0.05). The median survival, as estimated from the published survival curves, was increased from about 5.6 months to 8.0 months.

The Gastrointestinal Tumor Study Group (GITSG) undertook a three-arm study of 60 Gy double-split radiotherapy with two two-week rest periods compared with the same radiation dose combined with 5-FU, or 40 Gy single-split course with 5-FU (6-8) (Table 1a). In the chemotherapy-containing arms, the 5-FU was given at a dose of 500 mg/m2 IV on the first three days of each 20 Gy of radiation, and then continued as a weekly bolus infusion for two years. The radiation-alone arm was stopped after only 25 patients had been enrolled because it had become clear that both the median survival time and the one-year survival rate were half those in the chemotherapy-containing arms (p<0.01). There was no significant survival difference between the two combined-modality arms, although there was a nonsignificant trend towards prolonged time to progression (p=0.14) and improved survival (p=0.19) for 60 Gy over 40 Gy, suggesting a dose-response relationship. Local failure was a component of progression in about 25% of patients. Toxicity mostly consisted of nausea and vomiting and leukopenia, which occurred in all groups. However, severe toxicity (up to 5% of patients) and mucositis only occurred in patients receiving 5-FU.

Chemoradiotherapy versus Chemotherapy (Table 1b)

There were two randomized trials of chemoradiotherapy compared with chemotherapy alone (10,11) (Table 1b). A study by the Eastern Cooperative Oncology Group (ECOG) suggested that 5-FU alone was as effective as combined therapy with 5-FU and radiation (9). The fluorouracil was given at a dose of 600 mg/m2 weekly until disease progression. Chemoradiotherapy consisted of 5-FU 600 mg/m2 IV on the first three days of radiation, which was administered to a total dose of 40 Gy. Patients receiving chemoradiotherapy were given maintenance 5-FU afterwards, as administered in the chemotherapy arm. The trial closed early due to poor accrual, with 91 pancreatic cancer patients enrolled (patients with gastric cancer were also included). The median time to treatment failure for the patients with pancreatic cancer was 4.4 months with 5-FU versus 4.2 months with chemoradiotherapy (p-value not reported). There was more toxicity (leukopenia accompanied by sepsis) in patients receiving combined-modality treatment. There was no difference in local control between the arms. The results of this study have been questioned because of the poor survival seen in both arms, the less than optimal radiation planning and delivery in the radiation arm, the brevity...
of the course of chemotherapy in the combined-modality arm compared with other studies, and the possibility that the observed survival equivalence is a power issue due to poor accrual and early closure.

In 1988, the GITSG reported a randomized controlled trial evaluating multi-drug chemotherapy with streptozocin 1 g/m² day 1, mitomycin-C 10 mg/m² day 1, and 5-FU 600 mg/m² days 1, 8, 29, and 36 (SMF) given in eight-week cycles for two years, or until disease progression, versus 54 Gy of radiation given with 5-FU 350 mg/m²/day on the first three and last three days of radiotherapy (10) (Table 1b). The single course of 54 Gy was felt to be radiobiologically equivalent to the 60 Gy double-split regimen used in earlier studies by the GITSG. Following radiation, patients were given SMF for up to two years. The study was closed early due to lack of funding with only 24 patients in each arm. Overall survival was significantly better with combined-modality treatment (median survival 42 weeks, 41% at one year) compared with chemotherapy alone (median survival 32 weeks, 19% at one year) (p<0.02). At 18 months, 18% of patients in the combined-modality arm were alive, but none were alive in the SMF-only arm. Severe toxicity was experienced by 50% of patients in the chemoradiotherapy group, with life-threatening leukopenia in four patients and life-threatening thrombocytopenia in one patient. There were no life-threatening adverse effects in the SMF-only arm. The GITSG results have been questioned because the study closed after accruing only 24 patients in each arm due to lack of funding. Therefore, any observed difference could be attributed to a statistical power issue caused by inadequate accrual, not any treatment effect.

**Chemoradiotherapy Comparing Different Chemotherapeutic Agents (Table 1c)**

Three randomized trials of chemoradiotherapy evaluated different chemotherapeutic agents (12-14) (Table 1c). The Southwest Oncology Group (SWOG) randomly allocated 69 patients to 60 Gy of radiation with methyl-CCNU (methyl lomustine)125 mg/m² po every six weeks and 5-FU 400 mg/m² weekly, with or without testalactone 200 mg po daily (12). Survival was similar in each arm (p=0.68). Among 62 evaluable patients, the most common adverse effects were myelosuppression (87%) and gastrointestinal toxicity (23%), and there was one treatment-related death associated with granulocytopenia.

The GITSG compared 5-FU given with 60 Gy of radiation in a double-split course, with doxorubicin 15 mg/m² on day 1 followed by 10 mg/m² weekly given with 40 Gy of radiation administered in a continuous course (11) (Table 1c). After radiation, the doxorubicin was continued on a 3-4 week schedule until the maximum safe dose had been given, at which time patients were switched to 5-FU. A total of 143 patients were analyzed, and there was no significant survival difference. However, toxicity was significantly increased for patients receiving doxorubicin: more of those patients suffered hematologic toxicity, mucositis, and diarrhea. Additionally, the only treatment-related death, one due to a perforated viscus, occurred in the doxorubicin arm. Both arms found some palliation of pain in about a third of the patients. However, over half of the patients in both arms had local disease progression as their initial site of progression.

A randomized phase II study compared the radiation sensitizer hycanthone, given at 60 mg/m² IV on days 1-5 and days 29-33, to standard 5-FU given at 500 mg/m² for the first three days of each of three 20 Gy split radiation courses (total dose 60 Gy) (13) (Table 1c). There was no difference in survival (p=0.82) or disease-free survival (p=0.27). Furthermore, hycanthone was associated with hepatic toxicity that resulted in one death.

**Chemoradiotherapy Comparing Different Types of Radiation Beams (Table 1d)**

The Radiation Therapy Oncology Group (RTOG) randomized 49 evaluable patients to receive radiation treatment radiobiologically equivalent to 64 Gy of photon radiation
treatment. Either pure photons or neutrons, or a combination (mixed-beam irradiation) of both, was used (14) (Table 1d). Neutron irradiation was postulated to have several advantages due to its high linear energy transfer (LET) properties, and thus the possibility of improved local control. In this poorly powered study, there were no statistically significant differences in survival or local control among the arms. Median disease-free survival was also similar among treatment groups: 3.7 months with neutron irradiation, 3.4 months with mixed radiation beams, and 3.7 months with pure photon irradiation. However, three neutron-irradiated patients suffered moderate-to-life-threatening gastrointestinal toxicity compared with one patient treated with photons.

Update

Chemotherapy versus other Chemotherapy Regimens (Table 1e)

Updating obtained seven trials comparing chemotherapy regimens with other chemotherapy regimens (1u-7u). Six of the seven trials obtained did not detect a statistically significant difference between the treatment arms (1u-5u,7u). The trial by Heinemann et al (6u) did detect a statistically significant difference in median survival favouring treatment with gemcitabine combined with cisplatin versus gemcitabine alone by the Wilcoxon test (p=0.046) but not by the log-rank test (p=0.12).

Although the treatment was well-tolerated in the Bramhall et al (1u) study, the results obtained provide no evidence to support combining gemcitabine with marmistat for patients with advanced pancreatic cancer. Compared to treatment with gemcitabine alone, treatment with gemcitabine plus marmistat, produced no significant difference in overall response rate, progression-free survival, or time to treatment failure. The trial by Maisey et al (2u) did detect a statistically significant difference in response rate favouring protracted-venous-infusion (PVI) 5-FU plus mitomycin-C (MMC) compared with PVI 5-FU alone, but this did not result in an overall survival advantage. Maisey et al examined quality of life as an outcome of interest. The Van Cutsem et al trial (3u), while concluding that gemcitabine plus Zarnestra does have an acceptable toxicity profile compared to gemcitabine alone, did not detect a survival difference between the treatment groups. The trial by Wang et al (4u) concluded that gemcitabine plus cisplatin have similar responses, but noted that gemcitabine alone produced statistically fewer adverse events. The trial by Moore et al (5u) concluded that both median and estimated one-year survival for gemcitabine was significantly superior to BAY 12-9566 in the treatment of advanced pancreatic cancer. The trial by Heinemann et al (6u) concluded that combined gemcitabine and cisplatin prolonged progression-free survival (5.4 months versus 2.8 months; p<0.01) and median survival in locally advanced and metastatic pancreatic cancer compared to gemcitabine alone.

The conclusion by Heinemann et al (6u) is in contrast to the finding of Wang et al (4u), where the addition of cisplatin to gemcitabine increased one-year survival by almost three fold. The trial by Rocha Lima (7u) comparing gemcitabine combined with irinotecan with gemcitabine alone detected no statistically significant difference in time to progression, median survival, or one-year survival. In that trial, the toxicity profiles between the regimens were similar, except for diarrhea, which was significantly greater in the gemcitabine combined with irinotecan treatment arm (18.5% versus 1.8%; p=NR).

