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Evidence-based Series 2-23 Version 2

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

Chemotherapy or Radiotherapy for Resectable Pancreatic Adenocarcinoma

The Gastrointestinal Cancer Disease Site Group

An assessment conducted in November 2014 deferred the review of Evidence-based Series (EBS) 2-23 Version 2, which means that the document remains current until it is assessed again next year. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

This EBS report, which is available on the CCO web site consists of the following four sections:

Section 1:	**Clinical Practice Guideline (ENDORSED)**
Section 2:	**Systematic Review**
Section 3:	**Guideline Development and External Review**
Section 4:	**Document Review Summary and Review Tool**

Release Date: June 12, 2013

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Guideline Citation (Vancouver Style): Jonker D, Bouttell E, Kamra J, Spithoff K; Gastrointestinal Cancer Disease Site Group. Chemotherapy or radiotherapy for resectable pancreatic adenocarcinoma. Jonker, D, Ismaili N, reviewers. Toronto (ON): Cancer Care Ontario; 2007 Nov 1 [Endorsed 2013 June 12]. Program in Evidence-based Care Evidence-based Series No.: 2-23 Version 2

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Nov 2007	1976-2007	Full Report	Web publication	NA
Version 2 Jun 2013	2007-2012	New data found in section 4: Document Review Summary and Tool	Updated Web publication	2007 recommendations is **ENDORSED**

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Evidence-based Series #2-23 version 2: Section 1

Chemotherapy or Radiotherapy for Resectable Pancreatic Adenocarcinoma: Clinical Practice Guidelines

D Jonker, E Bouttell, J Kamra, K Spithoff,
and the Gastrointestinal Cancer Disease Site Group

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

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.
Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2007 and 2012, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: April 2, 2013

QUESTION

Should patients with resectable adenocarcinoma of the exocrine pancreas receive preoperative or postoperative chemotherapy and/or radiation? Outcomes of interest were overall survival, quality of life, and adverse effects.

TARGET POPULATION

These recommendations apply to adult patients with resectable pancreatic adenocarcinoma for whom a pancreatectomy is planned.

RECOMMENDATIONS

- Postoperative chemotherapy is recommended for patients with resectable pancreatic adenocarcinoma. Patients should be referred to a medical oncologist to discuss chemotherapy after gross complete excision of a pancreatic adenocarcinoma. Acceptable regimens include six months of 5-fluorouracil (5FU) plus folinic acid or single-agent gemcitabine.
- The role of postoperative radiotherapy is not clear and warrants further study. Postoperative radiotherapy is not recommended when used in a split-course schedule for patients with

negative margins. In margin-positive patients, there may be a role for postoperative radiotherapy.

- There is insufficient evidence to support the use of preoperative chemotherapy or radiotherapy or the use of intraoperative radiotherapy.

QUALIFYING STATEMENTS

- Trials comparing 5FU to gemcitabine in the postoperative setting have demonstrated that both regimens are effective in reducing risk of recurrence and improving survival. While minor, toxicity (gr3-4 diarrhea 13 vs 2%, stomatitis 10 vs 0%, leucopenia 6 vs 10%) and schedule (25 vs 18 treatments) differences between 5FU vs gemcitabine, respectively guide choice of adjuvant regimen.
- Evidence of a possible role for radiotherapy in patients with margin-positive resections is limited to a subgroup analysis in which the effect of therapy was dependent on margin status. Recommendations that there may be a role for postoperative radiotherapy in suitable patients are based on the expert opinion of the panel since this is the best available evidence.
- The studies available used a split-course radiotherapy regimen, and conventional radiotherapy has not been studied in a randomized trial. There is currently no evidence to support or refute the use of postoperative radiotherapy when used with more modern treatment-planning techniques.
- As there are insufficient data available on preoperative therapy for resectable pancreatic adenocarcinoma, such therapy should only be considered in the setting of a clinical trial.

EVIDENCE

Preoperative Therapy

- One abstract report of a randomized trial of 38 patients reported no significant survival benefit for preoperative gemcitabine and accelerated hyperfractionated radiotherapy compared to no preoperative therapy (1).

Postoperative Therapy

- Seven phase III randomized controlled trials (RCTs) have examined postoperative combinations of chemotherapy and/or radiotherapy in comparison to a surgery-alone control arm. A published individual-patient-data meta-analysis of five of the seven reported trials demonstrated no advantage to postoperative combination chemoradiotherapy but supported an advantage of postoperative chemotherapy alone, with the mature evidence available being for 5FU-based chemotherapy (2).
  - The Gastrointestinal Tumour Study Group (GITSG) trial of 43 patients reported an improvement in survival with four weeks of combined radiotherapy and 5FU followed by two years of weekly 5FU (median survival 21.0 months versus [vs.] 10.9 months; one-sided log rank p=0.035) (3).
  - The European Organization for Research and Treatment (EORTC) trial including 114 patients with pancreatic head cancer demonstrated no advantage to split-course radiotherapy administered concurrently with infusional 5FU without a subsequent two years of postoperative chemotherapy (median survival 17.1 months vs. 12.6 months; two-sided log rank p=0.099) (4).
  - The European Study Group for Pancreatic Cancer (ESPAC-1) trial demonstrated no advantage for combination radiotherapy and 5FU (median survival 15.9 months vs. 17.9 months, favouring no CRT) but a significant survival benefit with six months of 5FU and leucovorin, using the Mayo regimen (median survival 20.1 months vs. 15.5 months) (5).

- A Norwegian trial including patients with carcinoma of the ampulla of Vater indicated a survival benefit for postoperative chemotherapy with 5FU, doxorubicin, and mitomycin C (MMC) up to two years post-surgery (median survival 23 months vs. 11 months) but no significant long-term survival (6).
- A Japanese study reported no survival benefit for adjuvant perioperative plus postoperative chemotherapy with 5FU plus MMC and oral 5FU until progression.
- The German Charité Onkologie (CONKO)-001 trial demonstrated a significant increase in disease-free survival for gemcitabine compared to observation alone (8); however, in the intention-to-treat population, no significant difference in overall survival was reported.
- A second Japanese trial reported no significant survival benefit for postoperative 5FU plus cisplatin over observation alone (9).

RELATED PEBC GUIDELINES

- PG#2-7 *The Treatment of Locally Advanced Pancreatic Cancer*
- PG#2-10 *Use of Gemcitabine in the Treatment of Advanced Pancreatic Adenocarcinoma*

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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