Chemoradiotherapy versus Observation Alone (Table 1f)

Updating obtained one trial comparing chemoradiotherapy versus observation alone (8u). In this trial by Shinchi et al, a statistically significant difference was detected between the treatment arms, and the fact was noted that external-beam radiotherapy combined with 5-FU increased both overall survival, and quality of life.
Update

Chemoradiotherapy versus Chemoradiotherapy

The trial by Li et al (9u) compared gemcitabine given with radiotherapy with bolus 5-FU given with the same radiotherapy regimen. That trial detected a statistically significant difference in median survival favouring treatment with gemcitabine combined with radiotherapy (14.5 versus 6.7 months; p<0.027). One-year survival was not reported in that abstract publication.

Update

Meta-analysis

A meta-analysis, reported in abstract form by Fung et al (10u), examined the data from 29 randomized trials including 3458 patients (Table 2). The two main findings of the meta-analysis are that 5-FU-based chemotherapy regimens show better survival outcomes over best supportive care (p<0.0001), and that gemcitabine-based chemotherapy regimens show better survival outcomes than 5-FU based regimens (p<0.005). The authors of the meta-analysis recommend that future trials examine gemcitabine-based chemotherapy regimens in advanced pancreatic cancer.

Table 2. Results of the Fung et al (10u) meta-analysis.

<table>
<thead>
<tr>
<th>Number of trials</th>
<th>Regimens</th>
<th>Number of patients</th>
<th>Average median survival time (months)</th>
<th>Pooled Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Best supportive care versus 5-FU-based combinations</td>
<td>434/262</td>
<td>3.87/6.38</td>
<td>0.53 (0.44 - 0.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7</td>
<td>5-FU/other agent alone versus 5-FU-based combination</td>
<td>428/414</td>
<td>5.23/4.98</td>
<td>0.88 (0.76 - 1.02)</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>5-FU-based combination versus 5-FU-based combination</td>
<td>121/121</td>
<td>3.75/4.38</td>
<td>0.85 (0.65 - 1.12)</td>
<td>0.25</td>
</tr>
<tr>
<td>1</td>
<td>5-FU versus Gemcitabine</td>
<td>63/63</td>
<td>4.41/5.65</td>
<td>0.56 (0.39 - 0.82)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>2</td>
<td>Miscellaneous new agent versus Gemcitabine</td>
<td>241/242</td>
<td>3.70/6.08</td>
<td>0.61 (0.50 - 0.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7</td>
<td>Gemcitabine versus Gemcitabine-based combination</td>
<td>758/745</td>
<td>6.62/6.98</td>
<td>0.92 (0.82 - 1.03)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Quality of Life

None of the randomized trials in Table 1 included quality of life as an outcome of interest. One report indicated that the proportion of patients who experienced palliation of pain and the average amount of weight loss 10 to 12 weeks into the study was similar for chemoradiotherapy with 5-FU versus doxorubicin (13).

Update

Six of the nine RCT reports provided data on quality of life (1u-3u,5u,8u,9u). The trial by Bramhall et al (1u) examined quality of life using the Memorial Pain Assessment card, level of analgesic used, Karnofsky performance status, surgical interventions required to alleviate symptoms, weight changes, and formal assessment with the Functional Assessment of Cancer Therapy-Pancreatic cancer (FACT-Pa) questionnaire. Analysis did not detect a statistically significant difference favouring either treatment with respect to any of the examined
criteria, except for FACT-Pa, which detected a difference at two months favouring treatment with gemcitabine alone (p=0.048, Wilcoxon rank sum test).

The trial by Maisey et al (2u) examined quality of life with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 at baseline and again every 12 weeks. No differences between the two treatment arms were detected at baseline or at any subsequent interval. The trial did detect statistically significant differences between baseline and the 24 week results for global and pain measures in the 5-FU plus MMC treatment arm.

Although no discrete values were given, the trial by Van Cutsem et al (3u) noted that quality of life was significantly improved in the gemcitabine plus Zarnestra treatment arm.

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) trial reported by Moore et al (5u) measured quality of life using the EORTC Quality of Life questionnaire C30, the Functional Assessment of Cancer Therapy Fatigue subscale, and a trial-specific pain checklist. All measures were completed at baseline and at every four weeks while patients were in the study. At four weeks, the scores for role, pain, insomnia, and constipation were significantly worse for patients in the BAY 12-9566 arm compared with patients in the gemcitabine arm. At eight weeks, patients in the BAY 12-9566 arm had significantly poorer scores in all quality-of-life domains except emotional, social, nausea, constipation, dyspnea, diarrhea, and financial difficulty.

The trial by Li et al (9u) measured the Karnofsky performance status and quality-adjusted life months for both the gemcitabine combined with radiotherapy and the bolus 5-FU combined with radiotherapy treatment arms and reported the differences between the average scores. The average monthly Karnofsky score for the gemcitabine plus radiotherapy group was 72 (95% confidence interval [CI], 69 to 75) compared with the bolus 5-FU combined with radiotherapy groups score of 63 (95% CI, 60 to 66), a statistically significant difference favouring treatment with gemcitabine plus radiotherapy (p<0.05). The average monthly quality-adjusted life months score for the gemcitabine plus radiotherapy group was 11.2 (95% CI, 10.7 to 11.7) compared to the bolus 5-FU combined with radiotherapy groups score of 6.0 (95% CI, 5.7 to 6.3), which was also statistically significant (p<0.05).

The trial by Shinchi et al (8u) measured quality of life by synthesizing Karnofsky performance status scores, quality-adjusted life months, total hospital days, and total hospital days per month of survival. Results detected statistically significant differences favouring treatment with chemoradiation for Karnofsky performance status (p=0.0001), Quality-adjusted life months, and number of hospital days per month of survival (p<0.05).

**Adverse Effects of Chemoradiotherapy**

Chemoradiotherapy can be associated with cytopenias, nausea, vomiting, and diarrhea (6-11). However, these adverse effects are generally tolerable, and treatment-related deaths are unusual. Combination 5-FU and radiation is also well tolerated. Although not superior to 5-FU in efficacy, other chemotherapeutic regimens appear to be more toxic (13,14).

**V. INTERPRETIVE SUMMARY**

Three randomized trials have shown chemoradiotherapy to be superior to either chemotherapy alone or radiation alone in terms of improved survival (6-9,11). Among three randomized trials of chemoradiotherapy comparing different chemotherapeutic agents, no chemotherapy regimen was superior to 5-FU in combination with radiation (12-14). These data support the use of chemoradiotherapy as standard practice for medically suitable patients. Outside of a clinical trial, 5-FU is the preferred chemotherapeutic agent to combine with radiotherapy. However, the optimal mode and duration of 5-FU delivery is unclear. Although different from the regimens actually used in the trials, common protocols give 5-FU
either by continuous infusion at a dose of 200 mg/m$^2$/day during radiation or by bolus injection of 500 mg/m$^2$/day on days 1-3 and the last three days of radiation, usually without subsequent maintenance treatment. The dose of radiation treatment ranges from 45 Gy to 54 Gy, given at 1.8 Gy per fraction over five to six weeks.

There were no randomized studies of chemotherapy and/or radiation compared with supportive care alone. Although studies of chemotherapy or immunotherapy for the treatment of metastatic pancreatic cancer enrolled patients with locally advanced disease, none reported the results of treatment separately for patients with locally advanced disease. Consequently, chemotherapy alone, radiotherapy alone, and immunotherapy cannot be recommended routinely for patients with locally advanced disease.

VI. ONGOING TRIALS

As of February 17, 2004, the following ongoing trials have been identified. Results for the locally advanced, non-resectable patient subgroups included in these studies will be added to this practice guideline report as the information becomes available.

<table>
<thead>
<tr>
<th>Protocol I.D. and Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAIICHI-8951A-PRT031, MSKCC-02011</td>
<td>Closed</td>
</tr>
<tr>
<td>Phase III randomized study of exatecan mesylate and gemcitabine versus gemcitabine alone in patients with chemotherapy-naive locally advanced or metastatic cancer of the exocrine pancreas (summary last modified January 2004)</td>
<td>• A randomized, open-label, multicentre study. • 340 patients (170 per treatment arm) will be accrued for this study within 18 months. • Daiichi Pharmaceutical Corporation sponsorship.</td>
</tr>
<tr>
<td>CAN-NCIC-PA3, OSI-NCIC-PA3</td>
<td>Closed</td>
</tr>
<tr>
<td>Phase III randomized study of gemcitabine with or without erlotinib in patients with unresectable locally advanced or metastatic pancreatic cancer (summary last modified January 2004)</td>
<td>• A randomized, double-blind, placebo-controlled, multicentre study. • 800 patients (400 per treatment arm) will be accrued for this study within 11 months. • NCIC-Clinical Trials Group sponsorship.</td>
</tr>
<tr>
<td>CWRU-010224M, LILLY-H3E-MC-JMES, LILLY-LILY-1201, NCI-G02-2125</td>
<td>Closed</td>
</tr>
<tr>
<td>Phase III randomized study of gemcitabine with or without pemetrexed disodium in patients with stage II, III, or IV unresectable pancreatic cancer (summary last modified March 2003)</td>
<td>• A randomized, open-label, parallel, multicentre study. • 520 patients (260 per treatment arm) will be accrued for this study. • NCI and pharmaceutical company sponsorship.</td>
</tr>
<tr>
<td>EORTC-05962</td>
<td>Closed</td>
</tr>
<tr>
<td>Phase III randomized multicentre trial of infusional fluorouracil with or without cisplatin and with or without chronomodulation against locally advanced or metastatic pancreatic cancer (summary last modified July 2003)</td>
<td>• A multicentre, randomized study. • 200 patients will be accrued. • EORTC Chronotherapy Group sponsorship.</td>
</tr>
<tr>
<td>Protocol I.D. and Description</td>
<td>Status</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td><strong>FRE-GERCOR-GEM-GEMOX/D00-3; EU-20324</strong>&lt;br&gt;Phase III randomized study of gemcitabine with or without oxaliplatin in patients with locally advanced or metastatic unresectable pancreatic adenocarcinoma (summary last modified December 2003).&lt;br&gt;• A randomized, multicentre study. Patients are stratified according to participating center, ECOG performance status (0 or 1 versus 2), and extent of disease (locally advanced versus metastatic). Patients are randomized to 1 of 2 treatment arms.&lt;br&gt;• A total of 230 patients (115 per treatment arm) will be accrued for this study within 24 months.&lt;br&gt;• Groupe d’Etude et de Recherche Clinique en Oncologie et Radiothérapie (GERCOR) sponsorship.&lt;br&gt;• a preliminary report is available (11u).</td>
<td>• Recruiting</td>
</tr>
<tr>
<td><strong>LORUS-LOR-VIR-P03-002</strong>&lt;br&gt;Phase III randomized study of gemcitabine with or without virulizin followed by optional second-line therapy with virulizin or placebo with or without fluorouracil in patients with chemotherapy-naive locally advanced or metastatic pancreatic cancer (summary last modified January 2004)&lt;br&gt;• A randomized, double-blind, parallel group, multicentre study.&lt;br&gt;• A total of 400 patients (175 per treatment arm, first randomization) will be accrued for this study.&lt;br&gt;• Sponsored by Lorus Therapeutics, Incorporated</td>
<td>• Recruiting</td>
</tr>
<tr>
<td><strong>PRONEURON-401.00.001, UAB-0105, UAB-F010524008, WELLSTAT-401.00.001</strong>&lt;br&gt;Phase III randomized study of triacetyluridine and high-dose fluorouracil versus gemcitabine in patients with unresectable locally advanced or metastatic pancreatic cancer (summary last modified January 2004)&lt;br&gt;• A randomized, open-label, multicentre study.&lt;br&gt;• 260 patients (130 per treatment arm) will be accrued for this study within 30 months.&lt;br&gt;• Sponsored by Wellstat Therapeutics</td>
<td>• Recruiting</td>
</tr>
<tr>
<td><strong>CPMC-IRB-8544, NCCAM, NCI-V99-1538</strong>&lt;br&gt;Phase III study of gemcitabine versus intensive pancreatic proteolytic enzyme therapy with ancillary nutritional support in patients with stage II, III, or IV adenocarcinoma of the pancreas (summary last modified December 2003)&lt;br&gt;• An open label study.&lt;br&gt;• Approximately 72-90 patients will be accrued for this study within 3 years.&lt;br&gt;• National Center for Complementary and Alternative Medicine sponsorship</td>
<td>• Recruiting</td>
</tr>
<tr>
<td><strong>SWS-SAKK-44/00, CECOG/PAN-1.3.001, EU-20142</strong>&lt;br&gt;Phase III randomized study of gemcitabine with or without capecitabine in patients with advanced pancreatic cancer (summary February 2002)&lt;br&gt;• This is a randomized, multicentre study&lt;br&gt;• A total of 300 patients (150 per treatment arm) will be accrued for this study within 3 years&lt;br&gt;• Swiss Institute for Applied Cancer Research and the Central European Cooperative Oncology Group sponsorship</td>
<td>• Recruiting</td>
</tr>
<tr>
<td><strong>CRUK-GEM-CAP, EU-20116</strong>&lt;br&gt;Phase III randomized study of gemcitabine with or without capecitabine in patients with locally advanced or metastatic pancreatic cancer (summary last modified July 2002)&lt;br&gt;• This is a randomized, open-label, multicentre study&lt;br&gt;• A total of 508 patients (254 per treatment arm) will be accrued for this study&lt;br&gt;• Cancer Research UK - Trials Office sponsorship</td>
<td>• Recruiting</td>
</tr>
</tbody>
</table>
### Protocol I.D. and Description

<table>
<thead>
<tr>
<th>Protocol I.D. and Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>URCC-2200, NCI-5012, NCI-CCC-99-45, NCI-P02-0212</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>
| Phase III randomized study of gemcitabine with or without dalteparin in patients with unresectable or metastatic pancreatic cancer (summary last modified December 2002) | • This is a randomized, multicentre study  
• A total of 400 patients (200 per treatment arm) will be accrued for this study within 40 months  
• NCI sponsored trial at the James P. Wilmot Cancer Center |
| ECOG-4201 | Recruiting |
| Phase III randomized study of gemcitabine with or without radiotherapy in patients with locally advanced, unresectable pancreatic cancer (summary last modified April 2003) | • This is a randomized, multicentre study  
• Approximately 332 patients will be accrued for this study within 2 years  
• NCI sponsorship (Eastern Cooperative Oncology Group) |
| ECOG-6201 | Recruiting |
| Phase III randomized study of prolonged infusion gemcitabine with versus without oxaliplatin versus standard infusion gemcitabine in patients with locally advanced or metastatic pancreatic cancer (summary last modified March 2003) | • Patients are stratified according to ECOG performance status (0 or 1 versus 2) and disease stage (locally advanced versus metastatic). Patients are randomized to 1 of 3 treatment arms.  
• A total of 666 patients (222 per treatment arm) will be accrued for this study within 37 months  
• NCI sponsorship (Eastern Cooperative Oncology Group) |

#### VII. DISEASE SITE GROUP CONSENSUS PROCESS

The Gastrointestinal Cancer DSG reached fairly easy consensus on the guideline recommendations. Since the evidence for radiation is relatively weak, there was discussion around whether treatment with gemcitabine alone should be presented as an equally acceptable alternative. The only randomized data on gemcitabine is the study by Burris et al (17), which demonstrated that gemcitabine improves symptoms and modestly improves survival compared with 5-FU as single-agent chemotherapy in patients with locally advanced or metastatic pancreatic cancer. These patients were symptomatic, had a life expectancy of at least twelve weeks, and a Karnofsky performance status of at least 50% (equivalent to an ECOG performance status of less than 3). This randomized trial is discussed in detail in another guideline (18) developed by the Gastrointestinal Cancer DSG, which concludes that gemcitabine is a reasonable treatment option in patients with locally advanced or metastatic pancreatic cancer. Since 26% of the patients included in the randomized trial by Burris et al (17) had locally advanced disease (although they were not reported separately) and since the overall results detected a benefit with gemcitabine, the Gastrointestinal Cancer DSG inferred that patients with locally advanced disease unable to undergo radiation may be appropriately treated as having metastatic disease. A qualifying statement noting this was added to the recommendations.

The majority of Gastrointestinal Cancer DSG members felt that changing the phrase that states combined chemoradiotherapy is the “recommended standard” to “current conventional practice” was appropriate. Also, a qualifying statement that indicates to the reader that the evidence on which current conventional practice is based is modest at best was added to the recommendations. Based on feedback from the DSG members, some suggested chemotherapy regimens were added to the text of the document.
VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence above, the Gastrointestinal Cancer DSG drafted the following recommendations:

Target Population
These draft recommendations apply to adult patients with locally advanced (unresectable but non-metastatic) adenocarcinoma of the exocrine pancreas.

Draft Recommendations
- For medically suitable patients, combined chemotherapy and radiotherapy is the current conventional practice.
- Outside of a clinical trial, 5-FU given as bolus or infusion is the preferred chemotherapeutic agent to combine with radiotherapy. The optimal mode and duration of 5-FU delivery is unclear.
- For patients unable to undergo radiotherapy, chemotherapy alone with gemcitabine is an acceptable alternative.

Related Guideline

Practitioner Feedback
Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
Practitioner feedback was obtained through a mailed survey of 152 practitioners in Ontario (29 medical oncologists, 20 radiation oncologists, and 103 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer DSG reviewed the results of the survey.

Results
Key results of the practitioner feedback survey are summarized in Table 2. Ninety-four surveys (64%) were returned. Forty-eight respondents (51%) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and completed the survey.

Table 2. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>45 (94%)</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>41 (85%)</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>37 (77%)</td>
</tr>
<tr>
<td>The results of the trials described in the report are</td>
<td>40 (83%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 (94%)</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>41 (85%)</td>
<td>5 (10%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>37 (77%)</td>
<td>8 (17%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>40 (83%)</td>
<td>5 (10%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>
Summary of Written Comments

Seventeen respondents (35%) provided written comments. The main points contained in the written comments were:

1. The survival benefit of 5-FU plus radiotherapy is modest and may not be worth the complications. Gemcitabine may be a reasonable alternative. Symptomatic care only should be included as one of the alternative recommendations.
2. The data on gemcitabine should be presented in the results.
3. The statement in the section on biliary and bowel decompression that “biliary and intestinal stenting are usually done endoscopically” is incorrect for the gastrointestinal outlet or small bowel obstruction. Surgery is usually required in this situation.

Modifications/Actions

1. The first and third bullets of the recommendations were modified slightly to reflect these points, and a fourth bullet was added to indicate that supportive care alone is a reasonable alternative.
2. The only randomized data on gemcitabine is the study by Burris et al (17). This trial is discussed in detail in another guideline developed by the Gastrointestinal Cancer DSG, which addresses the use of gemcitabine for the treatment of advanced pancreatic cancer (18). Some patients with locally advanced disease were included in the trial by Burris et al (17), but the results for these patients were not reported separately. For these reasons, data on gemcitabine were not included in the results section of the present guideline report.
3. The statement in the section on biliary and bowel decompression was corrected.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Ten of 11 members of the PGCC returned ballots. Eight members approved the practice guideline as written, and two members approved the guideline conditional on the Gastrointestinal Cancer DSG addressing specific concerns. PGCC members requested that the following issues be addressed prior to the approval of the guideline report:

One member expressed a concern about the lack of support for the recommendation on the use of gemcitabine. It was noted that there is no description of data evaluating the use of gemcitabine and that the case for its use as a treatment option was made only in the Interpretive Summary.

Another member expressed a concern about the critical appraisal of trials cited in the Outcomes section of the guideline report. This member noted that in the discussion of chemoradiotherapy versus chemotherapy trials there are only two studies described and stated that one suffered from a power issue and the other was closed early due to lack of funding. These were major problems, and the accrual in these trials creates a credibility problem. This member suggested that a more critical analysis of CT/RT versus CT alone is needed.
**Modifications/Actions**

The trial on gemcitabine that provided the evidence for the recommendation did not meet the inclusion criteria because patients with locally advanced disease were not reported separately. An additional statement was added to the literature search Results section to clarify why the trial did not meet the inclusion criteria for the systematic review component of the guideline report, and discussion of this trial had been moved from the Interpretive Summary to the DSG Consensus section.

A discussion noting the possibility that both the ECOG and GITSG trials were underpowered has now been added into the guideline report and discussed in the Results section. Additionally, the weakness of the evidence is noted up front in the Qualifying Statements. All minor editing changes were also made.

**Approved Practice Guideline Recommendations**

The practice guideline presented in Section IX reflects the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Gastrointestinal Cancer DSG and the Practice Guidelines Coordinating Committee.

**Update**

Based on new evidence that was published after the original practice guideline was completed, the Gastrointestinal Cancer DSG decided to modify the qualifying statements. The updated qualifying statement was not distributed to practitioners, as the Gastrointestinal Cancer DSG considered the modification minor. The new qualifying statement is listed below:

Supportive care alone is not recommended in patients who are medically suitable for chemotherapy and radiation treatment.

**IX. PRACTICE GUIDELINE**

**Target Population**

These recommendations apply to adult patients with locally advanced (unresectable but non-metastatic) adenocarcinoma of the exocrine pancreas.

**Recommendations**

The intent of treatment of locally advanced pancreatic cancer is palliation in symptomatic patients and prolongation of life in medically suitable cases. The following options are appropriate:

- For medically suitable patients, current conventional practice is to offer combined chemotherapy and radiotherapy.
- Outside a clinical trial, 5-fluorouracil (5-FU) given as bolus or infusion is the preferred chemotherapeutic agent to combine with radiotherapy. The optimal mode and duration of 5-FU delivery is unclear, however infusional therapy appears to give better treatment outcome.

**Qualifying Statements**

- Specific anti-cancer treatments (such as resection, chemotherapy, and radiation) may be supplemented with supportive care (such as pain control, nutritional support, biliary stenting, and bowel decompression as needed) if appropriate.
- The evidence on which current conventional practice is based is relatively weak.
- Chemotherapy alone with gemcitabine is an acceptable alternative.

**Update**

- Supportive care alone is not recommended in patients who are medically suitable for chemotherapy and radiation treatment.
Related Guideline

X. JOURNAL REFERENCE

XI. ACKNOWLEDGEMENTS
The Gastrointestinal Cancer Disease Site Group would like to thank Dr. C. Earle, Dr. O. Agboola, Dr. J. Maroun, and Ms. L. Zuraw for taking the lead in drafting and revising this practice guideline report. The Gastrointestinal Cancer Disease Site Group would like to thank Dr. O. Agboola, Dr. J. Maroun, and Mr. R.B. Rumble for taking the lead in updating this practice guideline report.

For a complete list of the Gastrointestinal Cancer Disease Site Group members, please visit the PEBC section of the CCO Web site at http://www.cancercare.on.ca/.
REFERENCES


**Update:**

This section includes all references obtained from the review and updating activities.


The Treatment of Locally Advanced Pancreatic Cancer

Guideline Summary Review in 2010
C.C. Earle, R. Tey, and members of the Gastrointestinal Cancer Disease Site Group

First Review Date: July 29, 2010

OVERVIEW
Evidence-based Series History
This guidance document was originally released by the Program in Evidence-based Care, Cancer Care Ontario, in 2002 and its first update released in February 2004. In July 2010 the PEBC guideline update strategy was applied and the new updated document released in September 2011. The Summary and the Full Report in this version are the same as in the February 2004 version.

Update Strategy
Using the Document Assessment and Review Tool, the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Questions Considered
What is the optimal treatment for locally advanced pancreatic cancer?
  i. in patients with unresectable but non-metastatic cancer
  ii. in patients with borderline resectable but non-metastatic cancer

Literature Search and New Evidence
The new search (2004 to March 2010) yielded 28 relevant new publications from 22 randomized controlled trials (RCTs). Four RCTs were already included in the original document. Brief results of these publications are shown in the Document Assessment and Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations
The new data supports existing recommendations with the following additions/modifications:

- For medically suitable patients, current conventional practice is to offer combined chemotherapy and radiotherapy for palliation.
• Outside a clinical trial, 5-fluorouracil (5-FU), given as bolus or infusion, or gemcitabine are the preferred chemotherapeutic agents to combine with radiotherapy. The optimal mode and duration of 5-FU delivery is unclear, however infusional therapy appears to give better treatment outcome.

• Chemotherapy alone with gemcitabine is an acceptable alternative for palliation.

Hence, in 2010, the Gastrointestinal Cancer DSG ENDORSED the 2004 guideline and recommendations on the treatment of locally advanced pancreatic cancer.


<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>UPG #2-7 Treatment of Locally Advanced Pancreatic Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of current version</td>
<td>February 20, 2004</td>
</tr>
<tr>
<td>Clinical reviewer</td>
<td>Dr. Craig Earle</td>
</tr>
<tr>
<td>Research coordinator</td>
<td>Rovena Tey</td>
</tr>
<tr>
<td>Date initiated</td>
<td>December 11, 2009</td>
</tr>
<tr>
<td>Date and final results / outcomes</td>
<td>July 29, 2010 (ENDORSED)</td>
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</table>

Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

1. Is there still a need for a guideline covering one or more of the topics in this document? Answer Yes or No, and explain if necessary:
   1. YES
      If No, then the document should be ARCHIVED with no further action; go to 11. If Yes, then go to 2.

2. Are all the current recommendations based on the current questions definitive or sufficient, and have less than 5 years elapsed since the latest search? Answer Yes or No, and explain if necessary:
   2. NO (not definitive, not sufficient, >5 years elapsed)
      If Yes, the document can be ENDORSED with no further action; go to 11. If No, go to 3.

3. Is there expected or known evidence that contradicts the current recommendations, such that they might cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:
   3. NO
      If Yes, the document should be taken off the Web site as soon as possible. A WARNING should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, go to 4.

4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:
   4. YES
      • There is a designated research co-ordinator at the PEBC to carry out the literature search
      • Updated search to be completed by April 2010
      If No, a DEFERRAL should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go to 5.

5a. List below any new, relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Changes in BOLD.
   • No significant changes to the existing guideline Q because it is the right question for the recommendation. The guideline Q should be kept broad to cover all possible treatments for locally advanced pancreatic cancer, even those that we may be unaware of.
   • However, the emphasis has probably shifted so that gemcitabine is now a completely reasonable
option and should be moved from the Qualifying Statements section into the Recommendations section (please see Chauffert et al. 2006, full reference in box 5b).
  o This can be revisited after the literature search to see if evidence will reflect this.

- What is important is whether there should be chemotherapy either before or after chemo-RT but don’t need to change Q to specify the comparison groups because with the existing guideline Q, the literature search should include these studies anyway. Please see Huguet et al. 2007, full reference in box 5b. For organizational purposes, comparisons of interest are:
  o Chemotherapy $\rightarrow$ chemotherapy + RT versus (vs.) Chemotherapy + RT
  o Chemotherapy + RT $\rightarrow$ chemotherapy vs. Chemotherapy + RT
  o Chemotherapy $\rightarrow$ chemotherapy + RT vs. Chemotherapy alone
  o Chemotherapy + RT $\rightarrow$ chemotherapy vs. chemotherapy alone

- Addressing borderline resectability might be another important question. Chemo-RT would be preferred in borderline resectable cases. The guideline Q was sub-divided into 2 parts to describe the population groups of interest.

- The NCCN definition of borderline resectable is:
  o HEAD/BODY
    ▪ Severe unilateral or bilateral SMV/portal impingement
    ▪ Less than 180 degree tumour abutment on SMA
    ▪ Abutment or encasement of hepatic artery, if reconstructible.
    ▪ SMV occlusion, if of a short segment and reconstructible.
  o TAIL
    ▪ SMA or celiac encasement less than 180 degree

**Question:**
What is the optimal treatment for patients with locally advanced (unresectable but non-metastatic) pancreatic cancer?
  iii. in patients with unresectable but non-metastatic cancer
  iv. in patients with borderline resectable but non-metastatic cancer

The outcomes of interest were overall survival, disease-free survival, local control, adverse effects, and quality of life.

**Target Population:**
These recommendations apply to adult patients with locally advanced (unresectable or borderline resectable but non-metastatic) adenocarcinoma of the exocrine pancreas.

5b. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence). Changes in BOLD.

- Focus on phase 3 RCTS
- Omit “supportive care” from the inclusion criteria because it is not expected to find many studies evaluating it

**Inclusion Criteria:**
Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized trials and meta-analyses comparing combinations of chemotherapy, radiotherapy, and/or immunotherapy to each other or supportive care alone in patients with locally advanced pancreatic cancer. Data on overall survival for patients with locally advanced pancreatic cancer had to be reported. Other outcomes of interest were disease-free survival, local control, adverse effects, and quality of life. If patients with metastatic disease were included in the study, results had to be reported separately for patients with locally advanced disease.
Exclusion Criteria:
1. Phase I and II randomized and non-randomized studies were not considered for inclusion in this report because of the availability of phase 3 randomized trials.
2. Letters and editorials were not considered.

Other Documents to Consider:


5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

Full Selection Criteria, Including Types of Evidence (e.g., randomized, non-randomized, etc.):
Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized trials and meta-analyses comparing combinations of chemotherapy, radiotherapy, and/or immunotherapy to each other in patients with locally advanced pancreatic cancer. Data on overall survival for patients with locally advanced pancreatic cancer had to be reported. Other outcomes of interest were disease-free survival, local control, adverse effects, and quality of life. If patients with metastatic disease were included in the study, results had to be reported separately for patients with locally advanced disease.

Exclusion Criteria:
1. Phase I and II randomized and non-randomized studies were not considered for inclusion in this report because of the availability of phase 3 randomized trials.
2. Letters and editorials were not considered.

Search Period:
- 2004 to 31 March 2010 (Embase + Medline)
- 2004 to 2009 (ASCO Annual Meeting)
- 2004 to 2010 (ASCO GI Symposium)
- 2004 to 2009 (ASTRO)

Brief Summary/Discussion of New Evidence:
Of 971 total hits from Medline + Embase and 1537 total hits from ASCO + ASTRO conference abstract searches, 28 references representing 22 RCTs evaluated treatment strategies for locally advanced pancreatic cancer. 4 RCTs were already mentioned and/or included in the existing guideline (rows highlighted in grey). The other 18 RCTs are potentially new studies, of which 6 are in abstract form and 12 have full-text publications.

<table>
<thead>
<tr>
<th>Interventions</th>
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<tr>
<td>Name of RCT</td>
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<td>Phase of RCT</td>
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<td>Population</td>
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<td>Outcomes</td>
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<td>Brief results</td>
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<tr>
<td>References</td>
</tr>
</tbody>
</table>

Intraoperative RT + doranidazole vs. intraoperative RT + placebo 3 Unresectable LAPC 1 = 1-y survival, survival time, safety 2 = effective response, 3-y survival • Grps did not differ for 1-y survival • No severe toxicity with doranidazole For doranidazole vs. placebo, 3-y survival = 23% vs. 0% (p=0.02) survival time = 318 d vs. 286 d (Karasawa K et al. 2008)
<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
<th>Treatment</th>
<th>Survival, effective response, tumour mass reduction rate</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative RT + PR-350 vs. intraoperative RT + placebo</td>
<td>3</td>
<td>Unresectable LAPC</td>
<td>Survival, effective response, tumour mass reduction rate</td>
<td>Grps did not differ for survival or effective response</td>
<td>(Sunamura MMD et al. 2004)</td>
</tr>
<tr>
<td>Tumour necrosis factor (TNF) + 5-FU + adjuvant gemcitabine + option of erlotinib + RT vs. adjuvant gemcitabine + option of erlotinib + RT (std of care)</td>
<td>PACT</td>
<td>LAPC</td>
<td>1 = OS, 2 = ORR, 3 = DFS</td>
<td>Interim analysis showed that for TNF vs. std of care,</td>
<td>(Chang KJ et al. 2009; Posner M et al. 2007)</td>
</tr>
<tr>
<td>5-FU + mitomycin-C + RT vs. RT</td>
<td>3</td>
<td>Unresectable LAPC</td>
<td>1 = OS, 2 = DFS, toxicity</td>
<td>Chemo-RT led to more toxicity</td>
<td>(Cohen SJ et al. 2005)</td>
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<tr>
<td>5-FU + RT vs. gemcitabine + RT</td>
<td></td>
<td>Unresectable pancreatic cancer</td>
<td></td>
<td>Grps had similar QoL</td>
<td>(Heras P et al. 2009)</td>
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<tr>
<td>5-FU + RT with 32P → gemcitabine + RT vs. 5-FU + RT → gemcitabine</td>
<td></td>
<td>Unresectable LAPC</td>
<td>OS, TTP, TTF, DoR, ORR, toxicity</td>
<td>For 32P vs. no 32P,</td>
<td>(Rosenmurgy A et al. 2008)</td>
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<tr>
<td>5-FU + RT vs. gemcitabine + RT</td>
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<td>1-y survival = 5.2 mo vs. 12.2 mo</td>
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<td>Gemcitabine + doxifluridine + RT vs. paclitaxel + doxifluridine + RT</td>
<td></td>
<td>LAPC</td>
<td>OS, ORR, TTP, CBR, toxicity</td>
<td>Grps did not differ for OS, TTP, CBR</td>
<td>(Chung HW et al. 2004)</td>
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<tr>
<td>Intensive 5-FU + cisplatin + RT vs. gemcitabine</td>
<td>FFCD/SFRO 2000-01</td>
<td>Unresectable LAPC, no distant metastases</td>
<td>1 = OS, 2 = PFS, 1-y survival, toxicity</td>
<td>Toxicity was mild to moderate in both grps</td>
<td>(Chauffert B et al. 2008)</td>
</tr>
<tr>
<td>Gemcitabine + RT vs. gemcitabine</td>
<td>E4201</td>
<td>Unresectable LAPC</td>
<td>OS, ORR, PFS, QoL, toxicity</td>
<td>For gemcitabine + RT vs. gemcitabine,</td>
<td>(Loehrer PJ, Sr et al. 2008)</td>
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<td>Median survival time = 11 mo vs. 9.2 mo (p = 0.04)</td>
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<td>ORR = 8.8% vs. 2.7%</td>
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<td>PFS = grps did not differ</td>
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<td>Grd 4 toxicity = 41% vs. 5.7% (p&lt;0.0001)</td>
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<tr>
<td>Gemcitabine + erlotinib vs. gemcitabine + placebo</td>
<td>3</td>
<td>Unresectable LAPC and metastatic pancreatic cancer</td>
<td>1 = OS 2 = ORR, PFS, DoR</td>
<td>Subgroup analysis showed that in pts with LAPC, grps did not differ for survival (Senderowicz AM et al. 2007)</td>
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<td>Gemcitabine + erlotinib vs. gemcitabine + placebo</td>
<td>NCIC CTG PA.3</td>
<td>LAPC and metastatic pancreatic cancer</td>
<td>1 = OS 2 = PFS, ORR, DoR, toxicity</td>
<td>In pts with LAPC, grps did not differ for survival (Moore MJ et al. 2007); (Moore MJ et al. 2005a; Moore MJ et al. 2005b) [abstracts]</td>
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<tr>
<td>Gemcitabine + capecitabine vs. gemcitabine</td>
<td>GEM-CAP</td>
<td>LAPC and metastatic pancreatic cancer</td>
<td>1 = OS 2 = PFS, ORR, toxicity, QoL</td>
<td>In the subgroup of pts with LAPC, grps did not differ for survival (Cunningham D et al. 2009)</td>
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<tr>
<td>Gemcitabine + capecitabine vs. gemcitabine</td>
<td>SAKK/C ECOG</td>
<td>LAPC and metastatic pancreatic cancer</td>
<td>1 = OS 2 = PFS, ORR, CBR, QoL, toxicity</td>
<td>In pts with non-metastatic cancer, grps did not differ for OS (Herrmann R et al. 2005) [abstract]</td>
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</table>
| Gemcitabine vs. no follow-up treatment | | Unresectable pancreatic cancer and obstructive jaundice, previously treated with covered metal biliary stent | Survival, QoL | Grps did not differ for survival  
Gemcitabine grp had worse QoL (Xinopoulos D et al. 2008) |
| Gemcitabine + exatecan mesylate vs. gemcitabine | 3 | LAPC and metastatic pancreatic cancer | 1 = OS 2 = TTP, ORR, QoL, toxicity | In pts with LAPC, grps did not differ for OS (O'Reilly EM et al. 2004) [abstract] |
| Exatecan mesylate vs. gemcitabine | 3 | LAPC and metastatic pancreatic cancer | 1 = OS 2 = TTP, TTF, CBR, DoR, QoL | In pts with LAPC, for exatecan vs. gemcitabine  
Median OS = 222 d vs. 341 d (Cheverton P et al. 2004) [abstract] |
| Imatinib mesylate vs. gemcitabine | | Unresectable pancreatic cancer | Survival time, ORR, QoL, toxicity | Grps did not differ for median survival time or QoL (Ebert M et al. 2004) [abstract] |
| Gemcitabine + cisplatin vs. gemcitabine | 3 | LAPC and metastatic pancreatic cancer | 1 = OS 2 = PFS, ORR, QoL, toxicity | In pts with LAPC, for gemcitabine + cisplatin vs. gemcitabine,  
PFS = 8.6% vs. 3.2% (p=0.005)  
OS = grps did not differ (Heinemann V et al. 2006)  
(Boeck S et al. 2005) [abstract] |
| Gemcitabine + irinotecan vs. gemcitabine | 3 | LAPC and metastatic pancreatic cancer | 1 = OS 2 = ORR, TTP, QoL, safety | In pts with LAPC, for gemcitabine + irinotecan vs. gemcitabine,  
OS = 9.8% vs. 12%  
ORR = 26% vs. 4.2%  
Median TTP = 7.7 mo vs. 4 mo (Rocha Lima CM et al. 2004) |
<p>| Gemcitabine + GERCO | 3 | Unresectable | 1 = OS | In pts with LAPC, for survival (Louvet C et |</p>
<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>R/G</th>
<th>LAPC and metastatic pancreatic cancer</th>
<th>Endpoint 1</th>
<th>Endpoint 2</th>
<th>Endpoint 3</th>
<th>Endpoint 4</th>
<th>Endpoint 5</th>
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<th>Endpoint 15</th>
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<tr>
<td>Gemcitabine + tipifarnib vs. gemcitabine + placebo</td>
<td>3</td>
<td>Unresectable LAPC and metastatic pancreatic cancer</td>
<td>1 = OS</td>
<td>2 = PFS, ORR, DoR, QoL, toxicity</td>
<td>In the subgroup of pts with LAPC, grps did not differ for OS or PFS</td>
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<td>Gemcitabine + oxaliplatin vs. gemcitabine</td>
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<td>• ORR = 27% vs. 15%</td>
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<td>• CBR = 45% vs. 34%</td>
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<td>• PFS = 7.4 mo vs. 5.3 mo</td>
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<td>• OS = grps did not differ</td>
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<td>• Toxicity = combination grp had more grade 3-4 toxicity</td>
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<td>New References Identified (alphabetical order):</td>
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</table>


**Literature Search Strategy:**

**Medline**
1. meta-analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summa$ or mathematical summa$ or quantitative synthesis$ or quantitative overview).tw.
5. (systematic adj (review$. or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliography$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or Jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. (random allocation/ or double blind method/ or single blind method/)
18. (random$ control$ trial/ or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and randomized.tw.
24. ((sing$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebo/
26. (placebo$ or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. exp pancreatic neoplasms/
39. (pancreas and (cancer$ or tumor or neoplasm or carcinoma$)).tw.
40. 38 or 39
41. chemotherapy.mp. or chemotherapy, adjuvant/
42. (radiotherapy or radiation therapy).mp. or radiotherapy, adjuvant/
43. exp radiotherapy/
44. chemoradiotherapy.mp. or exp combined modality therapy/
45. 41 or 42 or 43 or 44
46. 40 and 45
47. 37 and 46
48. (200402S or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$).ed.
49. 47 and 48

**Embase**

1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis$ or quantitative overview$).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 54 and (55 or 56)
9. or/61-63
10. (cochrane or embase or psychlit or psychlit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (random$s control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/61-63
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 65 and random$s.tw.
18. (clinical adj trial$1).tw.
19. ((singl$ or double$ or treb$ or trip$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo$ or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/67-71
24. practice guidelines/
25. practice guideline?.tw.
27. or/73-75
28. 58 or 59 or 60 or 64 or 66 or 72 or 75
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 77 not 78
31. limit 79 to english
32. limit 80 to human
33. exp pancreatic neoplasms/
34. (pancreas and (cancer$ or tumor or neoplasm or carcinoma$)).tw.
35. 38 or 39
36. chemotherapy.mp. or chemotherapy, adjuvant/
37. (radiotherapy or radiation therapy).mp. or radiotherapy, adjuvant/
38. exp radiotherapy/
39. chemoradiotherapy.mp. or exp combined modality therapy/
40. 82 or 83
41. 85 or 86 or 87 or 88
42. 84 and 89
43. 81 and 90
44. (200407$ or 2005S or 2006S or 2007$ or 2008$ or 2009$ or 2010$).ew.
45. 91 and 92

<table>
<thead>
<tr>
<th>6. Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?</th>
<th>6. NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Yes, then the document should be ARCHIVED with no further action; go to 11. If No, go to 7.</td>
<td></td>
</tr>
<tr>
<td>7. On initial review, does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:</td>
<td>7. YES, this document can be ENDORSED with the following additional/altered recommendations:</td>
</tr>
<tr>
<td>- For medically suitable patients, current conventional practice is to offer combined chemotherapy and radiotherapy for palliation.</td>
<td></td>
</tr>
<tr>
<td>- Outside a clinical trial, 5-fluorouracil (5-FU), given as bolus or infusion, or gemcitabine are the preferred chemotherapeutic agents to combine with radiotherapy. The optimal mode and duration of 5-FU delivery is unclear, however infusional therapy appears to give better treatment outcome.</td>
<td></td>
</tr>
<tr>
<td>- Chemotherapy alone with gemcitabine is an acceptable alternative for palliation.</td>
<td></td>
</tr>
<tr>
<td>If Yes, the document can be ENDORSED. If No, go to 8.</td>
<td></td>
</tr>
<tr>
<td>8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:</td>
<td>8. Not applicable.</td>
</tr>
<tr>
<td>If Yes, a WARNING note will be placed on the web site. If No, go to 9.</td>
<td></td>
</tr>
<tr>
<td>9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:</td>
<td>9. Not applicable.</td>
</tr>
<tr>
<td>If Yes, the document update will be DEFERRED, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10.</td>
<td></td>
</tr>
<tr>
<td>10. An update should be initiated as soon as possible. List the expected date of completion of the update:</td>
<td>10. Not applicable.</td>
</tr>
<tr>
<td>An UPDATE(^1) will be posted on the Web site, indicating an update is in progress.</td>
<td></td>
</tr>
<tr>
<td>11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.</td>
<td></td>
</tr>
</tbody>
</table>

**DSG Approval Date:** July 29, 2010
## DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART

<table>
<thead>
<tr>
<th>STEPS</th>
<th>Outcomes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 1: Initiation of the Document Assessment &amp; Review process</strong></td>
<td></td>
<td>RC emails DSG reviewer(s) the protocol</td>
</tr>
<tr>
<td><strong>STEP 2: First teleconference to determine:</strong></td>
<td></td>
<td>Discuss questions #1-5</td>
</tr>
<tr>
<td>- the clinical relevance of the guideline,</td>
<td></td>
<td>Please note: No teleconference needed, IF the answers lead to one of these outcomes, PLUS the reviewer(s) complete &amp; return the form with the answers &amp; explanations.</td>
</tr>
<tr>
<td>- if a new literature search is needed, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- if Yes, the search criteria.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#1. Is there still a NEED for a guideline covering one or more of the topics in this document?</td>
<td>No</td>
<td>Archive¹</td>
</tr>
<tr>
<td>#2. Are all the current recommendations based on the current questions definitive* or sufficient§, and have less than 5 years elapsed since the latest search?</td>
<td>Yes to all</td>
<td>Endorse²</td>
</tr>
<tr>
<td>#3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?</td>
<td>Yes</td>
<td>Warning¹</td>
</tr>
<tr>
<td>#4. Do current resources allow for an updated literature search to be conducted at this time?</td>
<td>No</td>
<td>Deferral³</td>
</tr>
<tr>
<td>#5. List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.</td>
<td>Yes</td>
<td>New search</td>
</tr>
<tr>
<td><strong>STEP 3: A NEW literature search based on input from #5 will be conducted,</strong> and the result will be sent to the reviewers with a follow-up date</td>
<td></td>
<td>RC conducts new search</td>
</tr>
</tbody>
</table>
FLOW CHART (cont.)

**STEP 4: Second teleconference to determine the ultimate status of the document**

- **#6.** Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?
  - Yes → **Archive**
  - No → **#7.** Does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?
    - Yes to all → **Endorse**
    - No → **#8.** Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?
      - Yes → **Warning**
      - No → **#9.** Is there a good reason (e.g., new, stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?
        - Yes → **Deferral**
        - No → **#10.** An update should be initiated as soon as possible. List the expected date of completion of the update.

- **STEP 5: Final outcome approval; Document Assessment & Review questions #11**

  **#11.** Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.
DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

* DEFINITIVE RECOMMENDATIONS - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§ SUFFICIENT RECOMMENDATIONS - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶ WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the Web site, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.
The Treatment of Locally Advanced Pancreatic Cancer

Guideline Summary Review in 2015

C.C. Earle, X. Yao, and members of the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Current Review Date: November 23, 2015

The 2012 guideline recommendations are Education and Information

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario’s Program in Evidence-based Care in 2004. In December 2009, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist (RT) conducted an updated search of the literature. A clinical expert (CE) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Gastrointestinal Cancer Disease Site Group (DSG) endorsed the recommendations found in Section 2 (Summary) with some updated information on July 29, 2010.

In November 2015, this document was assessed again in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. A PEBC methodologist (XY) conducted an updated search of the literature. A clinical expert (CE) reviewed and interpreted the new eligible evidence and proposed that the existing recommendations should be moved to Education and Information section on the CCO website. The Gastrointestinal Cancer Disease Site Group (DSG) members agreed this decision in January 2016.
DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered
What is the optimal treatment for locally advanced pancreatic cancer?
1. in patients with unresectable but non-metastatic cancer
2. in patients with borderline resectable but non-metastatic cancer

Literature Search and New Evidence
The new search (March 2010 to September 2015) yielded one systematic review and 10 original studies (five fulltexts and five conference abstracts) representing 6 phase III RCTs that compared combinations of chemotherapy, radiotherapy, and/or immunotherapy to each other in patients with locally advanced pancreatic cancer. Brief results of these searches are shown in the Document Review Tool on page 35.

Impact on Guidelines and Its Recommendations
The update of existing literature did not identify any studies that contradict the current recommendations. However, the recommendations from 2004 do not cover currently funded treatment options in common use (FOLFIRINOX and gemcitabine plus Abraxane) for which extrapolation has been made from the metastatic setting. Therefore, the Gastrointestinal Cancer DSG decided to move the #2-7 guideline into the Education and Information section on the CCO website until such time as resources for the creation of a new guideline become available. This means the recommendations will no longer be maintained but may still be useful for academic or other information purposes.
Number and title of document under review | 2-7 The Treatment of Locally Advanced Pancreatic Cancer
--- | ---
Current Report Date | October 17, 2013
Clinical Expert | Craig Earle
Health Research Methodologist | Xiaomei Yao
Date Assessed by GI DSG chairs | November 2014
Current Literature Search Date | September 28, 2015
Approval Date and Review Outcome (once completed) | January 5, 2016 [Education and Information]

Original Question:
What is the optimal treatment for locally advanced pancreatic cancer?
  3. in patients with unresectable but non-metastatic cancer
  4. in patients with borderline resectable but non-metastatic cancer

Target Population:
These recommendations apply to adult patients with locally advanced (unresectable or borderline resectable but non-metastatic) adenocarcinoma of the exocrine pancreas.

Study Section Criteria:
Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized trials and meta-analyses comparing combinations of chemotherapy, radiotherapy, and/or immunotherapy to each other in patients with locally advanced pancreatic cancer. Data on overall survival for patients with locally advanced pancreatic cancer had to be reported. Other outcomes of interest were disease-free survival, local control, adverse effects, and quality of life. If patients with metastatic disease were included in the study, results had to be reported separately for patients with locally advanced disease.

Exclusion Criteria:
1. Phase I and II randomized and non-randomized studies were not considered for inclusion in this report because of the availability of phase 3 randomized trials.
2. Letters and editorials were not considered.
3. Studies that were published in non-English languages were excluded.

Search Details:
The search date and time period for the following literature search database, the Cochrane Library, and conference abstracts were showed below:
- Medline and Embase: March 2010 to September 28, 2015
- The Cochrane Library: 2010 to 2015
- American Society of Clinical Oncology (ASCO) Annual Meeting: 2010 to 2015
- ASCO Gastrointestinal Symposium: 2011 to 2015
- American Society for Therapeutic Radiology and Oncology (ASTRO): 2010 to 2015

The search strategies for Medline, Embase, and the Cochrane Library were listed in Appendix 1.

Brief Summary/Discussion of New Evidence:
There were 2,181 hits from Medline, Embase, and the Cochrane Library; and 1,477-abstract hits from ASCO and ASTRO conferences. Among them, one systematic review and 10 original studies (five fulltexts and five conference abstracts) representing 6 phase III RCTs met our study selection criteria. One of the fulltexts
No conflict of interest was declared.

Clinical Expert Interest Declaration:
No conflict of interest was declared.

### Meta-Analyses/Systematic Reviews

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Study</th>
<th>Population (N)</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT vs. RT/CT; CRT vs. CT; CRT vs. RT</td>
<td>15 RCTs (no phase info, but our previous report and this update should cover all phase III RCTs in this systematic review)</td>
<td>Initially diagnosed LAPC without metastasis (1,128)</td>
<td>OS, Toxicity</td>
<td>CRT was superior in the 6- and 12-mo survivals to the RT alone group or CT alone group (P=0.0001 and 0.02, respectively); the 18-mo survival showed no significant difference (p=0.23). CRT vs. CT: no significant difference for 6-, 12-, and 18-mo (p=0.07, p=0.23, p=0.91, respectively) CRT group was superior to RT alone group for 6-, 12-, and 18-mo survivals (all p&lt;0.01). CRT group had significantly more grade 3-4 treatment-related hematologic and non-hematologic toxicities than CT or RT group (all p&lt;0.01).</td>
<td>Chen 2013 [1]</td>
</tr>
</tbody>
</table>

### Phase III Randomized Control Trials (fulltexts and conference abstracts)

**a) Chemotherapy vs. chemoradiotherapy**

<table>
<thead>
<tr>
<th>Trial name, Interventions</th>
<th>Population</th>
<th>N</th>
<th>Median follow up</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ECOG trial: Gemcitabine vs. gemcitabine+RT</td>
<td>Unresectable LAPC, aged 47-84 years</td>
<td>74 (sample size should be 316 pts)</td>
<td>Unclear</td>
<td></td>
<td></td>
<td>Loanherr 2011 [2]</td>
</tr>
<tr>
<td>LAP07 study: CT (2 mo additional gemcitabine or gemcitabine+erlotinib) vs. CRT (RT+capecitabine)</td>
<td>Pts with unresectable LAPC, mean aged 62-63 years, were randomized to receive gemcitabine or gemcitabine+erlotinib, only pts with controlled disease were then randomized again to receive CT or CRT</td>
<td>269 (preplanned interim analysis)</td>
<td>36 mo for interim analysis; the trial will be completed in 2016</td>
<td>OS, LTPR, MTT</td>
<td></td>
<td>Huguet 2014 (abstract) [3], Hammel 2013 (abstract) [4]</td>
</tr>
</tbody>
</table>

**b) Chemotherapy vs. chemotherapy regimens**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>N</th>
<th>Median follow up</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMST study (Gemcitabine and S-1 Trial): S-1 (an oral fluoropyrimidine derivative) vs. gemcitabine; S-1 plus gemcitabine vs. gemcitabine</td>
<td>Locally advanced PC, no prior chemotherapy or radiotherapy for PC, age &gt; 20 years but &lt; 80 years, an ECOG performance status score of 0 to 1</td>
<td>202 (subgroup analysis)</td>
<td>18.4 mo</td>
<td>OS</td>
<td>Median OS: S-1 vs. gemcitabine =13.8 mo vs. 12.7 mo; HR=0.84, 95% CI=0.57-1.22. S-1 plus gemcitabine vs. gemcitabine =15.9 vs. 12.7; HR=0.67, CI=0.46-0.99.</td>
<td>Ueno 2013 [7], Fukutomi 2012 (abstract) [8], Ioka 2011 (abstract) [9]</td>
</tr>
<tr>
<td>GIP-1 study: Gemcitabine+ gemcitabine+ cisplatin</td>
<td>Unresectable stage II and III LAPC, aged 35-75 years</td>
<td>64 (subgroup analysis)</td>
<td>38.2</td>
<td>OS</td>
<td>Median OS for all pts (including metastatic pts) was 8.3 mo. Gemcitabine vs. gemcitabine+ cisplatin: HR=1.135, CI=1.038-1.227, p&lt;0.02.</td>
<td>Colucci 2010 [10]</td>
</tr>
</tbody>
</table>

**c) Chemoradiotherapy vs. chemoradiotherapy + immunotherapy**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>N</th>
<th>Median follow up</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TeloVac trial: Gemcitabine+ capecitabine vs.</td>
<td>Locally advanced PC, &gt;18 years, an ECOG</td>
<td>325 (subgroup analysis)</td>
<td>Unclear (trial lasted 4.5</td>
<td>OS</td>
<td>Gemcitabine+ capecitabine vs. Gemcitabine+ capecitabine with sequential GM-CSF+CV1001</td>
<td>Middleton 2014 [5], Wild 2012 (abstract) [6]</td>
</tr>
</tbody>
</table>
| Gemcitabine+ capecitabine with sequential GM-CSF +CV1001 (telomerase vaccination); Gemcitabine+ capecitabine vs. Gemcitabine+ capecitabine with concurrent GM-CSF+CV1001 | performance status of 0-2, unresectable or patients who had relapsed following previously resected pancreatic cancer. | 304 | 9.1 mo | ● OS  
● PFS  
● Time to radiologic progression  
● Toxicity | ● Median OS was 10.0 months for both groups, SOC+TNFerade vs. SOC: HR=0.90, CI=0.66-1.22, p=0.26.  
● Median PFS for SOC+TNFerade vs. SOC=6.8 mo vs. 7.0 mo; HR=0.96, CI=0.69-1.32, p=0.51.  
● Time to radiologic progression for SOC+TNFerade vs. SOC=11.6 mo vs. 10.8 mo; HR=1.07, CI=0.71-1.62, p=0.82.  
● Grade 1 to 2 toxicities: more pts experienced in SOC+TNFerade than SOC group (81.7% vs. 14.3%, p<0.001); grade 3-4 toxicities were similar for 2 groups (3.2% vs.1.1%, p=0.43). | Herman 2013 [11] |

### Abbreviations:
- CI = 95% confidence interval, CRT = chemotherapy plus radiotherapy, CT = chemotherapy, ECOG = Eastern Cooperative Oncology Group, Egr-1 = the early growth response protein 1, GM-CSF = granulocyte-macrophage colony-stimulating factor, HR = hazard ratio, HRQOL = health-related quality of life, LAPC = locally advanced pancreatic cancer, LTPR = local tumour progress rate, mo = months, MTT = median time without treatment ORR = overall response rate, OS = overall survival, PC = pancreatic cancer, PFS = progression-free survival, pts = patients, RCTs = randomized controlled trials, RT= radiotherapy, vs. = versus.
- This trial was included in 2010 updated review as a conference abstract (Loehrer 2008, ASCO Abstr: 4, 506).
- Data came from Figure 3 on page 1,648 (measured by eyeball).

### Instructions.

**For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.**

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?  
   - **No.**

2. On initial review,  
   a. Does the newly identified evidence support the existing recommendations?  
      - **a. Yes.**  
      - **b. No.**

3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:  
   - **No.**

4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?  
   - **Not applicable**

### Review Outcome

**Education and Information**
This guideline accurately reflects current evidence. However, current practice has changed based on consensus in the absence of published evidence. Although the DSG members have voted “Education and Information”, they would be interested in doing an update sometime in the future.

New References Identified (from March 2010 to September 2015):

### Appendix 1. Search strategies

1). Medline search on September 28, 2015

**Database(s):** Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

**Search Strategy:**

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
<th>Results</th>
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<tbody>
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</tr>
<tr>
<td>2</td>
<td>meta analysis.pt.</td>
<td>60214</td>
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<td>mathematical summar$ or quantitative synthesis$ or quantitative overview).tw.</td>
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<td></td>
<td>scisearch or bids or sigle or cancerlit).ab.</td>
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<td>(reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.</td>
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<td>12 and 13</td>
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28 or/23-27
29 practice guidelines/
30 practice guideline?.tw.
31 practice guideline.pt.
32 or/29-31
33 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
   (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education
   handout or case report or historical article).pt.
35 33 not 34
36 exp pancreatic neoplasms/
37 (pancrea$ and (cancer$ or tumor$ or neoplasm$ or carcinoma$)).tw.
38 36 or 37
39 exp Combined Modality Therapy/
40 exp radiotherapy/
41 (chemotherap$ or radiotherap$ or radiation therap$ or chemoradiotherap$).mp.
42 antineoplastic agent$.mp. or exp Antineoplastic Agents/
43 or/39-42
44 35 and 38 and 43
45 Animal/ not Human/
46 44 not 45
   (201003: or 201004: or 201005: or 201006: or 201007: or 201008: or 201009: or 20101: or 2011: or 2012: or 2013: or
   2014: or 2015:).dc.
47 46 and 47
49 limit 48 to english language
50 remove duplicates from 49

2). Embase search on September 28, 2015
Database(s): Embase 1996 to 2015 Week 39
Search Strategy:

<table>
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<th>Searches</th>
<th>Results</th>
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<tr>
<td>1</td>
<td>exp meta analysis/ or exp systematic review/</td>
<td>153276</td>
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<td>2</td>
<td>(meta analy$ or metaanaly$).tw.</td>
<td>104272</td>
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<tr>
<td>(systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or</td>
<td>94900</td>
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<td>mathematical summar$ or quantitative synthes$ or quantitative overview).tw.</td>
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4 (systematic adj (review$ or overview?)).tw. 87983
5 exp review/ or review.pt. 1645834
6 (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab. 222296
7 (study adj selection).ab. 9952
   (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or
8 scisearch or bids or sigle or cancerlit).ab.
9 (reference list$ or bibliography$ or hand-search$ or relevant journals or manual search$).ab. 31515
10 or/1-9
11 exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/ 350332
12 randomization/ or single blind procedure/ or double blind procedure/
13 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. 185649
14 or/11-13
15 (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/ 1136615
16 15 and random$.tw. 350650
17 (clinic$ adj trial$1).tw. 289317
18 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw. 129141
19 placebo/
20 (placebo? or random allocation or randomly allocated or allocated randomly).tw. 194213
21 (allocated adj2 random).tw. 305
22 or/17-21
23 practice guideline/
24 practice guideline?.tw. 20776
25 or/23-24
26 10 or 14 or 16 or 22 or 25 2787721
27 (editorial or note or letter or erratum or short survey).pt. or letter/ or case study/ 1932540
28 Animal/ not Human/
29 27 or 28 2425654
30 exp pancreatic neoplasms/ 78309
31 (pancrea$ and (cancer$ or tumo?r or neoplasm$ or $carcinoma$)).tw. 77541
32 or/30-31
33 multimodality cancer therapy/ 41379
   cancer chemotherapy/ or adjuvant chemotherapy/ or chemotherapy/ or combination chemotherapy/ or cancer
34 combination chemotherapy/ 307044
35 exp radiotherapy/ 322106
36 (chemotherap$ or radiotherap$ or radiation therap$ or chemoradiotherap$).mp. 635571
37 antineoplastic agent$.mp. or exp Antineoplastic Agents/ 1204404
38 or/33-37 1582111
39 (26 and 32 and 38) not 29 11364
(201003: or 201004: or 201005: or 201006: or 201007: or 201008: or 201009: or 20101: or 2011: or 2012: or 2013: or
2014: or 2015:).dd. 8032020
41 39 and 40 6940
42 limit 41 to english language 6734
43 limit 42 to exclude medline journals 892

3). The Cochrane Library search on September 28, 2015
Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials August 2015, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to August 2015
Search Strategy:

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<td>1816</td>
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<td>3</td>
<td>1 or 2</td>
<td>1960</td>
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<td>4</td>
<td>exp Combined Modality Therapy/</td>
<td>15647</td>
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<tr>
<td>5</td>
<td>exp radiotherapy/</td>
<td>4479</td>
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<td>7</td>
<td>antineoplastic agent$.mp. or exp Antineoplastic Agents/</td>
<td>35510</td>
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<td>8</td>
<td>or/4-7</td>
<td>71090</td>
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<td>9</td>
<td>Animal/ not Human/</td>
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<tr>
<td>11</td>
<td>limit 10 to english language [Limit not valid in CDSR; records were retained]</td>
<td>679</td>
</tr>
<tr>
<td>12</td>
<td>limit 11 to yr=&quot;2010 -Current&quot;</td>
<td>354</td>
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OUTCOMES DEFINITION

1. EDUCATION AND INFORMATION - A document in EDUCATION AND INFORMATION is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “EDUCATION AND INFORMATION”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DELAY - A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.